J Thromb Haemost. Author manuscript; available in PMC 2016 August 19.

Published in final edited form as:

J Thromb Haemost. 2015 March ; 13(3): 457–464. doi:10.1111/jth.12813.

Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review

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Summary

Background—The burden of severe bleeding in adults and children with immune thrombocytopenia (ITP) has not been established.

Objectives—To describe the frequency and severity of bleeding events in patients with ITP, and the methods used to measure bleeding in ITP studies.

Patients/Methods—We performed a systematic review of all prospective ITP studies that enrolled 20 or more patients. Two reviewers searched Medline, Embase, CINAHL and the Cochrane registry up to May 2014. Overall weighted proportions were estimated using a random effects model. Measurement properties of bleeding assessment tools were evaluated.

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Disclosure of Conflict of Interests

D. M. Arnold reports grants from Amgen and Glaxo-SmithKline and honoraria from Amgen and Bristol Meyers Squibb outside of the submitted work. The other authors state that they have no conflict of interests.

Addendum

C. Neunert performed the research, analyzed the data and wrote the paper; N. Noroozi performed the research, secured funding and wrote the paper; G. Norman performed the analysis and wrote the paper; G. R. Buchanan performed the research, analyzed the results and edited the paper; J. Goy performed the research and analyzed the results; I. Nazi and J. G. Kelton analyzed the results and edited the paper; D. M. Arnold performed the research, analyzed the results, secured funding and wrote the paper.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Severe bleeding events: definition and frequency in clinical studies of adults and children with immune thrombocytopenia that reported bleeding as a categorical variable ($n = 29$).

Table S2. Reported associations between platelet count and bleeding in prospective clinical studies of adults or children with immune thrombocytopenia.

Table S3. Evaluation of the measurement properties of bleeding assessment tools used in clinical studies of immune thrombocytopenia.

Results—We identified 118 studies that reported bleeding (n = 10 908 patients). Weighted proportions for intracerebral hemorrhage (ICH) were 1.4% for adults (95% confidence interval [CI], 0.9–2.1%) and 0.4% for children (95% CI, 0.2–0.7%; $P < 0.01$), most of whom had chronic ITP. The weighted proportion for severe (non-ICH) bleeding was 9.6% for adults (95% CI, 4.1–17.1%) and 20.2% for children (95% CI, 10.0–32.9%; $P < 0.01$) with newly-diagnosed or chronic ITP. Methods of reporting and definitions of severe bleeding were highly variable in primary studies. Two bleeding assessment tools (Buchanan 2002 for children; Page 2007 for adults) demonstrated adequate interrater reliability and validity in independent assessments.

Conclusions—ICH was more common in adults and tended to occur during chronic ITP; other severe bleeds were more common in children and occurred at all stages of disease. Reporting of non-ICH bleeding was variable across studies. Further attention to ITP-specific bleeding measurement in clinical trials is needed to improve standardization of this important outcome for patients.

Keywords

bleeding; intracranial hemorrhages; outcome assessment health care; platelets; purpura; thrombocytopenic

Introduction

Immune thrombocytopenia (ITP) is a hematological disorder characterized by a reduced number of circulating platelets and an increased risk of bleeding. The platelet count is most often used to assess disease status and response to therapy; however, bleeding is the most clinically important outcome [1] because it has a direct impact on morbidity, mortality, quality of life and treatment decisions [2–4].

The frequency of bleeding events across a broad range of adults and children with ITP has not been established. Furthermore, the measurement of bleeding poses significant challenges: First, patients commonly experience bruising, purpura and petechiae, which are difficult to quantify; second, the criteria used to define ‘severe’ bleeding have not been standardized; and third, life threatening bleeding such as intracerebral hemorrhage (ICH) is relatively uncommon [5]. Current estimates of bleeding derive largely from ITP registries; however, registry data generally cannot capture day-to-day bleeding events prospectively [6].

Standard measurement tools for the assessment of bleeding have been developed for specific patient groups, including chemotherapy-induced thrombocytopenia [7], surgical patients receiving anti-thrombotic therapy [8] and critically ill patients [9]. A widely-accepted and validated bleeding measurement tool that is specific for ITP is lacking. Several previous tools have been used and a new tool has recently been proposed [10].

We performed a systematic review of all prospective ITP studies with two objectives. The primary objective was to determine the frequency of overall bleeding, severe bleeding and ICH in adults and children. The secondary objective was to evaluate the methods used to measure bleeding to help standardize bleeding assessments and reporting.

