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Original Articles

Guidance on Platelet Transfusion for Patients With Hypoproliferative Thrombocytopenia

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ABSTRACT

Patients with hypoproliferative thrombocytopenia are at an increased risk for hemorrhage and alloimmunization to platelets. Updated guidance for optimizing platelet transfusion therapy is needed as data from recent pivotal trials have the potential to change practice. This guideline, developed by a large international panel using a systematic search strategy and standardized methods to develop recommendations, incorporates recent trials not available when previous guidelines were developed. We found that prophylactic platelet transfusion for platelet counts less than or equal to 10×10^9/L is the optimal approach to decrease the risk of hemorrhage for patients requiring chemotherapy or undergoing allogeneic or autologous transplantation. A low dose of platelets ($1.41 \times 10^{11}/m^2$) is hemostatically as effective as higher dose of platelets but requires more frequent platelet transfusions suggesting that low-dose platelets may be used in hospitalized patients. For outpatients, a median dose ($2.4 \times 10^{11}/m^2$) may be more cost-effective to prevent clinic visits only to receive a transfusion. In terms of platelet products, whole blood–derived platelet concentrates can be used interchangeably with apheresis platelets, and ABO-compatible platelet should be given to improve platelet increments and decrease the rate of refractoriness to platelet transfusion. For RhD-negative female children or women of child-bearing potential who have received RhD-positive platelets, Rh immunoglobulin should probably be given to prevent immunization to the RhD antigen. Providing platelet support for the alloimmunized refractory patients with ABO-matched and HLA-selected or crossmatched products is of some benefit, yet the degree of benefit needs to be assessed in the era of leukoreduction.

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One of the most common indications for platelet transfusion is for supportive care of patients with marrow suppression due to primary bone marrow dyscrasias, infiltrative disorders, cytoreductive therapy, or hematopoietic stem cell transplantation (SCT). As more intensive therapies are developed, the number of patients with severe hypoproliferative thrombocytopenia and the duration of thrombocytopenia have increased, as has the need for platelet support to reduce the risk of hemorrhage. This guideline was developed by an international panel of experts to incorporate information from recently published key platelet transfusion trials. There have been various national guidelines published for platelet transfusion therapy [1-9], some of which are now over 10 years old since publication.

An international team of adult and pediatric hematologists, hematopathologists, methodologists, and transfusion medicine physicians was convened to complete a guideline for the management of platelet transfusion using a systematic approach and standardized method to develop recommendations. This guideline is aimed to assist hematologists, oncologists, and transfusion medicine specialists on optimizing platelet transfusion therapy for patients with hypoproliferative thrombocytopenia, as the benefits of platelet transfusion need to be balanced against the risks. Unless otherwise specified, the data available are generalizable to the adult and pediatric population but not to neonates.

Methods

The Process of Guideline Development

The International Collaboration for Transfusion Medicine Guidelines (ICTMG) was established in 2009 to develop guidelines promoting evidence-based transfusion therapy to optimize patient care. The expert panel that developed this guideline was composed of 24 members representing 6 countries and included internationally recognized specialists in platelet transfusion therapy (C-LS, MF, PR, RD, RV, SS, and SSt).

The scope of the guideline included the need for prophylactic platelet transfusions; the threshold platelet count for prophylactic platelet transfusion; the need for ABO, Rh, HLA, and crossmatch compatibility; and the merits of using apheresis or whole blood–derived (WBD) platelets.

Relevant questions were formatted using the analytic framework developed by the US Preventative Services Task Force [10]. A question was developed for each topic that considered the primary and surrogate outcomes and adverse events including cost and inventory. Each question was discussed by teleconference before finalizing the search strategy.

A systematic literature search was conducted of 3 databases: Medline, EMBASE, and the Cochrane Library from 1946 until December 2013. The Transfusion Evidence Library was also searched for systematic reviews (http://www.transfusionguidelines.org.uk). References identified from bibliographic searches and by panel members were also included. Conference proceedings were not routinely searched. All evidence tables and search strategies are included in Appendices A and B, respectively. If a systematic review was published, it was included, and the database search started at the year of publication. If a systematic review on the topic had not been previously published, the ICTMG conducted the systematic review.

Two reviewers for each systematic review independently assessed citations to identify studies that met all the following inclusion criteria: (1) original article; (2) included 10 or more patients with hypoproliferative thrombocytopenia; and (3) included any of the outcomes of interest, that is, mortality, hemorrhage, refractoriness, alloimmunization, adverse events, increment, and platelet utilization. Content experts with previous related publications did not partake in the systematic review. We limited the search to patient studies that

were published in English. We also made the assumption that leukoreduced platelets are the standard products used in most countries with access to the type of platelet transfusion therapy discussed in this guideline (eg, apheresis collections, HLA matching, etc), so we elected not to generate a specific recommendation regarding leukoreduction.

Design of the data collection forms and tables was guided by the clinical questions in the analytical framework. Data in the tables included (1) study characteristics (year of publication, country, whether single or multicenter, and patient population), (2) quality assessment, and (3) outcomes (primary: mortality, hemorrhage as well as surrogate outcomes: platelet refractoriness/alloimmunization, platelet utilization, platelet increments, and transfusion reactions).

