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ORIGINAL RESEARCH

TRANSFUSION

Quality of evidence-based guidelines for platelet transfusion and use: A systematic review

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Abstract

Background: Guidelines for platelet (PLT) transfusion are an important source of information for clinicians. Although guidelines intend to increase consistency and quality of care, variation in methodology and recommendations may exist that could impact the value of a guideline. We aimed to determine the quality of existing PLT transfusion guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument and to describe the inconsistencies in recommendations.

Study Design and Methods: A systematic search was undertaken for evidence-based guidelines from January 1, 2013, to January 25, 2019. Citations were reviewed in duplicate for inclusion and descriptive data extracted. Four physicians appraised the guideline using the AGREE II instrument and the scaled score for each item evaluated was calculated. The protocol was registered in PROSPERO.

Results: Of 6744 citations, 6740 records were screened. Seven of 28 full-text studies met the inclusion criteria. The median scaled score (and the interquartile range of the scaled score) for the following items were as follows:

Abbreviations: AGREE II, Appraisal of Guidelines for Research and Evaluation; EB-CPG(s), evidence-based clinical practice guideline(s); ICTMG, International Collaboration for Transfusion Medicine Guidelines.

scope and purpose, 94% (8%); stakeholder involvement, 63% (18%); rigor of development, 83% (14%); clarity of presentation, 94% (6%); applicability, 58% (20%); and editorial independence, 77% (4%). Overall quality ranged from 4 to 7 (7 is the maximum score). Inconsistent recommendations were on prophylactic PLT transfusion in hypoproliferative thrombocytopenia in the presence of risk factors and dose recommendations.

Conclusion: Inconsistencies between guidelines and variable quality highlight areas for future guideline writers to address. Areas of specific attention include issues of stakeholder involvement and applicability.

KEYWORDS

AGREE II, evidence-based guidelines, platelet transfusion

1 | INTRODUCTION

Clinical practice guidelines are a well-recognized source of information for clinicians and health care professionals in transfusion medicine.[1] If developed properly, they can drive clinical decisions based on published evidence and hence facilitate the treatment of patients to achieve maximum benefit while reducing unnecessary and harmful interventions.[2]

Although evidence-based clinical practice guidelines (EB-CPGs) are intended to increase consistency and efficiency of care delivery, variation in EB-CPGs undoubtedly exists, which may impact on the usefulness of the guidelines for clinicians. Variation between transfusion EB-CPGs may occur for several reasons including the numbers and roles of different experts involved in the write-up of the guidelines, professional societies, organizations, and blood services. EB-CPGs recommendations may become outdated with emerging evidence and development of guidelines is laborious and costly.[2,3] Guidelines may also not always meet the required quality standards.[4,5]

Platelet (PLT) transfusions are commonly administered in the health care setting.[6] Multiple audits have documented unnecessary PLT transfusions in clinical practice, suggesting the need for interventions to improve use in the clinical setting and optimize utilization,[7–9] but also raising questions about the role of existing educational initiatives. To ensure an efficient use of PLTs, PLT transfusions must be used appropriately because they have a short shelf life and are costly to manufacture. PLT transfusions have risks as established in a recent randomized trial in preterm infants with severe thrombocytopenia and seem to be inferior to standard care for patients taking anti-PLT therapy before intracranial hemorrhage.[10,11] There has been no systematic evaluation of existing guidelines for PLT transfusions.

The aim of this systematic review was to appraise the quality of EB-CPGs pertaining to PLT transfusions. This review was completed by members of the International Collaboration for Transfusion Medicine Guidelines (ICTMG) adopting the same method used in its assessment of guidelines for red blood cell (RBC) and plasma transfusion and in preparation for updating its EB-CPGs on PLT transfusion published in 2015.[12,13] The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument was applied to the identified guidelines to evaluate a range of domains relevant to guideline quality.[14–17]

2 | MATERIALS AND METHODS

2.1 | Data sources

The systematic review was conducted according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18,19] ICTMG members, including hematologists, transfusion medicine physicians, pathologists, and methodologists performed a systematic review of existing EB-CPGs for PLT transfusion and use. The review protocol was registered at PROSPERO: CRD42019139312.[19,20]

We conducted a comprehensive database search for EB-CGPs using OVID/MEDLINE, EMBASE, and Cochrane Library from January 1, 2013, to January 25, 2019. The ICTMG has previously performed a systematic review of PLT use that included publications from 1946 until 2013.[13] The search period reflected the time from that previous search until the inception of the current systematic review so that is why the 6-year time period was considered to reflect current practice. The full search is available in Appendix S1. In addition, bibliographies of identified guidelines were hand searched. The

6-year period was considered to reflect current practice. Conference proceedings and gray literature were not included.