Methods

Article search and selection

To identify eligible studies for this systematic review, two reviewers (CN and DA) independently searched Medline, Embase, CINAHL and the Cochrane central registry of controlled trials using the subject headings 'Purpura, Thrombocytopenic, Idiopathic', and the keywords 'idiopathic thrombocytopenic purpura', 'immune thrombocytopenic purpura', 'ITP' and 'immune thrombocytopenia' up to May 2014. Results were combined with a search of prospective studies, randomized controlled trials and prospective cohort studies. Articles published before 1970 were excluded to ensure consistency in methods of counting platelets. We hand-searched bibliographies of relevant review articles and canvassed experts for additional studies.

Included studies enrolled at least 20 patients of any age with primary ITP. We excluded: laboratory-based and biomarker studies; assessments of different surgical techniques for splenectomy; retrospective studies; studies of secondary ITP in the context of drugs, pregnancy, infection or malignancy; duplicate and redundant publications; review articles; and non-English-language and abstract-only publications. Registry studies with periodic clinical assessments were excluded from this analysis because bleeding evaluations in those studies relied on retrospective information. Three reviewers (CN, NN and DA) screened article titles for relevance and assessed articles for eligibility based on a review of the abstract and full text. Agreement on article selection was determined by Cohen's kappa [11]. Disagreements were resolved by consensus in all cases.

Data abstraction

Data abstraction was carried out in duplicate and independently (by CN, NN and DA in pairs). We collected patient demographics, study design and methods of reporting bleeding events for each study. Discrepancies in data abstraction were verified at source and adjudicated by both reviewers.

Measurement properties of bleeding tools

We assessed the quality of reporting of bleeding in primary studies based on the characteristics of the bleeding assessment tool used. We defined high-quality reporting to be bleeding assessments that were specifically developed for ITP patients. Moderate quality of reporting was defined as bleeding assessments by severity grades with clear definitions. Otherwise, reporting of bleeding was considered low quality. In addition, we evaluated whether reliability and validity of bleeding measurement tools were assessed, and if so, whether reliability and validity were good. These assessments were based on criteria established in the consensus-based standards for the selection of health measurement instruments (COSMIN) criteria [12] and standard definitions with the aid of an expert psychometrician (GN) experienced in health measurement scales.

Statistical analysis

Weighted proportions, reported as percentages with 95% confidence intervals (CIs), for ICH and severe bleeding were estimated by meta-analysis using a random effects model (using

Stats Direct). Differences between subgroups of adults vs. children and chronic vs. newly-diagnosed ITP were evaluated by logistic regression (SAS 9.3; SAS Institution Inc, Cary, NC, USA). We explored the correlation between platelet count and bleeding where possible.

Results

We identified 2582 citations in our initial literature search. After exclusions, we reviewed 1363 abstracts and full text articles in duplicate for eligibility. In the end, 147 clinical studies that prospectively enrolled 20 or more adults or children with primary ITP were included in this systematic review (Fig. 1). Agreement between reviewers on study selection was very good (kappa = 0.76).

All 147 ITP studies reported platelet count levels. Of those, 118 (80.3%) enrolling 10 908 patients reported bleeding events (Table 1). The other 29 studies (19.7%) did not report bleeding. Bleeding was reported as an efficacy outcome in 67 of 118 studies (56.8%; n = 4810), and in 30 of 51 randomized trials (58.8%; n = 2082). Otherwise, bleeding was reported as a safety outcome (n = 12 studies) or as a baseline variable or inclusion criterion only (n = 39 studies).

Intracerebral hemorrhage

The estimated frequency of ICH was obtained from 51 studies (n = 4782 patients) that specifically reported the presence or absence of ICH (Table 2). The weighted proportion of patients with ICH was 1.0% overall (95% CI, 0.7–1.3). Weighted proportions of adults and children with ICH were 1.4% (95% CI, 0.9–2.1) and 0.4% (95% CI, 0.2–0.7), respectively (P < 0.01). ICH occurred more often in patients who had chronic ITP (1.6%; 95% CI, 1.0–2.2) at the time of study enrollment compared with patients who were newly diagnosed (0.4%; 95% CI, 0.1–0.8) (P < 0.01).

