Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group

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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 end points such as bleeding manifestations and that platelet count may not be the ideal parameter for capturing 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 database collection form is provided), and 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. (*Blood*. 2013;121(14):2596-2606)

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. Use of terms such as "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 for making 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 article describes an ITP-specific Bleeding Assessment Tool (ITP-BAT), version 1.0, 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 to facilitate collection of information and communication among physicians and investigators.

Methods

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, Florida, a first half-day conference was formally convened. After

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The online version of this article contains a data supplement.

Table 1. Definition of bleeding manifestations based on physical examination

Site of bleeding	Manifestation	Definition
Skin (epidermis and dermis)		
	Petechiae	Red (recent) or purplish (a few days old) discoloration in the skin with a diameter of 0.5-3 mm that does not blanche with pressure and is not palpable
	Ecchymosis (purpuric macule, bruises, or contusions)	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
Skin (subcutaneous tissue)		
	Hematoma	Bulging localized accumulation of blood, often with discoloration of overlying skin
Visible mucous membranes		
	Petechiae, purpuric macules, and ecchymosis	Same as for skin
	Bulla, vesicle, and blister	Visible raised, thin-walled, circumscribed lesion containing blood. Each bulla (>5 mm) is larger than a vesicle. Bullae, vesicles, and blisters should be counted together as bulla
	Epistaxis	Any bleeding from the nose may be anterior or posterior and unilateral or bilateral
	Gingival bleeding	Any bleeding from the gingival margins
	Subconjunctival hemorrhage	Bright red discoloration underneath the conjunctiva at onset; may assume the appearance of an ecchymosis over time
Muscles and soft tissues		
	Hematoma	Any localized collection of blood visible, palpable, or revealed by imaging. May dissect through fascial planes

a focused review of the available literature, the IWG concluded that because of the lack of robust evidence to support any specific existing scale, a consensus-based approach was preferable. The widely used World Health Organization (WHO) scale[4] (and its many variations), which has often been adopted in recent clinical trials, was designed to grade bleeding in patients with chemotherapy-induced thrombocytopenias, but it 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 vs 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 (United Kingdom) and Amsterdam (The Netherlands) and the ASH 2011 meeting in San Diego (California).

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 clinical and research contexts. 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 for defining bleeding events and making correlations with QoL measures, for other bleeding determinants, for risk factors and platelet counts, and 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. More detailed information is available in supplemental Appendix 1, Methodology.

Literature review

An analysis of the literature was carried out by M.R. and R.S. Articles 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. Articles published subsequently, up to the end of 2011, were identified by using the same criteria. Articles that reported on bleeding assessment in patients with thrombocytopenia secondary to chemotherapy were also considered. For more detailed information, see 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 the 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 medical textbooks differ in the terms they use to describe bleeding manifestations, particularly for skin and visible mucosae, and that adherence to single definitions is limited.

Because 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

Table 2. Grading of bleeding symptoms at presentation and at each subsequent evaluation

	Grade based on the worst incident episode since last visit*				
Type of bleeding	**0**	**1**	**2**	**3**	**4**
Skin					
Petechiae (does not include steroid-induced or senile purpura)	[ ] No	[ ] Less than or equal to 10 in a patient's palm-sized area† in the most affected body area‡ [ ] Any number if reported by the patient	[ ] More than 10 in a patient's palm-sized area or more than 5 in at least 2 patient's palm-sized areas located in at least 2 different body areas,‡ one above and one below the belt (in the most affected body areas)	[ ] More than 50, if scattered both above and below the belt	
Ecchymoses	[ ] 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§	[ ] 3 or more in the same body area,‡ but all smaller than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§ [ ] At least 2 in two different body areas,‡ smaller than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§ [ ] Any number and size if reported by the patient	[ ] From 1 to 5 larger than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§ with or without smaller ones	[ ] More than 5 larger than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§	
Subcutaneous hematomas	[ ] No	[ ] 1 smaller than a patient's palm-sized area [ ] Any number and size if reported by the patient	[ ] 2 smaller than a patient's palm-sized area, spontaneous [ ] 2 smaller than a patient's palm-sized area, disproportionate to trauma§	[ ] More than 2 smaller or at least 1 larger than a patient's palm-sized area, spontaneous [ ] More than 2 smaller or at least 1 larger than a patient's palm-sized area, disproportionate to trauma§	

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, refer to 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 nonovert skin and nonovert mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vesicles, 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 and tongue, or after deciduous tooth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should also be taken into account for grading. Requirement for ITP-specific treatments and antifibrinolytics (apart from menorrhagia) were not considered for grading because of their subjective nature and their adoption to control actual bleeding and to reduce the risk of impendent or future bleeding (see supplemental Appendix 1). In the 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.