Two reviewers independently extracted data from the full articles to the data collection tables and independently assessed the quality of each study. Design of the data collection forms and tables was guided by the clinical questions in the analytical framework. The quality of the randomized controlled clinical trials (RCTs) was assessed using a number of tools including the Cochrane Collaboration's tool for assessing risk of bias for RCTs [11]; a checklist developed by Fowkes and Fulton [12], for nonrandomized studies; a checklist for the reporting of diagnostic accuracy, the Standards for Reporting of Diagnostic Accuracy [13]; and the AMSTAR checklist for systematic reviews [14]. Meta-analyses were not conducted due to considerable heterogeneity in the measurements of study outcomes.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used for the development of recommendations [15,16]. The level of evidence was graded as strong, moderate, weak, or very weak [17], based on GRADE criteria listed in Table 1[18]. The strength of the ensuing recommendation was graded as either strong or weak, based predominantly on the level of the evidence [19]. Evidence was downgraded, according to the GRADE criteria, if there was inconsistency, small benefit, absence of high-quality evidence, and imprecise estimates of benefits or harms. A strong recommendation was made based on the GRADE criteria if the panel was "confident that the desirable effects of adherence to a recommendation balanced any undesirable effects of the intervention" [16]. A weak recommendation was made if the panel concluded that the "desirable effects of adherence to a recommendation likely outweighed any undesirable effects," but the panel was uncertain about these "trade-offs" [16]. Weak recommendations were also made to reflect differences in individual patient circumstances that would need to be taken into consideration. The term *should* was used to reflect strong recommendations, and *probably should* was used to reflect weak recommendations. Weak recommendations may not be applicable to all patients. Most of the studies were noncontrolled trials; thus, the estimates for net benefit and net harm could not be accurately depicted in the GRADE tables but were described following each recommendation.

Consensus-based methods were used as previously described [20]. A Web-based survey was sent to panel members to gauge agreement. All disagreements were resolved by consensus. Any recommendations that could not be resolved by consensus were subjected to a vote with majority decision leading to acceptance or deletion of the recommendation. Based upon this process, 2 recommendations were not included (ie, maintenance of higher hemoglobin concentrations in thrombocytopenic patients and the use of antifibrinolytic agents). We did not undertake a formal economic evaluation of our recommendations.

All members involved completed disclosure statements yearly. Members who had potential conflicts of interest were not excluded from voting. However, the recommendations were tabulated according to disclosure to assure that conflicts of interest did not influence recommendations. The guidelines were validated by 6 external reviewers, selected by the panel based on their expertise, who completed a standardized questionnaire rating the overall guideline and assessing their agreement with each recommendation. Comments by external reviewers were discussed by teleconference, and recommendations were revised based on consensus/majority by electronic survey.

Table 1
GRADE criteria

Level of evidence	Explanation
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very weak	Any estimate of effect is very uncertain.

Results

Literature Search

The search strategies are displayed in Appendix B. The systematic reviews used for this guideline are illustrated in Table 2. Three published systematic reviews were included [21-23], and 5 systematic reviews were conducted by the ICTMG. Two [24,25] of the 5 conducted systematic reviews are published as full articles. Two [21,23] of the 8 systematic reviews included mainly randomized controlled trials, whereas 4 had mostly nonrandomized studies, for example, ABO matching, HLA matching, and crossmatching for platelet transfusions [22,24,25] and use of Rh immunoglobulin.

A summary of all recommendations and an algorithm are demonstrated in Table 3 and Figure, respectively.

Question 1: Should Patients With Hypoproliferative Thrombocytopenia Receive Prophylactic Platelet Transfusions?

Recommendation 1

Prophylactic platelet transfusion should be given to patients with hypoproliferative thrombocytopenia (moderate level of evidence, strong recommendation for adults and weak level of evidence, strong recommendation for pediatric patients).

Summary of Evidence and Rationale for Recommendations

Platelet transfusions have been available since the 1960s, when routine use of platelet transfusions to support patients with chronic hypoproliferative thrombocytopenia began. Observational data suggested a relationship between bleeding and severity of thrombocytopenia (but without evidence of a marked threshold effect) [26] and a reduction in the number of days with both minor and major bleeding [27] and hemorrhage-associated mortality with transfusion [28]. Three small RCTs, from the 1970s, evaluating the benefits of prophylactic platelet transfusions vs no prophylaxis, comprising 87 patients, were identified in a review by the Cochrane collaboration [21]. In the study [21] reporting bleeding outcomes, there was a nonsignificant increase in the number of patients with a significant bleeding event and no difference in the number of days with bleeding. There were no differences in mortality.

Following the Cochrane Collaboration review (Appendix A, Supplementary Tables S1 and S2), 2 large RCTs [29,30] comparing prophylactic and no-prophylactic platelet transfusion in patients with hematologic malignancies receiving high-dose chemotherapy (induction for leukemia or conditioning for SCT) have been completed. Supplementary Tables S3 to S6 in Appendix A describe the quality and characteristics of these studies. The quality of the studies was classified as moderate because of the lack of blinding of attending physicians (Appendix A, Supplementary Table S6). In addition, the lack of standard criteria to

Table 2
Citations used for the systematic reviews

Guideline topics	Systematic reviews by first author, year	No. of citations included	
		Randomized controlled trials	Nonrandomized/observational studies
Platelet thresholds	Estcourt et al [21]	6	0
Platelet dose	Estcourt et al [21]	6	0
ABO-matched platelet transfusion	Shehata et al [22]	3	18[a]
Use of Rh immunoglobulin	–	0	7
Apheresis vs whole blood–derived platelets	Heddle et al [23]	13[b]	3[c]
HLA-selected platelet transfusion	Pavenski et al [24]	1	29
Crossmatching for platelet transfusion	Vassallo et al [25]	0	31
Red cell transfusion threshold	–	1	0
Use of antifibrinolytics	–	2	2

[a] Includes 2 studies published after 2009.
[b] Eight full articles, 2 abstracts, and 3 secondary publications in the systematic review.
[c] Studies published after 2008.

classify and record hemorrhage, which has been identified previously [31], is likely to contribute to variable bleeding rates.

Wandt et al [29] randomized 397 patients to receive prophylactic (for morning platelet counts $<10 \times 10^9$/L) or no-prophylactic platelet transfusions (given for World Health Organization [WHO] grade ≥ 2 bleeding unless at high risk for hemorrhage). A significant increase in the proportion of patients with WHO grade greater than or equal to 2 bleeding (42% vs 19%; $P < .0001$) and WHO grade 4 bleeding (5% vs 1%; $P = .0159$) in patients receiving no-prophylactic platelet transfusions was reported. In subgroup analysis, patients receiving induction chemotherapy had a significant increase in WHO grade 4 bleeding with 6 minor and 2 fatal intracerebral bleeds in the therapeutic arm and no intracerebral bleeding in the prophylactic arm [29]. However, there was no WHO grade 4 bleeding in patients undergoing autologous transplantation (autoSCT) nor significant differences in WHO grade 3 bleeding in either group. Stanworth et al [30] randomized 600 patients to prophylactic or no-prophylactic platelet transfusions. A higher rate of WHO grade 2 to 4 bleeding events (50% vs 43%) in patients randomized to no-prophylactic platelet transfusions was found. The adjusted difference in proportions was 8.4% (90% confidence interval [CI], 1.7%-15.2%; $P = .06$ for noninferiority). The post hoc superiority analysis demonstrated that the difference in grade 2 and higher bleeds was significant ($P = .04$) [30]. In a predetermined subgroup analysis of patients undergoing autoSCTs, there were similar rates of WHO grade 2 to 4 bleeding in the no-prophylaxis (47%) and prophylaxis groups (45%) [30].