2.2 | Study selection, data extraction, and quality assessment

Four authors independently reviewed the citations by title, author, and abstract for inclusion. Any disagreements were resolved by retrieval of the full text and consensus. We included EB-CPGs of PLT transfusion and use defined as (a) guidelines with a specified clinical question, (b) using a systematic search strategy, (c) including an assessment of risk of bias, and (d) with a description of the development of recommendations. Moreover, non-English papers were included and translated using an Internet-based translation tool (Google Translate Module).[21] The translation was subsequently verified by the group and a native language reader. We aimed to focus on guidelines where PLT transfusion was the predominant focus for patient care. We excluded guidelines with less than a 30% focus on PLT transfusion, non–peer-reviewed guidelines, and systematic reviews that were not EB-CPGs. We considered less than 30% to be a liberal threshold for inclusion thus would not limit generalizability There were no restrictions based on blood component modifications, such as irradiation or use for PLTs for nontransfusion purposes or the indication for the PLT transfusion, prophylactic or therapeutic.

Three assessors underwent training on the AGREE II instrument. The assessors were given access to the AGREE II user manual, the AGREE II reporting checklist, and an online tutorial on the use of AGREE II instrument. After reviewing these, the assessors were given a published guideline and an Excel sheet to evaluate the guideline independently. Scores obtained were collected by a methodologist and were compiled and compared. A meeting followed to discuss any outliers. A fourth assessor did not require training due to previous experience. All four physicians independently used AGREE II to appraise each guideline. Data were extracted to a prepiloted data abstraction form that included the guideline publication details (first author, year, country, and guideline group) and quality assessment according to AGREE II.[14] The AGREE II instrument consists of 23 items categorized into six main domains: the clarity of the scope and purpose, the stakeholder involvement in the guideline development group, the transparency and methodologic rigor of development, the clarity of presentation, the independence from funding agencies when developing recommendations, and the overall quality. The validity of each domain has been previously assessed.[16] No assessor was assigned a guideline for which they had been a coauthor or significant contributor. A fifth assessor was added as required for assessing these guidelines.

2.3 | Data synthesis

Each domain was scored from one to seven points as recommended by the AGREE II consortium, seven representing the highest score. Minimum domain scores have not been established by the AGREE II consortium and the AGREE II consortium also does not recommend aggregating scores, because each domain is independent.[17] Each domain was described using the scaled domain score as recommended by the AGREE II consortium as well as using medians and interquartile ranges (IQRs) of the scaled domain score. The maximum possible score was calculated as $7 \times n$ (items) $\times$ n (appraisers). The minimum possible score was calculated as $1 \times n$ (items) $\times$ n (appraisers). The scaled domain score was calculated as: (Obtained score – Minimum possible score)/(Maximum possible score – Minimum possible score) = __%. Assessors were also asked to rate the overall quality of the guideline and whether the guideline should be recommended.

For guidelines where there was a variation in scoring as defined by a 3-point difference in AGREE II, the discordant domains were discussed in teleconferences to provide clarification on specific reviewers' scoring. A total of five rounds of reviews were made until agreement was reached. We also abstracted the recommendations from each guideline to assess consistency of recommendations.

3 | RESULTS

3.1 | Study selection and characteristics of the included guidelines

The results of the search strategy are described in Figure 1. Four studies met the inclusion criteria.[13,22–24] Three additional studies were added after a manual search of the literature.[25–27] Twenty-one guidelines were excluded because either the guideline had less than 30% of the focus on PLT components (n = 11) or publications were not EB-CPGs (n = 10).