Severe bleeding

Information on the frequency of severe (non-ICH) bleeding was restricted to 29 studies (N = 2225 patients) that used a predefined bleeding measurement tool and reported bleeding as a categorical variable (e.g. grade 1, 2, 3) rather than an overall score (Table S1). The weighted proportion of severe bleeding was 15.0% overall (95% CI, 9.3–21.8). We analyzed rates of severe bleeding for adults and children from studies that reported these populations separately: Severe bleeding occurred in 9.6% (95% CI, 4.1–17.1) of adults and 20.2% (95% CI, 10.0–32.9) of children (P < 0.01). Heterogeneity among studies precluded a statistical comparison of severe bleeding for newly diagnosed and chronic ITP patients. The definition of non-ICH severe bleeding was not consistent across studies due to inherent differences in the bleeding measurement tools used; however, extensive mucosal bleeding was the minimum criterion in most studies. Anatomical sites of severe bleeding events were seldom reported; rather, bleeding events (including multiple sites of bleeding) were typically reported in aggregate by severity grade.

Predictors of severe bleeding

Predictors of severe bleeding as reported in individual studies were: severe thrombocytopenia, defined as a platelet count either less than 10×10^9 L^{-1} [13] or 20×10^9 L^{-1} [14] (Table S2); newly-diagnosed ITP [13–15]; and previous minor bleeding [15,16]. In several randomized clinical trials, such as those examining the effect of thrombopoietin (TPO) receptor agonists, response to therapy reduced the frequency of significant bleeding [17–21]; however, this effect did not appear to be treatment specific [22].

Correlation between bleeding and platelet count

The correlation between low platelet counts and bleeding was examined in five studies (Table S2). Khellaf *et al.* reported a moderate correlation between a platelet count $< 20 \times 10^9$ L^{-1} and bleeding ($r = -0.40$; $P < 0.01$) [23]. Page *et al.* did not observe a correlation between thrombocytopenia ($< 30 \times 10^9$ L^{-1}) and bleeding [24]. Pansy *et al.* observed an association between platelets and bleeding score at diagnosis among treated patients ($r = -0.61$, $P = 0.022$) and at days 5–8 among untreated patients ($r = -0.65$, $P = 0.015$); however, there was not a consistent correlation across all study visits or patient groups [25]. In a large follow-up study of 292 patients treated with romiplostim, 51% of all bleeding events (mostly mild) occurred at platelet count levels below 50×10^9 L^{-1} [26]. In that study, 61% of severe bleeding events occurred at platelet counts $< 20 \times 10^9$ L^{-1} and none were considered life threatening. Overall, most bleeding events occurred with platelets $< 30 \times 10^9$ L^{-1}, with frequent exceptions, including one patient with ICH and a platelet count of 120×10^9 L^{-1} [27].

Quality of reporting of bleeding outcomes

The quality of reporting of bleeding was low in the majority of ITP studies because they reported bleeding by its presence or absence only, by anatomical site only, or without clear definitions of severity grades ($n = 77$ studies, 65.3%). Quality of reporting of bleeding was moderate in those studies that used a generic assessment tool such as the World Health Organization (WHO) bleeding score [28] or the Common Terminology Criteria for Adverse Events (CTCAE) [29] ($n = 8$ studies, 6.8%), in studies that used non-descriptive categorical criteria (e.g. severe, life-threatening or fatal) [19,30] and in studies that used a tool that lacked specific severity criteria [31,32] ($n = 4$, 3.4%). One study used a bleeding tool designed for anticoagulation studies [33]. Quality of reporting of bleeding was high in 28 studies that used one of 10 ITP-specific bleeding measurement tools [10,13,23,24,34–39] (Table 3). Two of those tools had undergone an independent validation study [13,24] and both demonstrated good inter-rater reliability and validity compared with platelet count criteria (Table S3). The measurement properties of the WHO bleeding scale for ITP patients were also evaluated in a separate validation study [40], but the findings did not conclusively give information on reliability or validity.

Discussion

Bleeding is the most clinically important outcome in ITP studies. It is what motivates physicians to institute treatment [41,42]; it provokes physician, patient and parental anxiety; and it is an important cause of morbidity and mortality [43]. Our findings show that the rates

of ICH were higher in adults than children (1.4% vs. 0.4%) and rates of (non-ICH) severe bleeding were higher in children than adults (20.2% vs. 9.6%).

Our estimates of ICH are supported by previous data [4,44–46], including the Intercontinental Cooperative ITP Study (ICIS) Registry II, in which the frequency of ICH at diagnosis among 863 children was 0.15% [4]. The frequency of ICH may be higher in adults due to frequent comorbidities, anti-hemostatic medications or longer periods of observation. Other severe bleeds may be more common in children because children are more prone to trauma and less likely to have thrombocytopenia detected incidentally (as part of other investigations). The rate of severe bleeding in children reported in the ICIS II Registry (n = 1106) was 3% [5]; however, severe bleeding was defined as requiring hospitalization, requiring a blood transfusion or interfering seriously with quality of life [47]. The Nordic registry also reported a 3% rate of severe bleeding among children (n = 501) at diagnosis, defined as requiring a blood transfusion [14]. Our estimate of severe bleeding in children may be higher because of the more liberal definitions applied in primary studies, more frequent assessments in prospective studies and the inclusion of both incident and prevalent bleeds. Conversely, severe bleeding in adults may have been underestimated in our review because of the exclusion of some patients from primary studies with severe bleeding before enrollment.