As there were increased WHO grade 2 to 4 bleeding events in patients receiving predominantly no-prophylactic platelet transfusions, patients with hypoproliferative thrombocytopenia should receive prophylactic platelet transfusions. Although pediatric data are limited, clinical similarities in indications advocate for analogous recommendations. Separate recommendations for patients undergoing autoSCT or allogeneic SCT cannot be made because of the dissimilar bleeding rates of the 2 large randomized clinical trials.

Question 2: What Platelet Transfusion Threshold Should Be Used?

Recommendation 2

A threshold of less than or equal to 10×10^9/L should be used for prophylactic platelet transfusion for patients with hypoproliferative thrombocytopenia (moderate level of evidence, strong recommendation for adults and weak level of evidence, strong recommendation for pediatric patients).

Recommendation 3

Patients with hypoproliferative thrombocytopenia with clinically significant bleeding attributed to thrombocytopenia should probably

Table 3
Recommendations for platelet transfusion in patients with hypoproliferative thrombocytopenia

1. Prophylactic platelet transfusion should be given to patients with hypoproliferative thrombocytopenia (moderate level of evidence, strong recommendation for adults and weak level of evidence, strong recommendation for pediatric patients).
2. A threshold of $\leq 10 \times 10^9$/L should be used for prophylactic platelet transfusion for patients with hypoproliferative thrombocytopenia (moderate level of evidence, strong recommendation for adults and weak level of evidence, strong recommendation for pediatric patients).
3. Patients with hypoproliferative thrombocytopenia with clinically significant bleeding attributed to thrombocytopenia should probably receive platelet transfusions even if the platelet count is above 10×10^9/L (very weak level of evidence, weak recommendation).
4. Low- or standard-dose platelet transfusion (ie, $1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$, respectively), as opposed to high-dose platelet transfusion ($4.4 \times 10^{11}/m^2$), should be given to hospitalized patients with hypoproliferative thrombocytopenia who require prophylactic platelet transfusion (high level of evidence, strong recommendation).
5. Platelet concentrates that are ABO identical should probably be used in patients with hypoproliferative thrombocytopenia, if available (weak level of evidence, weak recommendation).
6. Female children and females of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD negative should probably receive Rh immunoglobulin before, immediately after, or within 72 hours of receiving an RhD-positive platelet component (unless antibody testing demonstrates the persistence of anti-D from a previous dose of Rh immunoglobulin) (very weak level of evidence, weak recommendation).
7. Males and females who are not of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD-negative and are transfused with RhD-positive platelet components probably do not require Rh immunoglobulin (very weak level of evidence, weak recommendation).
8. Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have class I HLA antibodies should probably receive class I HLA-selected or crossmatch-selected platelet transfusion to increase the platelet count (weak level of evidence, weak recommendation).
9. Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have HPA antibodies should probably receive HPA-selected or crossmatch-selected platelet transfusion to increase the platelet count (very weak level of evidence, weak recommendation).
10. Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions solely due to nonimmune factors should probably not receive HLA-selected or crossmatch-selected platelets (weak level of evidence, weak recommendation).
11. Patients with hypoproliferative thrombocytopenia who are not refractory to platelet transfusion should probably not receive HLA-selected, HPA-selected, or crossmatch-selected platelets (weak level of evidence, weak recommendation for HLA selection and crossmatch selection, very weak level of evidence and weak recommendation for HPA selection).
12. When leukoreduced platelet products are available, WBD platelets (from buffy coat or PRP methods) should be used as equivalent products to apheresis platelets (moderate level of evidence, strong recommendation).