Table 1 describes the characteristics of the reviewed EB-CPGs. Three were from the United Kingdom, two were from the United States, and two were from international societies. All guidelines with exception of two developed recommendations specifically for PLT

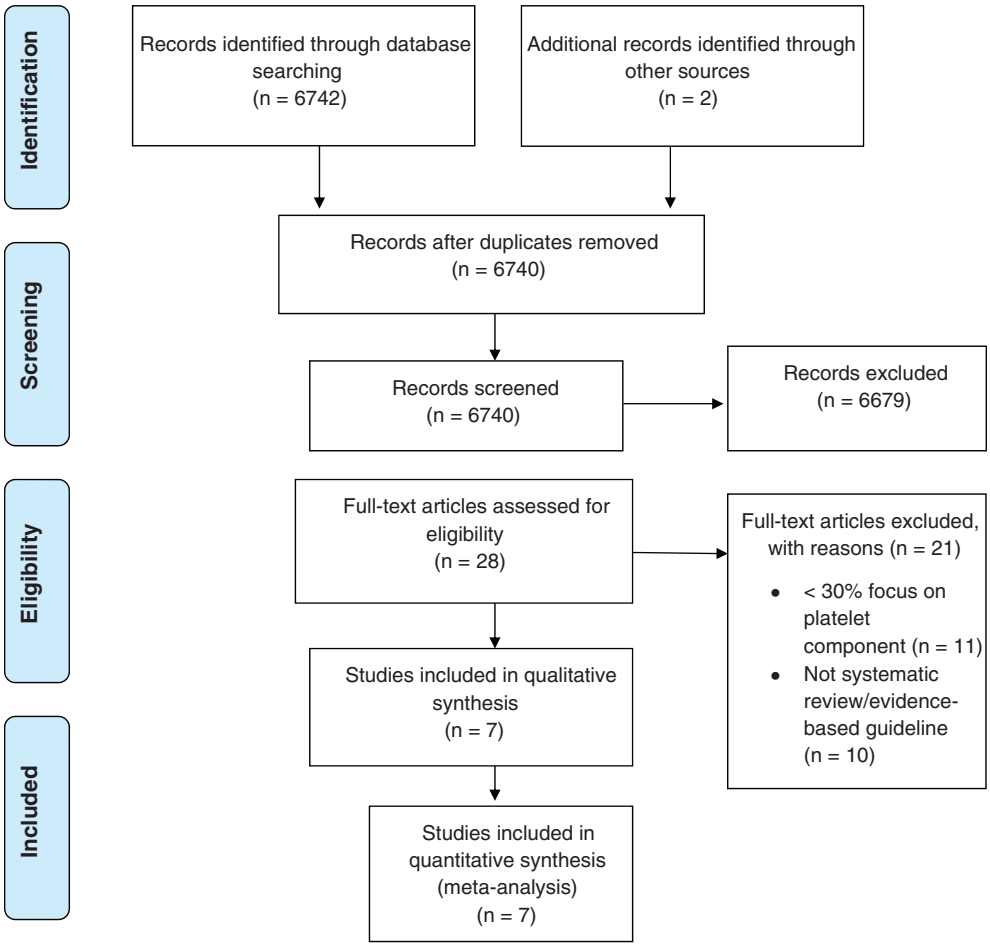

FIGURE 1 Results of the search strategy [Color figure can be viewed at wileyonlinelibrary.com]

transfusion. One guideline covered the use of PLTs in regenerative medicine[27] and the other transfusion support in aplastic anemia patients.[26] One guideline focused on transfusion for fetuses, neonates, and older children, including recommendations on PLT thresholds for prophylactic and therapeutic PLT transfusions,[25] while two other guidelines included recommendations for prophylactic PLT transfusion for pediatric patients with hypoproliferative thrombocytopenia.[13,22]

3.2 | AGREE II appraisal

Table 2 describes the scaled domain scores according to the AGREE II tool. Individual domain scores ranged from 1 (low) to 7 (high), while scaled domain scores ranged from 18% to 100%. The median individual scores, the median scaled scores, and the IQR of the scaled scores were as follows: scope and purpose—median score 21, median scaled score 94%, (IQR 8%); stakeholder involvement—15, 63% (IQR 18%); rigor of development—52, 83%, (IQR 14%); clarity of presentation—21, 94%, (IQR 6%); applicability—19, 58%, (IQR 20%); and editorial independence—12, 77%, (IQR 4%).

All seven EB-CPGs were appraised to have a scaled domain score for rigor of development greater than 50% (Table 3). All guidelines included relevant stakeholders, and four reported having a methodologist on the panel.[13,22,24,27] Only one guideline involved patients during the development process but indicated that they did not necessarily approve or endorse the content of the guideline.[26] Four guidelines reported a plan for updating the guideline,[13,22,23,26] while one reported an explicit process for the review within a predefined time frame.[13] All guidelines were recommended for use by all appraisers. The overall quality of the guidelines ranged from 4 to 7. All guidelines had disclosures reported.