Predictors of severe bleeding were not readily identified in primary studies, but platelet counts below 10–20 × 10^9 L^{-1} and previous minor bleeding were frequent associations. Other retrospective studies have identified older age as a risk factor for severe bleeding [44,48]. A formal regression analysis of predictors was not possible in our study due to the lack of consistent reporting of incident bleeding and variability in bleeding definitions.

Bleeding was often omitted as an efficacy outcome even in randomized trials. Efficacy outcomes mandate more rigorous assessments than safety outcomes and improve the fidelity of reporting [49]. Our systematic review uncovered other limitations in the measurement and reporting of bleeding in ITP studies, including the lack of consistency in defining severity grades, the need for analyses that include time to bleeding events, and the low quality of reporting. While the data were insufficient to endorse any specific bleeding measurement tool, the Buchanan tool (for children) and the Page score (for adults) have been extensively used and have demonstrated adequate measurement properties in independent validation studies [13,24].

Recently, a group of experts designed the ‘SMOG’ bleeding score to quantify bleeding severity from different sites: skin (s), visible mucosa (m) and internal organs (o) [10]. A severity grade from 0 (none) to 5 (fatal) is assigned for each site and a cumulative score is calculated. A pilot study of 50 patients from five centers showed that the time needed to complete the SMOG questionnaire ranged from 5 to 20 min. The performance of this tool has not yet been evaluated in clinical studies.

Our study has limitations. For one, we found extreme heterogeneity in the definitions and methods of measuring bleeding, especially severe (non-ICH) bleeding. Thus, we reported rates of severe bleeding from each individual study in addition to the overall estimate with

its broad confidence limits (see Table S1). Second, case mix may explain the variability in the frequency of severe bleeding across studies. For example, studies of rapid-acting treatments (e.g. intravenous immune globulin) may have included patients with more severe bleeding, whereas trials of therapies with a slower onset of action (e.g. rituximab or TPO receptor agonists) tended to exclude patients with significant bleeding manifestations at the time of enrollment. Third, confounding by treatment may have led to an underestimate of bleeding risk overall. We excluded ITP bleeding scales that were applied retrospectively, including that of Bolton-Maggs and Moon [47], which has been widely used in pediatric studies. Our review did not capture global health assessment tools, which may have included bleeding, including the tool used in ICIS studies [50].

Our study represents the most comprehensive summary of bleeding frequency and severity from the ITP literature. These data improve our understanding of the natural history of ITP and help inform patients and physicians of the risks of withholding treatment during periods of observation, which is often indicated in managing ITP patients. Additional studies are needed to better delineate clinical predictors of bleeding and to further validate existing bleeding assessment tools for ITP so that we can standardize the assessment of this important outcome for patients.

Acknowledgments

We thank V. Blanchette for his ideas at the conception stage of this project and G. Wang for statistical support. This study was funded by the McMaster Division of Hematology & Thromboembolism and by the Canadian Institutes for Health Research (grant #102446).

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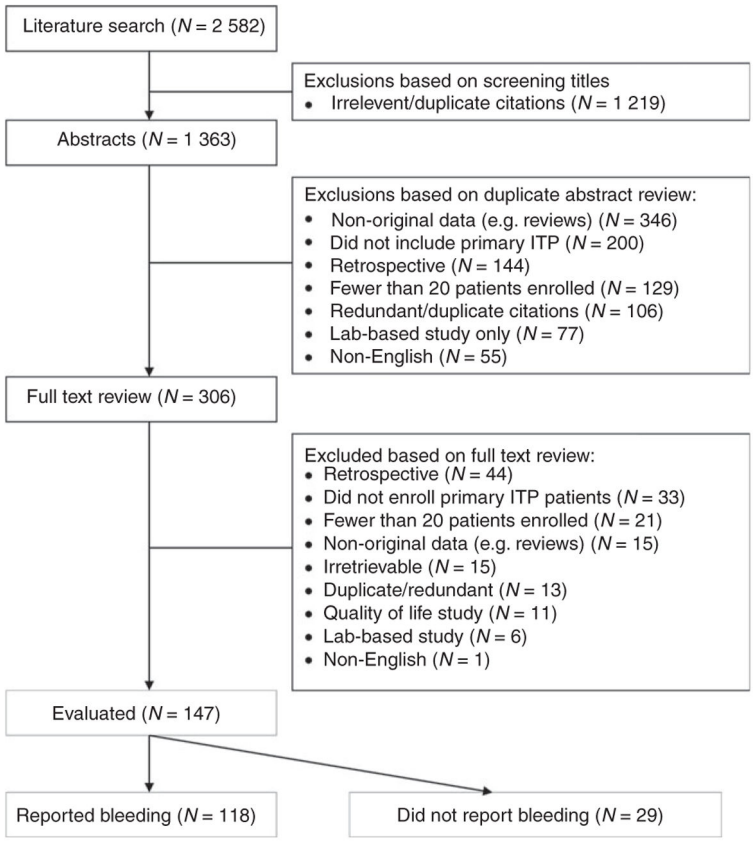