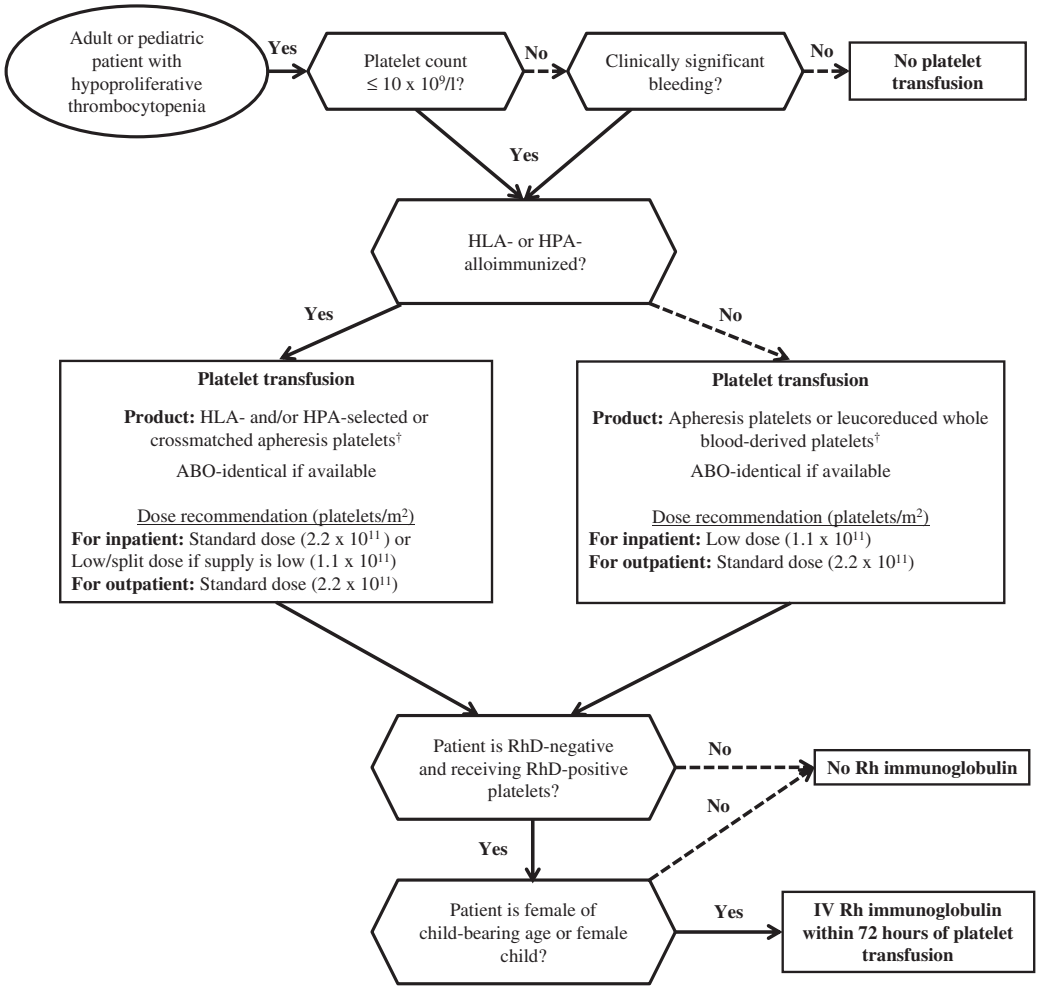

Figure. Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia. †Use apheresis platelets instead of whole blood–derived platelets if leukoreduced whole blood–derived platelet products are not available.

receive platelet transfusions even if the platelet count is above 10×10^9/L (very weak level of evidence, weak recommendation).

Summary of Evidence and Rationale for Recommendations

Three RCTs of prophylactic platelet transfusion thresholds [32-34] were identified in a systematic review, 2 comparing thresholds less than 10×10^9/L to less than 20×10^9/L [32,33] and 1 comparing less than 10×10^9/L to less than 30×10^9/L [34]. A difference in the number of patients with major bleeding events when using a prophylactic platelet transfusion trigger of less than 10×10^9/L compared to a higher threshold was not demonstrated (risk ratio [RR], 1.35; 95% CI, 0.95-1.90) [21]. There was a significant difference in the number of days with major bleeding (RR, 1.72; 95% CI, 1.33-2.22), but data were only available from 2 of the 3 RCTs. The clinical significance of an increase in the number of days with bleeding risk is not known. A reduction in the number of platelet transfusions was consistent among the studies (mean difference, −2.09; 95% CI, −3.20 to −0.99) [21].

Because of the lack of difference in major bleeding risk and reduction in the number of platelets transfused, decreasing adverse reactions and costs, a prophylactic platelet transfusion threshold of less than 10×10^9/L, as opposed to a higher threshold, was considered acceptable. Thresholds of less than 5×10^9/L [35,36] have been reported but were not rigorously assessed. Thresholds less than 20×10^9/L with clinically evident bleeding [30] have also been reported without a significant increase in hemorrhagic complications. In addition, Wandt et al [29] did not describe additional adverse events with fever, and the presence of fever did not change their platelet threshold. Thus, there was insufficient evidence to alter the platelet transfusion threshold in the setting of fever, infection, or administration of therapeutic agents. Individual patient requirements need to be evaluated for other factors, including the etiology of bleeding, which may make transfusion at higher levels appropriate under specific clinical circumstances (eg, before invasive procedures, intracranial hemorrhage, or acute promyelocytic leukemia), but may not be appropriate for less significant bleeding (eg, bruising or epistaxis). The upper platelet threshold for which a transfusion may be considered unnecessary in patients with hemorrhage has not been determined. Higher platelet thresholds may also be necessary for outpatients if distance precludes frequent clinic visits.

Question 3: What Platelet Dose Should Be Used?

Recommendation 4

Low- or standard-dose platelet transfusion (ie, $1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$, respectively), as opposed to high-dose platelet transfusion ($4.4 \times 10^{11}/m^2$), should be given to hospitalized patients with hypoproliferative thrombocytopenia who require prophylactic platelet transfusion (high level of evidence, strong recommendation).

(Conversion to platelet units can be performed using estimates of 50×10^9 per unit of WBD random-donor platelet products or 300×10^9 per unit apheresis or buffy coat pooled products.)

Summary of Evidence and Rationale for Recommendation

Historically, the dose for prophylactic platelet transfusions has varied between 4 and 10 units of WBD platelet units [37]. Over the past 10 years, 5 RCTs have examined the effect on bleeding outcomes of different platelet doses for prophylactic platelet transfusions in patients with hypoproliferative thrombocytopenia [21]. The largest study (PLADO) enrolled 1351 adult and pediatric inpatients with hypoproliferative thrombocytopenia to receive low-dose ($1.1 \times 10^{11}/m^2$), standard-dose ($2.2 \times 10^{11}/m^2$), or high-dose ($4.4 \times 10^{11}/m^2$) platelet transfusions [38]. Two studies compared low-dose (3 WBD platelet units or $150\text{-}299 \times 10^9$ per product) and standard-dose (5 WBD platelet units or $300\text{-}600 \times 10^9$ per product) platelet transfusions [39,40], and another compared standard-dose (0.5×10^{11}/10 kg) and high-dose (1×10^{11}/10 kg) platelet transfusions [41]. A meta-analysis reported no difference in clinically significant bleeding in the 3 trials comparing low- and standard-dose platelet transfusions (RR, 1.04; 95% CI, 0.95-1.13) [21]. Similarly, there were no differences in clinically significant bleeding in the 2 studies (Appendix A, Supplementary Table S2) comparing high and standard dose (RR, 1.02; 95% CI, 0.93-1.11) [21]. Although limited, there are data for dosing recommendations in pediatric patients in the PLADO trial, wherein no difference in the likelihood of hemorrhage at low, medium, or high doses was demonstrated [38,42].