Variability among the initial four appraisers (defined as more than a three-point difference in rating) was addressed by review of the scores to assess the discrepancies. Most discrepancies involved items under the applicability domain (14/33 of discrepancies). This domain remained to have the lowest median scaled score after resolution of the discrepancies between the appraisers.

Five guidelines addressed PLT transfusion for hypoproliferative thrombocytopenia.[13,22–24,26] One guideline was specific for patients diagnosed with aplastic anemia,[26] and another guideline included

TABLE 1 Characteristics of the seven included EB-CPGs

First author/year	Guideline group/ country	Target audience (if applicable)	Health problem	Guideline development group included		Explicit process for updating reported	EBG	Audit criteria
				Methodologist	Stakeholders			
Kaufman, 2015[24]	AABB/USA	NR	Adult patients who are candidates for PLT transfusion	Yes	Yes	No	GRADE	No
Nahirniak, 2015[13]	ICTMG/(Canada, USA, Italy, UK)	Hematologist, oncologists, and transfusion medicine specialists	Adult and pediatric patients with hypoproliferative thrombocytopenia (excluding neonates)	Yes	Yes	Yes, every 3 y	GRADE	No
New, 2016[25]	BCSH/UK	Health care professionals in the UK	Fetuses, neonates, older children	NR	Yes	No	GRADE	Yes
Killick, 2016[26]	BCSH/UK	Health care professionals in the UK	Adult aplastic anemia patients	NR	Yes	If new evidence is available	GRADE	Yes
Estcourt, 2017[23]	BCSH/UK	Clinicians in the UK	Adult patients who are candidates for PLT transfusion	NR	Yes	If new evidence is available	GRADE	Yes
Schiffer, 2018[22]	ASCO/USA	Clinicians administering intensive therapies to patients with cancer	Adults and children (≥4 mo of age) with hematologic malignancies, solid tumors or hypoproliferative thrombocytopenia	Yes	Yes	If new evidence is available	GRADE	No
Harrison, 2018[27]	ISTH (UK, Spain, Taiwan, South Korea, USA, Germany, France, the Netherlands, Italy)	Regenerative medicine	Burns, wound and bone healing, sport and muscle injury, osteoarthritis, skin cosmetic therapy	Yes	Yes	No	RAND	No

Abbreviations: ASCO, American Society of Clinical Oncology; BCSH, British Committee for Standards in Hematology; EBG, evidence-based guideline; GRADE, grading of recommendations assessment, development; NR, not reported; RAND, consensus method developed by the RAND corporation in the 1980s[38]; SSC of the ISTH, Scientific and Standardization Committee of the ISTH; TPO, thrombopoietin receptor.

TABLE 2 AGREE II: Categorical analysis of five domains of the seven EB-CPGs

Domain	Guideline/scaled domain scores (%)							Scaled score			
	Kaufman, 2015[24]	Nahirniak, 2015[13]	New, 2016[25]	Killick, 2016[26]	Estcourt, 2017[23]	Schiffer, 2018[22]	Harrison, 2018[27]	Median, % (IQR)	Mean	Minimum	Maximum
Scope and purpose	92	99	99	88	94	97	63	94 (8)	90	63	99
Stakeholder involvement	46	68	63	89	58	72	38	63 (18)	62	38	89
Rigor of development	71	95	83	90	81	90	36	83 (14)	78	36	95
Clarity of presentation	92	100	94	99	97	93	50	94 (6)	89	50	100
Applicability	33	58	73	57	79	58	18	58 (20)	54	18	79
Editorial independence	79	77	75	83	77	81	75	77 (4)	78	75	83
Average overall quality score	6	7	6	6	6	7	4	6 (1)	6	4	7
Recommended: yes/yes with modifications/no	3/1	4/0	3/1	3/1	3/1	3/1	2/2	NA	NA	NA	NA
Recommended (%)	75	100	75	75	75	75	50	NA	NA	NA	NA

Abbreviation: NA, not applicable.