GI, gastrointestinal; Hb, hemoglobin; PBAC, Pictorial Blood Assessment Chart (see supplemental Appendix 3); RBC. red blood cell;

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

†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).

‡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, it means the area below the knees).

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

||Minor wound means superficial skin cuts (eg, by shaving razor, knife, or scissors).

¶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.

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

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

††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 paragraph Refinement of the SMOG index).

Table 2. (continued)

	Grade based on the worst incident episode since last visit*				
Type of bleeding	**0**	**1**	**2**	**3**	**4**
Bleeding from minor wounds‖	[ ] No	[ ] Lasting ≤5 min [ ] Any episode if reported by the patient	[ ] Lasting >5 min or interfering with daily activities	[ ] Requiring protracted medical observation at the time of this visit [ ] Medical report describing patient's evaluation by a physician	
Mucosa					
Epistaxis¶	[ ] No	[ ] Lasting ≤5 min [ ] Any episode if reported by the patient	[ ] Lasting >5 min or interfering with daily activities	[ ] Packing or cauterization or in-hospital evaluation at the time of this visit [ ] Medical report describing packing or cauterization or in-hospital evaluation	[ ] RBC transfusion or Hb drop >2 g/dL
Oral cavity, gum bleeding¶	[ ] No	[ ] Lasting ≤5 min [ ] Any episode if reported by the patient	[ ] Lasting >5 min or interfering with daily activities	[ ] Requiring protracted medical observation at the time of this visit [ ] Medical report describing patient's evaluation by a physician	
Oral cavity, hemorrhagic bullae or blisters	[ ] No	[ ] Less than 3 [ ] Any number if reported by the patient	[ ] From 3 to 10 but no difficulty with mastication	[ ] More than 10 or more than 5 if difficulty with mastication	
Oral cavity, bleeding from bites to lips and tongue or after deciduous tooth loss	[ ] No	[ ] Lasting ≤5 min [ ] Any episode if reported by the patient	[ ] Lasting >5 min or interfering with daily activities	[ ] Interventions to ensure hemostasis or in-hospital evaluation at the time of this visit [ ] Medical report describing interventions to ensure hemostasis or in-hospital evaluation	
Subconjunctival hemorrhage (not due to conjunctival disease)	[ ] No	[ ] Petechiae/ hemorrhage partially involving 1 eye [ ] Any episode if reported by the patient	[ ] Petechiae/ hemorrhage partially involving both eyes, or diffuse hemorrhage in 1 eye	[ ] Diffuse hemorrhage in both eyes	

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, refer to 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 nonovert skin and nonovert mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vesicles, 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 and tongue, or after deciduous tooth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should also be taken into account for grading. Requirement for ITP-specific treatments and antifibrinolytics (apart from menorrhagia) were not considered for grading because of their subjective nature and their adoption to control actual bleeding and to reduce the risk of impendent or future bleeding (see supplemental Appendix 1). In the 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.

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‡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, it means the area below the knees).

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

‖Minor wound means superficial skin cuts (eg, by shaving razor, knife, or scissors).

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Table 2. (continued)