Fig. 1.
Article search and selection.

Table 1

Studies that reported bleeding in prospective studies of children and adults with primary ITP

	Number of studies (%) (*N* = 118; *n* = 10 908)
Population (*n*)	
Adults	5336
Children	5572
How bleeding was reported	
As an efficacy outcome	67 (56.8)
As a safety outcome	12 (10.2)
Other *	39 (33.1)
How bleeding was assessed	
Presence or absence of bleeding only	24 (20.3)
By anatomical site only	37 (31.4)
By severity only	7 (5.9)
By anatomical site and severity	49 (41.5)
Not reported	1 (0.8)
How bleeding information was obtained	
From history	1 (0.8)
From history and physical examination	14 (11.9)
Not specified	103 (87.3)
Bleeding measurement tools	
ITP-specific tool	29 (24.6)
WHO score	5 (4.2)
Adverse events tool (e.g. CTCAE)	3 (2.5)
Thrombosis bleeding assessment tool	1 (0.8)
No pre-existing tool used	80 (67.8)

* As a baseline variable or eligibility criterion.

CTCAE, Common Terminology Criteria for Adverse Events.

Table 2

Intracerebral hemorrhage in adults and children with immune thrombocytopenia (weighted proportions, reported as percentage with 95% confidence intervals)

	Newly-diagnosed, %	Chronic, %	All disease stages, %
Children only (n = 1965)	0.4 (0.1–0.9)	1.3 (0.4–2.7)	0.4 (0.2–0.7)
Adults only (n = 1896)	0.6 (0–1.8)	1.8 (0.9–2.8)	1.4 (0.9–2.1)
Either children or adults * (n = 921)	0.2 (0.2–1.6)	1.6 (0.5–3.1)	1.2 (0.4–2.4)
Overall (n = 4782)	0.4 (0.1–0.8)	1.6 (1.0–2.2)	1.0 (0.7–1.3)

* Data for children and adults were not reported separately in these studies.

Table 3

ITP-specific bleeding measurement tools used in prospective studies (n = 10)

Bleeding tool	Experience (Studies (patients, *n*))	Population	Description	Measurement properties*
Buchanan [13]	11 (480)	Pediatric	Grades (none, minor, mild, moderate, severe) for three anatomical sites, and overall	Good reliability and validity
Mazzucconi [37]	4 (201)	Adult	Severity grades 0–4, blood loss with or without sequelae	Not reported
Page [24]	4 (187)	Pediatric and adult	Ordinal scale from 0 (no bleeding) to 2 (more marked bleeding) at 11 anatomical sites, no overall score	Good reliability and validity
Buchanan [35]	2 (143)	Pediatric	Ordinal bleeding score 0 (definitely no new bleeding) to 4 (bleeding with a drop in hemoglobin> 1 g dL^{-1})	Not reported
Godeau [36]	1 (122)	Adult	Severity scores at seven anatomical sites plus age and overall	Not reported
Khellaf [23]	2 (120)	Adult	Severity scores for six anatomical sites and age, and overall	Not reported
Zhou [38]	1 (86)	Pediatric and adult	Ordinal scale from 1 to 4	Not reported
Dutch national pediatric ITP protocol [39]	1 (60)	Pediatric	Ordinal bleeding score 0 (none) to 4 (life threatening bleeding)	Not reported
Blanchette [34]	1 (53)	Pediatric	Bleeding grade: moderate or severe	Not reported
SMOG score [10]	1 (50)	Adult	Each of three anatomical sites (skin, mucosa, body organ) are graded from 0 to 4 based on explicit descriptions	Not reported

*Good reliability and validity were determined based on published criteria [12] by an expert in evaluation. For further details, see Table S3.