TABLE 3 Median scores for individual items of the rigor of development domain (minimum score = 1, maximum score = 7)

Items	Kaufman, 2015[24]	Nahirniak, 2015[13]	New, 2016[25]	Killick, 2016[26]	Estcourt, 2017[23]	Schiffer, 2018[22]	Harrison, 2018[27]
Systematic methods	7	7	7	7	7	7	3
Evidence criteria	7	7	7	6	6	7	3
Strengths/limits	7	6	7	7	7	7	3
Methods for recommendations	7	7	7	7	6	7	7
Benefits/risks	7	7	7	7	7	7	3
Links to evidence	7	7	7	7	7	7	2
External review	1	7	7	7	5	5	5
Update	1	6	1	6	6	6	2

recommendations for patients with reversible marrow failure with anticipated recovery and patients with chronic marrow failure where recovery was not anticipated.[23] All five guidelines consistently recommended that prophylactic PLT transfusion should be given for patients with hypoproliferative thrombocytopenia. All five guidelines recommended a PLT threshold of 10×10^9/L for prophylactic PLT transfusion in this group of patients. However, there was inconsistency in the recommendations for prophylactic PLT transfusion in the presence of additional risk factors such as bleeding and sepsis (Table 4). Two guidelines out of five recommended a higher threshold of 10×10^9 to 20×10^9/L[23] and 20×10^9/L,[26] one recommended transfusion in these settings even if the PLT count is higher than 10×10^9/L,[13] while another recommended that the threshold to transfuse should vary according to the patient's diagnosis, clinical condition, and treatment modality but suggested that transfusion at higher thresholds than 10×10^9/L may be advisable.[22] The fifth guideline did not specify a particular threshold in these settings.[24] Two guidelines recommended against prophylactic PLT transfusion in stable patients not on active treatment,[22,26] while one recommended to consider not giving prophylactic PLT transfusion in well patients with no evidence of bleeding after autologous marrow transplant and in asymptomatic patients with chronic bone marrow failure, including those taking low-dose oral chemotherapy or azacitidine.[23] Recommended dosing of PLTs was variable, with some recommending doses based on PLT count,[13] while others recommended doses based on adult dose[23,26] or a single apheresis unit[24] equivalence. One guideline did not include any PLT dosing recommendations.[22] Only one guideline addressed PLT transfusion in other situations, namely, prophylactic PLT transfusion for inpatients with critical illness in the absence of bleeding or planned procedures and PLT transfusion for PLT dysfunction disorders.[23] The same guideline addressed PLT thresholds for therapeutic PLT transfusion, contraindications, and alternatives to PLT transfusions.[23] One guideline addressed recommendations of PLT thresholds for prophylactic and therapeutic PLT transfusions in neonates and children.[25]

Three guidelines addressed PLT transfusions before surgeries and procedures.[22–24] All three guidelines were consistent with their recommendation of a PLT count of more than 20×10^9/L for inserting central venous catheters. Two guidelines were inconsistent with the PLT count threshold for a lumbar puncture procedure.[23,24] Recommendation for other indications was variable (Table 4).

Two guidelines addressed selection of PLTs based on ABO blood group with a recommendation of maximizing the use of ABO-identical or -compatible PLTs in patients with hypoproliferative thrombocytopenia[13] and in patients who require regular PLT transfusion support.[23] Three guidelines addressed prevention of anti-D alloimmunization in D– females who received D+ PLTs with similar recommendations on the use of anti-D immunoprophylaxis.[13,22,23] Similarly, one guideline recommended the use of prophylactic anti-D for D– female pediatric recipients who required D+ PLTs emergently.[25] Three guidelines addressed management of PLT refractoriness, with consistent recommendations on the use of HLA- and HPA-selected PLTs.[13,22,23] Two of these guidelines recommended the use of cross-matched PLTs as an option for this group of patients.[13,22]

Three guidelines described an intent to update their recommendations if new evidence became available,[22,23,26] while one defined a specific time frame for the update.[13] A summary of all recommendations is provided in the supplemental document (Appendix S2).