	Grade based on the worst incident episode since last visit*				
Type of bleeding	**0**	**1**	**2**	**3**	**4**
Organ (and internal mucosae)					
GI bleeding not explained by visible mucosal bleeding or lesion: hematemesis, melena, hematochezia, rectorrhagia	[ ] No	[ ] Any episode if reported by the patient	[ ] Present at the visit	[ ] Requiring endoscopy#or other therapeutic procedures or in-hospital evaluation at the time of this visit	[ ] RBC transfusion or Hb drop >2 g/dL
			[ ] Described in a medical report	[ ] Medical report prescribing endoscopy# or other therapeutic procedures or in-hospital evaluation	
Lung bleeding	[ ] No	[ ] Any episode if reported by the patient	[ ] Present at this visit	[ ] Requiring bronchoscopy# or other therapeutic procedures or in-hospital evaluation at the time of this visit	[ ] RBC transfusion or Hb drop >2 g/dL
Hemoptysis			[ ] Described in a medical report	[ ] An equivalent episode if described in a medical report	
Tracheobronchial bleeding				[ ] Medical report exhibited by the patient prescribing endoscopy or other procedures or in-hospital evaluation	
Hematuria	[ ] No	[ ] Any episode if reported by the patient	[ ] Macroscopic	[ ] Macroscopic, and requiring cystoscopy# or other therapeutic procedures or in-hospital evaluation at the time of this visit	[ ] RBC transfusion or Hb drop >2 g/dL
		[ ] Microscopic (laboratory analysis)	[ ] Described in a medical report	[ ] An equivalent episode if described in a medical report	
Menorrhagia (compared with pre-ITP or to a phase of disease with normal platelet count)**	[ ] No	[ ] Doubling number of pads or tampons in last cycle compared with pre-ITP or to a phase of disease with normal platelet count	[ ] Changing pads more frequently than every 2 h or clot and flooding	[ ] Acute menorrhagia requiring hospital admission or endometrial ablation (either at this visit or described in a medical report)	[ ] RBC transfusion or Hb drop >2 g/dL

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‡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, it means the area below the knees).

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

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Table 2. (continued)

Type of bleeding	Grade based on the worst incident episode since last visit*				
	0	1	2	3	4
		[ ] 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 combined treatment with antifibrinolytics and hormonal therapy or gynecologic investigation (either at this visit or described in a medical report)		
Intramuscular hematomas (only if diagnosed by a physician with an objective method)	[ ] No	[ ] 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,	[ ] RBC transfusion or Hb drop >2 g/dL
		[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report	
Hemarthrosis (only if diagnosed by a physician with an objective method)	[ ] No	[ ] Post trauma, diagnosed at this visit, function conserved or minimally impaired, if judged disproportionate to trauma	[ ] Spontaneous, diagnosed at this visit, function conserved or minimally impaired	[ ] Spontaneous or post trauma (if judged disproportionate to trauma), diagnosed at this visit and requiring immobilization or joint aspiration	[ ] Spontaneous or post trauma (if judged disproportionate to trauma) diagnosed at this visit and requiring surgical intervention
		[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report
Ocular bleeding (only if diagnosed by a physician with an objective method)	[ ] No		[ ] 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	[ ] Spontaneous vitreous or retinal hemorrhage involving one or both eyes with impaired/ blurred vision present at this visit	[ ] Spontaneous vitreous or retinal hemorrhage with loss of vision in one or both eyes present at this visit
			[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report	[ ] An equivalent episode if described in a medical report

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Table 2. (continued)

Type of bleeding	Grade based on the worst incident episode since last visit* 0	1	2	3	4
Intracranial bleeding††: intracerebral, intraventricular, subarachnoidal, subdural, extradural (only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)	[ ] No		[ ] Any post trauma event requiring hospitalization	[ ] Any spontaneous event requiring hospitalization in the presence of an underlying intracranial lesion	[ ] Any spontaneous event requiring hospitalization without an underlying intracranial lesion
Other internal bleeding: hemoperitoneum, hemopericardium, hemothorax, retroperitoneal bleeding, hepatic and splenic peliosis with organ rupture, retro-orbital bleeding metrorrhagia (only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)	[ ] No			[ ] Any event requiring hospitalization <48 h	[ ] Any event requiring hospitalization >48 h or RBC transfusion or Hb drop >2 g/dL

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, refer to 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 nonovert skin and nonovert mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vesicles, 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 and tongue, or after deciduous tooth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should also be taken into account for grading. Requirement for ITP-specific treatments and antifibrinolytics (apart from menorrhagia) were not considered for grading because of their subjective nature and their adoption to control actual bleeding and to reduce the risk of impendent or future bleeding (see supplemental Appendix 1). In the 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.

GI, gastrointestinal; Hb, hemoglobin; PBAC, Pictorial Blood Assessment Chart (see supplemental Appendix 3); RBC. red blood cell;

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

†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).