Although high-dose strategies for platelet transfusion will not have significant adverse effects with respect to bleeding, there are increased donor exposure risks, particularly when transfusing WBD units, and increased costs. A cost analysis based on the dosing strategies used in the PLADO trial at 1 center estimated that the total apheresis platelet and transfusion administration costs for the average SCT patient would be US $4504 for low doses, US $5658 for medium doses, and US $7015 for high doses [43].

Given the decreased transfusion intervals seen with low-dose platelet transfusions, a low-dose strategy may not be appropriate for outpatients, as it may increase the frequency of clinic visits.

Question 4: Should Patients Receive ABO-Matched Platelets?

Recommendation 5

Platelet concentrates that are ABO identical should probably be used in patients with hypoproliferative thrombocytopenia, if available (weak level of evidence, weak recommendation).

Summary of Evidence and Rationale for Recommendation

Platelets express ABH antigens, often at very high levels [44-46]. Naturally occurring A or B antibodies in the recipient may lead to destruction of A or B major-mismatched platelets, respectively (donor platelets are incompatible with the recipient's plasma, eg, an A or B donor into an O recipient) [46]. Transfusion of major-mismatched platelets usually results in lower platelet increments. Furthermore, transfusion of anti-A or anti-B in the plasma of ABO minor-mismatched platelets (donor plasma is incompatible with recipient's platelets) can lead to a hemolytic transfusion reaction particularly when group O platelets are administered to an A or B recipient [46-48]. The selection of ABO-identical platelet transfusion for all patients may not be feasible because of limited inventories.

Twenty-one clinical trials, 19 of which were part of a systematic review published in 2009 [22], have addressed the effectiveness of ABO-matched platelet transfusion. The 2 additional trials were identified during an updated search [49,50]. Overall, 3 randomized controlled trials, 5 prospective observational studies, 11 retrospective observational studies, and 1 secondary analysis of a randomized controlled trial were included (Appendix A, Supplementary Tables S7-S11). Most trials were small and were of low to very low quality (Appendix A, Supplementary Table S11).

Of the 3 trials that assessed mortality outcomes, 2 did not show a difference, and the third demonstrated improved survival by 12 months ($P = .02$) on post hoc analysis in a subgroup with acute leukaemia receiving ABO-identical platelet units [51]. Bleeding outcomes were reported in 3 studies, with the largest (740 patients) [50] showing no difference in time to WHO grade greater than or equal to 2 bleeding comparing recipients of ABO-identical transfusions to recipients of ABO minor- or major-mismatched transfusions, that is, hazard ratios of 0.85 (95% CI, 0.52-1.40) and 0.78 (95% CI, 0.56-1.09), respectively. Transfusion reactions were reported inconsistently in the assessed trials; those that did not show a difference were underpowered to detect infrequent events such as hemolysis.

Platelet refractoriness was reduced with ABO-identical units, but the importance of this difference was hindered by variability in platelet refractoriness definitions among the studies reporting this outcome. One showed a reduction in refractoriness of 39% ($P < .03$) [52] and the other, 61% ($P < .001$) [53] when comparing ABO-identical vs nonidentical or incompatible transfusions.

Platelet count increments after transfusion were the most frequently reported outcome in 18 of the 21 trials. ABO-identical platelet transfusions were shown to produce significant increases in posttransfusion platelet increments compared to major-mismatched units. The largest study of 740 patients demonstrated that major ABO-mismatched platelet transfusions were associated with smaller increments at both 4 hours and 24 hours posttransfusion (platelet decreases of 2.25×10^9/L [$P = .0001$] and 2.64×10^9/L [$P < .0001$], respectively) compared with ABO-identical platelet transfusions [50]. However, the significance of the platelet increment in predicting important clinical outcomes such as hemorrhage and death is unclear.

The recommendation places a relatively high value on the avoidance of hemolytic transfusion reactions (which have been known to occur with ABO-mismatched transfusions) and the development of refractoriness. The assignment of a weak recommendation reflects the insufficient data correlating platelet refractoriness and the platelet increment with hemorrhage and mortality and acknowledging that ABO-matched platelet transfusion may not always be an option because of limited platelet inventories.

Question 5: Do Patients Who Are Negative for the RhD Antigen Require Rh Immunoglobulin if They Receive RhD-Positive Platelets?

Recommendation 6

Female children and females of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD negative should probably receive Rh immunoglobulin before, immediately after, or within 72 hours of receiving an RhD-positive platelet component (unless antibody testing demonstrates the persistence of anti-D from a previous dose of Rh immunoglobulin) (very weak level of evidence, weak recommendation).

Recommendation 7

Males and females who are not of child-bearing age/potential, with hypoproliferative thrombocytopenia, who are RhD negative and are transfused with RhD-positive platelet components probably do not require Rh immunoglobulin (very weak level of evidence, weak recommendation).

Summary Evidence and Rationale for Recommendations

Platelets do not express RhD antigens, but platelet concentrates do contain some "contaminating" red blood cells (RBCs). Small quantities of RhD-positive RBCs can lead to anti-D alloimmunization [54]. In 1 study, a single injection of 0.5 mL of RhD-positive (R2R2) RBCs given to healthy RhD-negative male volunteers resulted in the

formation of anti-D in 83% (5/6) of subjects. Other studies have shown similar results [55-57].

Published data indicate that the number of RBCs in apheresis platelets has declined from levels as high as 3.0 mL per unit in the early 1980s to levels that may now, in some institutions, be less than 0.0002 mL per unit. Platelet-rich plasma (PRP) WBD platelet methods have been reported to result in approximately 0.4 to 0.6 mL of RBCs per unit. Using current technology, it is, therefore, likely that the RBC contamination of apheresis platelets is less than that found in PRP WBD platelets [58,59] and apheresis platelets may not cause a sensitization risk. However, there is not extensive published information concerning RBC contamination using any platelet preparation method, and current regulations/standards do not specify a maximum acceptable RBC content for platelet components.