4 | DISCUSSION

This systematic review identified seven recent EB-CPGs on PLT transfusion and use. Applicability and

TABLE 4 Summary of inconsistencies in included guideline recommendations

First author, year	Guideline group	Recommendation
Prophylactic PLT transfusion for patients with hypoproliferative thrombocytopenia if additional risk factors for bleeding exist; PLT threshold		
Nahirniak, 2015[13]	ICTMG	• Patients with hypoproliferative thrombocytopenia with clinically significant bleeding attributed to thrombocytopenia should probably receive PLT transfusions even if the PLT count is $>10 \times 10^9$/L. (*Very weak level of evidence, weak recommendation*)
Killick, 2015[26]	BSCH	• In patients judged to have additional risk factors for bleeding, such as fever or sepsis, a higher prophylactic transfusion threshold of 20×10^9/L is recommended. *(2C)* • Patients with chronic bleeding of WHO grade 2 or above require individual management according to the severity of their symptoms and signs. *(2C)*
Estcourt, 2017[23]	BSCH	Reversible marrow failure, recovery anticipated • Consider increasing the threshold for prophylactic PLT transfusion to between 10×10^9–20×10^9/L in patients judged to have additional risk factors for bleeding. Individual review is required. *(2C)* Chronic marrow failure, recovery is not anticipated • Manage patients with chronic bleeding of WHO Grade 2 or above individually, according to the severity of their symptoms and signs. Consider a strategy of prophylaxis (eg, twice a week). *(2C)*
Schiffer, 2017[22]	ASCO	• Prophylactic PLT transfusion should be administered to patients with thrombocytopenia resulting from impaired marrow function to reduce the risk of hemorrhage when the PLT count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality. (E*vidence based, high evidence quality, strong recommendation)* • The Panel recommends a threshold of $<10 \times 10^9$/L for prophylactic PLT transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid decrease of PLT count, or coagulation abnormalities (eg, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which PLT transfusions may not be readily available in case of emergencies, as might be the case in outpatients who live at a distance from the treatment center. (*Evidence based, high evidence quality, strong recommendation)* • The risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth and duration of the PLT nadir, although other factors contribute as well. The Panel recommends a threshold $<10 \times 10^9$/L for prophylactic PLT transfusion, based on extrapolation from studies in hematologic malignancies. PLT transfusion at higher levels is appropriate in patients with active localized bleeding which can sometimes be seen in patients with necrotic tumors. (*Informal consensus, low evidence quality, moderate recommendation)*
Prophylactic PLT transfusion for patients with hypoproliferative thrombocytopenia; PLT dose		
Kaufman, 2014[24]	AABB	• The AABB recommends transfusing up to a single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one-half of a standard apheresis unit are equally effective. (*Grade: strong recommendation; moderate-quality evidence)*
Nahirniak, 2015[39]	ICTMG	• Low- or standard-dose PLT transfusion (ie, $1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$, respectively), as opposed to high-dose PLT transfusion ($4.4 \times 10^{11}/m^2$), should be given to hospitalized patients with hypoproliferative thrombocytopenia who require prophylactic PLT transfusion. (*High level of evidence, strong recommendation).*
Killick, 2015[26]	BSCH	• Only one adult PLT dose is routinely required. *(1A)*
Estcourt, 2017[23]	BSCH	• Use only one adult dose (1 unit) routinely for prophylactic PLT transfusions. (*1A)*
Prophylactic PLT transfusion before procedures or surgery		
Kaufman, 2014[24]	AABB	• The AABB suggests prophylactic PLT transfusion for patients having elective diagnostic lumbar puncture with a PLT count $<50 \times 10^9$ cells/L. (*Grade: weak recommendation; very-low-quality evidence)*

TABLE 4 (Continued)

First author, year	Guideline group	Recommendation
		• The AABB suggests prophylactic PLT transfusion for patients having major elective nonneuraxial surgery with a PLT count $<50 \times 10^9$ cells/L. (*Grade: weak recommendation; very-low-quality evidence)*
Estcourt, 2017[23]	BSCH	• Consider performing the following procedures above the PLT count threshold indicated ○ Lumbar puncture when the PLT count is $\geq 40 \times 10^9$/L; (*2C)* ○ Major surgery when the PLT count is $>50 \times 10^9$/L. *(1C)*
Schiffer, 2017[22]	ASCO	• The Panel recommends a threshold of 40×10^9/L to 50×10^9/L for performing major invasive procedures, in the absence of associated coagulation abnormalities.