‡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, it means the area below the knees).

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

||Minor wound means superficial skin cuts (eg, by shaving razor, knife, or scissors).

¶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.

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

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

††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 paragraph Refinement of the SMOG index).

bleeding manifestations (eg, melena, gastrointestinal bleeding, hematuria), 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 for implementing 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

Table 3. Reporting of bleeding after hemostatic challenges or surgery

Type and date of intervention/ procedure	Platelet counts before and during	Bleeding grade 0	1	2	3	4
Permanent or deciduous tooth extraction* Date _____	[ ] _____ Date _____ [ ] _____ Date _____ [ ] _____ Date _____	[ ] No	[ ] Present	[ ] Requiring revisiting or antifibrinolytics	[ ] Resuturing or packing	[ ] RBC transfusion or Hb drop >2 g/dL
Invasive procedure†/surgery Date _____	[ ] _____ Date _____ [ ] _____ Date _____ [ ] _____ Date _____	[ ] No	[ ] Present but not requiring revisiting or protracted observation	[ ] Requiring revisiting or prolonged in-hospital stay	[ ] 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
Parturition Date _____	[ ] _____ Date _____ [ ] _____ Date _____ [ ] _____ Date _____	[ ] No	[ ] Present	[ ] Requiring iron therapy or prolonged in hospital stay	[ ] RBC transfusion or Hb drop >2 g/dL	[ ] Requiring critical care or surgical intervention

These criteria are proposed as provisional, are not used to calculate the patient's SMOG, and are provided to help in the description of bleeding after hemostatic challenges.
CNS, central nervous system.
*Spontaneous loss of a deciduous tooth is considered in Table 2.
†Biopsy, epidural anesthesia, catheter insertion, and so on.

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. Medical records based on direct observation by the attending physician should be included 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. Such medical records are acceptable for assigning 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 (eg, 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 with a total sum score of 4 that may be derived from a different combination of domain grades, such as S2M2O0, in which 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 (eg, petechiae 2, ecchymosis 1, mouth bleeding 1, epistaxis 2, and heavy menses 2). This approach might be useful for very detailed analyses (eg, to evaluate the relationship of particular bleeding manifestations with some determinants of the disease, such as 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, 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 for guiding the description of bleeding 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 feasibility of the SMOG, the readability and lack of ambiguities and inaccuracies in the data collection forms, and the understanding and applicability of the grading scale. Concordance between two observers (an expert physician and a trained nurse or a young investigator) who investigated the same patient separately, was evaluated in 40 cases. The time needed to complete the questionnaire ranged from 5 to 20 minutes (<15 minutes in 45 of 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 who could skip the data collection form and use Table 2 directly. 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 preestablished intervals, even if the patient was seen or received treatment before the end of the predetermined interval, to ensure 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 become shorter (eg, daily), this rate will approximate the true incidence of the signs and 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 that investigate the natural history of the disease or the long-term efficacy of some treatments such as rituximab or splenectomy, longer intervals (eg, 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 nonresponsive while not requiring treatment based on 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 by using the proposed ITP-BAT. The IWG agreed that a bleeding manifestation can generally be labeled "severe or clinically relevant" if it is grade 3 for skin and/or grade 2 or higher for mucosal domains and/or higher than grade 1 for organ domain (S >2 and/or M >1 and/or O >1).

For the purpose of classification and potential comparison, all bleedings at least grade 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 grade 3 and 4 in the WHO scale. No other particular SMOG combination has been linked to descriptive terms such as "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 (eg, 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] Although major bleeding in ITP, fortunately, is very infrequent, it is possible that the lack of sensitivity and standardization in bleeding assessment when these scales are used may have contributed to the failure of these studies to demonstrate a significant reduction in major bleeding compared with placebo.[13]

The IWG concluded that of the few scoring systems available in the literature, none can be adopted as a simple, reproducible, and clinically meaningful tool to describe the bleeding manifestations of ITP, and they unanimously decided that a new system based on the consensus of clinicians who are experts 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 because 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 alphanumeric system can easily be 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.

In conclusion, 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.

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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 secretary for the meetings and wrote the manuscript. J.B.B., D.B.C., A.G., and R.J.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.

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