The literature addressing anti-D alloimmunization in RhD-negative patients with hypoproliferative thrombocytopenia who receive RhD-positive platelets components is also limited. Our systematic search identified only 7 nonrandomized studies—1 prospective [60] and 6 retrospective [61-66] published between 1971 and 2009—with a total of only 270 recipients (Appendix A, Supplementary Tables S12-S14). Adult and pediatric patients were included, and no patient received anti-D prophylaxis. A variety of platelet component types were administered, but RBC contamination rates were not uniformly reported, nor was there complete information concerning ABO compatibility or leukoreduction. In 5 studies, anti-D alloimmunization was not detected in 266 patients. In 2 studies, alloimmunization did occur: in 1971, 8 of 102 RhD-negative recipients receiving RhD-positive platelets developed anti-D [66], and in 1990, alloimmunization occurred in 3 of 16 RhD-negative recipients [64]. Overall, the quality of the studies was graded as very low (Appendix A, Supplementary Table S14). A more recently published ADAPT paper by Cid et al [67] indicates that only 1.44% of 485 D− recipients developed an anti-D after transfusion of D+ platelets with no difference in the type of product (apheresis vs whole blood derived) in the 7 patients who developed an anti-D.

The decision to administer Rh immunoglobulin to prevent RhD alloimmunization from platelet transfusion should consider the risks and benefits of this therapy, including whether the patient received prior RhD-positive red cell transfusion and the potential clinical impact of future alloimmunization. With respect to potential risks, nonspecific intravenous immunoglobulins have been associated with thrombotic events, particularly when given in high doses and/or to patients with risk factors for thromboembolic disease [68,69]. However, thrombosis related to the use of anti-D immunoglobulin for prevention of RhD alloimmunization has not been reported. Rh immune globulins have been associated with hemolytic reactions at doses used for treatment for immune thrombocytopenia in RhD-positive patients, but these reactions have not been reported at the doses used for prevention of RhD alloimmunization in RhD-negative patients.

The decision as to whether to administer an Rh immunoglobulin preparation in this setting should also take into consideration the products available. Some products are manufactured in such a way that they can be safely administered (and are licensed for use) by either the intravenous or intramuscular route. Other preparations (notably Rhogam) must not be given by the intravenous route to avoid rare complications such as hypersensitivity and influenza-like reactions [70]. Intramuscular injection could result in a hematoma formation in a severely thrombocytopenic patient (although in this case, the Rh immunoglobulin could be given immediately after the platelet transfusion). There have been reports of successfully using intramuscular preparations by the subcutaneous route [71]. However, this route is not licensed.

In summary, the evidence for or against administering Rh immunoglobulin to patients who receive Rh positive (or Rh type unknown) platelets is inadequate to make a strong or definitive recommendation. The risks vs the benefits of administering Rh immunoglobulin in this situation should, therefore, be determined locally taking into consideration the topics addressed above. Further clinical research on this topic is encouraged.

Should Rh immunoglobulin be given, a 300-μg dose will eliminate 15 mL of red cells—hence, 1 dose may cover multiple platelet exposures. Rh immunoglobulin preparations typically have a half-life of 21 days, but the duration of passive protection will be impacted by the burden of RhD-positive cells present in the circulation.

Question 6: Should Patients Receive HLA/HPA-Selected or Crossmatch-Selected Platelets?

Recommendation 8

Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have class I HLA antibodies should probably receive class I HLA-selected or crossmatch-selected platelet transfusion to increase the platelet count (weak level of evidence, weak recommendation).

Recommendation 9

Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions and have HPA antibodies should probably receive HPA-selected or crossmatch-selected platelet transfusion to increase the platelet count (very weak level of evidence, weak recommendation).

Recommendation 10

Patients with hypoproliferative thrombocytopenia who are refractory to platelet transfusions solely due to nonimmune factors should probably not receive HLA-selected or crossmatch-selected platelets (weak level of evidence, weak recommendation).

Recommendation 11

Patients with hypoproliferative thrombocytopenia who are not refractory to platelet transfusion should probably not receive HLA-selected, HPA-selected, or crossmatch-selected platelets (weak level of evidence, weak recommendation for HLA selection and crossmatch selection, very weak level of evidence and weak recommendation for HPA selection).

Summary Evidence and Rationale for Recommendations

Platelet alloimmune refractoriness refers to persistent suboptimal platelet count increments after a platelet transfusion and results from exposure to contaminating white blood cells in platelet products (class I HLA antigens) or less commonly, to platelet specific antigens [72]. Alloimmunization accounted for only approximately 20% of cases of refractoriness [73], and leukoreduction of blood products has led to significantly decreased rates of alloimmunization and refractoriness [74,75]. Nonetheless, platelet refractoriness has been linked to inferior clinical outcomes, including bleeding and mortality [76,77] as well as higher health care costs [78]. HLA-selected or crossmatch-selected platelets are widely used to transfuse patients who are refractory to reduce the risk of hemorrhage and mortality rates, but their effectiveness on these rates has not been well defined.

There are a number of methods used to select HLA-matched platelet products for refractory patients. Commonly, recipient and donor are matched for HLA-A and HLA-B antigens, as the most commonly involved antibodies are directed against these antigens [79]. The grading of the quality of HLA matches is as follows: A (donor and recipient match at 4 of 4 antigens), B (all donor antigens are present in the recipient phenotype but the donor lacks 1 [B-1] or 2 [B-2] of the recipient antigens), and C (donor possesses ≥1 antigens not found in the recipient) [80]. The grading criteria were revised [81] to include "permissive" mismatches. HLA-A and HLA-B antigens can be organized into cross-reactive groups (CREGs) based on which public epitopes they share. Most HLA antibodies have been shown to be directed against public epitopes [82] so that precise HLA matching was not necessary. Platelets with 1 or 2 mismatches could be used as long as these antigens fell within the same CREG [83]. Because HLA epitopes can now be defined structurally,

the use of computer algorithms that determine donor-recipient compatibility at the epitope level takes advantage of allelic level typing and better predicts the specificities of HLA antibodies than CREG matching. The primary goal of serum analysis is to directly determine those antibody specificities. The combination of epitope-based HLA matching and the determination of HLA class I antibody reactivity may permit the identification and selection of the most suitable platelet donors for refractory patients.