Abbreviations: ASCO, American Society of Clinical Oncology; BCSH, British Committee for Standards in Hematology; SSC of the ISTH, Scientific and Standardization Committee of the ISTH; WHO, World Health Organization.

stakeholder involvement domains as assessed by AGREE II instrument scored the lowest. Only one guideline involved patients during the development process. These findings highlight multiple areas for PLT guideline developers to consider in the future. This includes a need for future guidelines to address aspects related to the applicability of the guidelines, including facilitators and barriers to guideline application, provision of advice and/or tools on guideline implementation, provision of monitoring and/or auditing criteria, and addressing the resource implications of applying the recommendations across practice settings. Applicability and utilization of the published guidelines in clinical practice requires assessment to address any existing barriers to implementation. Since patient involvement is becoming more prevalent in all areas of health care policy setting, and considering that the intent of the guidelines is to optimize patient care, more effort should be made to ensure that their views are captured in any future guidelines.

Inconsistencies were observed between the reviewed guidelines, despite the fact that the evidence these guidelines drew upon was the same (allowing for date of guideline). This can cause confusion between clinicians who may struggle to reconcile conflicting recommendations. The identified areas of inconsistent recommendations of appropriate PLT count threshold for prophylactic PLT transfusion in high-risk settings and dosage of PLTs that should be used are considered important questions for PLT transfusion therapy.[28] This is particularly the case in patients undergoing chemotherapy and/or allogeneic stem cell transplantation, as policy of no prophylaxis was shown to be associated with significant cost savings in a recent cost analysis of the UK–Australia Trial of Prophylactic PLT Transfusion.[29] Moreover, previous data have shown that the most important PLT unit characteristic associated with transfusion-related adverse events was PLT dose per transfusion.[30] One related issue might be how guideline writers approach recommendations in settings where there is little robust primary evidence required for guideline development.[31] Moreover, variation in the application of grading of recommendations by the guideline developers has been reported.[32] EB-CPGs are intended to improve the quality of clinical decision making, and such inconsistencies will likely lead to nonadherence to the recommendations as they find them inconvenient and time-consuming to use.[33]

The majority of the guidelines indicated an update is required when new evidence emerged but only one reported a time frame for the update. Given the expanding literature in PLT transfusion medicine, it is important that guidelines indicate a clear strategy and process for updating.[3] There is very limited guidance for application in pediatric and neonatal patient populations, highlighting the need for additional evidence to support development of guidelines in this group of patients.

A strength of this review is the use of the AGREE II instrument, which is a validated and transparent tool, that has consistently been identified as one of the best available methods to assess guideline quality.[14,34] However, this tool does not assess the clinical content or quality of evidence underpinning the guideline. A limitation of our systematic review is the initial variability between the appraisals of domain scores, which required repeat reviews of the scores between the appraisals until inconsistencies were resolved. This variability was also noted by the researchers undertaking a similar exercise for RBCs and plasma guidelines,[12] and several authors participated in both exercises. This was previously reported in particular for some items in the AGREE II instrument in other reports.[35] Guideline developers have been shown previously to rank domain scores lower than clinicians.[15] This suggests ongoing education and piloting is required to apply the AGREE II tool to ensure the findings are reproducible. Finally, the recently released AGREE-REX instrument was not used in the appraisal process. AGREE-REX aims at assessing the quality of the guideline recommendations with high-quality recommendations being defined as those that are clinically credible,

trustworthy, and implementable.[36] The decision to use the AGREE II instrument was made considering that the AGREE II tool targets the appraisal to the entire practice guideline process, while the AGREE-REX tool targets the recommendations.[37]

In conclusion, this systematic appraisal of PLT guidelines using the AGREE II instrument demonstrated variable rigor in guideline development. There are some areas with inconsistent recommendations and areas in need of focus with regard to implementation and stakeholder involvement. While the publication of multiple guidelines on a similar topic raises questions about unnecessary duplication of efforts and costs, our review also raises the question that it may create confusion as to which guideline should be implemented across health systems serving various specialties with variable access to resources. Such concerns could be addressed through a coordinated international effort for EB-CPGs development with a particular focus on facilitating implementation.

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CONFLICT OF INTEREST

S.N.—financial disclosures, advisory board services to Canadian Blood Services; S.S.—intellectual disclosures, guideline group member for British Society of Hematology (multiple topics including PLT transfusion), and research funding from NHSBT (related to PLT transfusion), but was not an appraiser for any guidelines in this review; N.S.—financial disclosures, consulting services to Canadian Blood Services; R.J., H.K., and D.L.—financial disclosures, employees of Canadian Blood Services; A.Z.A. and U.L.R. have no relevant financial or intellectual conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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