Most reports on the use of HLA-selected platelet transfusions were nonrandomized, single-center studies conducted in adult hematology/oncology patients developing refractoriness to WBD platelets, and all have been graded as weak level of evidence (Appendix A, Supplementary Tables S15 and S16). One RCT and 29 nonrandomized studies of 1600 patients comprised the systematic review [24]. Most studies did not include technologies currently in use for HLA typing or detection of HLA class I antibodies implicated, as 75% were conducted before the year 2000. HLA-selected platelets led to improved transfusion outcomes 1 hour after transfusion; however, the results at 18 to 24 hours were variable. Platelet increments were better in patients with evidence of alloimmune refractoriness and those receiving more closely HLA-matched or antigen-negative products. The effect of HLA selection appeared less evident in studies that used leukoreduced products compared to studies involving nonleukoreduced platelets (Appendix A, Supplementary Tables S15 and S16). There was no benefit of using HLA selection to reduce alloimmunization rates and refractoriness beyond the use of leukoreduced platelets in nonrefractory patients [24].

Methods for HLA selection varied and included functionally identical HLA matching, providing antigen-negative units; CREG matching; and use of the computer algorithm, HLAMatchmaker. In the context of this document, HLA crossmatched platelets are platelets that have had in vitro crossmatching performed vs platelets that are selected to be antigen negative for any patient HLA antibodies. There were 5 studies [24] that compared some of these methods. However, no definite inferences can be made as to the superiority of one method compared to the others.

Crossmatching techniques were developed to circumvent the need for large panels of HLA-typed donors. Although not dramatically impacting transfusion failure rates, crossmatching greatly improved the availability of platelets. Crossmatching is a popular support option for patients with hypoproliferative thrombocytopenia in hospitals without access to large panels of HLA-typed apheresis donors. Commercial and locally developed crossmatch assays have been used to identify alloimmunization in transfusion-refractory individuals as well as to choose potentially compatible units. Many techniques have been studied in a variety of settings, from highly selected transfusion refractory patients with few or none of the clinical conditions known to reduce transfusion responses, to randomly selected patients. In these studies, refractoriness has been variably defined, and posttransfusion counts have not been consistently reported both at 10 to 120 minutes and at 16 to 24 hours.

The systematic review for crossmatching platelets yielded 31 articles describing 29 patient cohorts graded as very weak level of evidence (Appendix A, Supplementary Table S17) [25]. All but 5 of the studies included in the systematic review enrolled transfusion-refractory, predominantly alloimmunized patients. Similar to the data available for HLA-selected platelets, there were limited data on mortality or hemorrhage, as no study was designed to evaluate these clinical outcomes, and there were no RCTs [84,85]. The degree of HLA alloimmunization appeared relatively stable throughout crossmatch support for the majority of patients, that is, the concern that broadening of HLA alloimmunization would result from crossmatched platelets was not substantiated. No studies examined the persistence of transfusion refractoriness throughout crossmatch support. Sixty to ninety-five percent of patients known to be alloimmunized and refractory to transfusion (including specifically identified cohorts without clinical conditions associated with poor platelet recovery and survival) may expect "successful" transfusion outcomes [25].

In nonrefractory, nonalloimmunized individuals, the frequency of very low increments and low test sensitivity (ie, the ability of crossmatching to identify units with poor increments, 0%-18%) demonstrated the lack of utility of crossmatching in this patient population [86,87]. In refractory, predominantly alloimmunized patients, crossmatched platelets yielded improved increments compared to crossmatch-incompatible or randomly selected platelets. Crossmatching appeared to be inferior to HLA-identical units, but because HLA-identical platelets often cannot be found, crossmatching represents an alternative for patients who are not broadly alloimmunized against most other HLA antigens or against high-frequency HPA antigens. No trend was observed regarding relative utility of the various commonly used crossmatch techniques, but platelet crossmatching assays based on detection of platelet bound recipient immunoglobulin appear superior to lymphocyte crossmatching and even older techniques. Identifying platelet compatibility using more than 1 technique may better predict successful platelet increments but is generally impractical.

Patients who continue to be refractory to HLA-selected or crossmatched platelets may have unrecognized immunological causes (HPA alloimmunization, expanding HLA alloimmunization, autoimmune or drug-related antibodies). In these situations, HPA alloimmunization should be considered, and if contributory, HPA-selected products may improve platelet increments.

Nonimmune conditions such as consumptive coagulopathy, sepsis, and splenomegaly are the most common causes of refractoriness and should be considered as etiologies for ongoing refractoriness with failure to respond to HLA/HPA-selected platelets. HLA/HPA-selected or crossmatched platelets are not effective for patients with predominantly nonimmune refractoriness. The use of these methods as part of a strategy to prevent alloimmunization may consume resources, increase costs, result in delays in the acquisition of platelets, and limit product availability for patients who actually require them.

Before designating a patient with hypoproliferative thrombocytopenia as refractory to platelet transfusions, evaluation of 10-minute to 1-hour posttransfusion increments is required as immune platelet destruction appears to have the greatest effect on 10 to 120 minutes posttransfusion platelet recovery [88]. Most nonimmune conditions have smaller effects initially but accelerate platelet consumption, resulting in poor 16- to 24-hour counts. In addition, the platelet increments should be determined with ABO-identical platelet products first before testing for class I HLA and HPA alloantibodies. Although there are many definitions in the literature, alloimmune refractoriness in the context of the above statement is defined as a 10-minute to 1-hour platelet increment less than 5×10^9/L on 2 consecutive transfusions in the absence of predominantly nonimmunologic factors known to cause refractoriness.

Question 7: Should Patients Receive Apheresis-Derived Platelets Instead of Whole Blood–Derived Platelets?

Recommendation 12

When leukoreduced platelet products are available, WBD platelets (from buffy coat or PRP methods) should be used as equivalent products to apheresis platelets (moderate level of evidence, strong recommendation).

Summary Evidence and Rationale for Recommendations

Platelets may be prepared from apheresis collections or from whole blood donations by the PRP method or the buffy coat method. There is significant variability in opinions regarding the optimal platelet product. However, in our consideration of the optimal platelet product, the effectiveness of the platelet product in reducing the risk of bleeding and the effect on the rate of transfusion reactions were the main considerations. Although the reduction in donor exposure is also theoretically beneficial, limited data are available to support the definitive benefit of reducing donor exposure in acute transfusion reactions or bacterial

transmission [89,90]. A previous systematic review [23] that evaluated 10 RCTs was updated by reviewing an additional 3 citations published after 2008 to address the effect of the type of platelet product on these outcomes (Appendix A, Supplementary Tables S18-S22). The quality of the evidence was graded as weak to very weak (Appendix A, Supplementary Table S22).

Three nonrandomized studies [50,91,92] were also included. The hazard ratio for WHO grade greater than or equal to 2 bleeding was 1.15 (95% CI, 0.81-1.65) in 1 nonrandomized study for apheresis compared to PRP WBD platelets [50]. Transfusion reactions were reported inconsistent in the assessed trials and those that reported reactions used different definitions and timing of capture for transfusion reaction interpretation as well as products that varied with respect to leukoreduction. Nonleukoreduced PRP WBD products have higher rates of transfusion reactions than apheresis platelet products, which are, in process, leukoreduced (odds ratio, 1.87; 95% CI, 1.1-3.1), but this increased reaction risk was negated when all products were leukoreduced [23]. Platelet refractoriness was variably defined. Although analyzed studies demonstrated an increase in refractoriness and alloimmunization with nonapheresis products, the products being compared varied in prestorage leukoreduction status. In the TRAP trial [74], there was no difference in alloimmunization rates when leukoreduced PRP WBD platelets were compared to leukoreduced apheresis platelets. In a study by Heddle et al [93], the source of platelet product (leukoreduced apheresis, prestorage leukoreduced PRP WBD, and plasma-removed platelets) favored the apheresis product with 53% achieving an 18- to 24-hour corrected count increment of greater than or equal to $4.5 \times 10^9/L/m^2/10^{11}$ platelets compared to 35% with prestorage leukoreduced WBD platelets and 38% with pretransfusion plasma removal platelets ($P = .00005$). Five additional studies compared platelet count increments from WBD and apheresis products [52,74,94-96], but the outcomes were variable, with only 2 demonstrating a statistically significant difference [52,92]. A correlation between the platelet increment and clinical outcomes has not been shown.

Summary

We convened an international panel of experts in platelet transfusion to develop a comprehensive guideline for patients with hypoproliferative thrombocytopenia who are at risk for hemorrhage and in whom platelet transfusion support needs to be optimized. Although a patient representative was not included in the panel, the potential that minor bleeding (eg, mucosal bleeding) could also potentially affect patient's quality of life was considered in generation of the recommendations [97]. This document incorporated new randomized controlled data, for example, in the area of prophylactic vs therapeutic-only platelet transfusions. The guideline will form a framework for new evidence and will be scheduled for review every 3 years to ensure that the recommendations remain current.

Because the benefits of leukoreduction have already been well described [75], we did not develop recommendations for leukoreduction. As such, our recommendations and the benefits of ABO, HLA, and crossmatched platelets need to be assessed in the context of leukoreduction.

We recommend that a prophylactic platelet transfusion with a threshold of less than $10 \times 10^9/L$ remain the standard of care. The provision of platelet support for the alloimmunized refractory patients with ABO-matched and HLA-selected or crossmatched products is of some benefit. However, patients continue to experience hemorrhage despite prophylactic transfusion, and new research should evaluate alternative strategies to decrease this bleeding risk, such as the utility maintaining a higher hemoglobin concentration to reduce the risk of bleeding or the use of antifibrinolytic agents. In addition, the need for Rh immune globulin to prevent RhD alloimmunization after platelet transfusion particularly after WBD platelet transfusion needs to be further assessed. These topics will be addressed in updated versions of this guideline when adequate data are available to support recommendations.

Whether patients undergoing autologous transplantation and patients requiring platelet support in ambulatory clinics should be transfused similarly (eg, prophylactically and with the same dose of platelets) cannot be determined based on recent trials. Future trials focusing on these patient populations are needed to balance the reduction in the risk of hemorrhage with the frequency of ambulatory visits. Standardized methods of measurement and recording of bleeding [31] are also needed as well as the inclusion of the assessment of quality of life when evaluating the impact of thrombocytopenia [97].

Although we did not undertake a formal economic evaluation, the absence of cost-effectiveness analyses should not be interpreted as the lack of the need for such evaluations. Platelet transfusion is costly, and economic evaluations are encouraged in future studies of different platelet products, such as a comparison of methods for HLA selection of platelets and the cost-effectiveness of high-, standard-, and low-dose platelet transfusions, as a low-dose strategy appears to increase the total number of transfusion episodes.

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Conflict of Interest

Heather Hume, Catherine Moltzan, Chee-Loong Saw, Brian Berry, Arjuna Ponnampalam, and Rene Duquesnoy have no financial or intellectual conflicts of interest to declare; Alan Tinmouth: financial disclosures, paid consultancy with Canadian Blood Services and honoraria from Amgen and GlaxoSmithKline; intellectual disclosures, funding from Canadian Institute for Health Research funding, guideline panel member for the American Association of Blood Banks, member of the National Advisory Committee for Blood and Blood Products; Katerina Pavenski and Susan Nahirniak: intellectual disclosures, members of Canada's National Advisory Committee for Blood and Blood Products; Simon Stanworth: intellectual, BCSH guideline working group member on selected topics; Susano Tanael is an employee of Canadian Blood Services; Ralph Vassallo: no financial disclosures; intellectual disclosure, research funding from Fenwal, Inc; Paolo Rebulla: scientific advisory board of Macopharma, research funding from Cerus and Terumo/BCT; Mark Fung: consulting services to Novartis, panel member for the

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Appendix A. Supplementary data

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