CME Article

Platelet transfusions for critically ill patients with thrombocytopenia

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Disclosures

Nancy Berliner, Editor, has received grants for clinical research from GlaxoSmithKline. The authors and CME questions author Laurie Barclay, freelance writer and reviewer, Medscape, LLC, declare no competing financial interests.

Learning objectives

1. Describe recommendations for or against the use of platelet transfusions in critically ill adults with thrombocytopenia, and the underlying evidence, based on a review.
2. Identify recommendations for or against the use of platelet transfusions in critically ill neonates with thrombocytopenia, and the underlying evidence.
3. List recommendations for or against the use of platelet transfusions in critically ill children with thrombocytopenia, and the underlying evidence.

Release date: February 20, 2014; Expiration date: February 20, 2015

Case presentation

Case 1. A 48-year-old male is admitted to the intensive care unit with worsening multiorgan system failure attributable to bacteremia from an abdominal wound. His platelet count was 160 × 10^9/L 5 days ago, and today his platelet count is 33 × 10^9/L. He has mild anemia (hemoglobin 115 g/L), normal prothrombin time (34 seconds), international normalized ratio (1.1), and fibrinogen (2.0 g/L). There are no overt signs of bleeding. You contemplate whether to administer a platelet transfusion.

Case 2. A 12-day-old female infant born at 29 weeks gestational age becomes irritable, stops tolerating enteral feeds, has increased apnea, and requires reventilation. Abdominal X-ray and head ultrasound are normal. Broad-spectrum antibiotics are started. A blood culture grows gram-negative bacilli within 24 hours of culture. Her platelet count has dropped to 33 × 10^9/L. You contemplate whether to administer a platelet transfusion.

Introduction

Thrombocytopenia is common among critically ill patients. In a recent systematic review, thrombocytopenia (defined as a platelet count below 150 × 10^9/L) was present in 8.3% to 67.6% of adult patients on admission to the intensive care unit (ICU) and acquired by 13% to 44% of patients during their ICU stay.[1] Thrombocytopenia in ICU patients is an independent predictor of mortality in adults[1]; is associated with bleeding[2]; and often deters practitioners from performing invasive procedures, which are frequently required in this setting. Thrombocytopenia also complicates critical illness in younger age groups: 20% to 50% of critically ill neonates develop thrombocytopenia,

Submitted February 21, 2013; accepted December 4, 2013. Prepublished online as *Blood* First Edition paper, December 12, 2013; DOI 10.1182/blood-2013-02-435693.

The online version of this article contains a data supplement.

Table 1. The impact of platelet transfusions on platelet-count increment in critically ill patients with thrombocytopenia

Reference	N	Population	Study design	Results	Study quality*
Adults					
4	1923	Medical ICU	Prospective cohort	Median increase was 15 $\times$ 10^9/L (IQR, 2-35 $\times$ 10^9/L)	Low
12	350	Dengue fever	Prospective cohort	Median PLT count yield† was 12.4% higher than baseline after transfusion (range, −3.9%-67.1%)	Low
9	216	Medical/surgical ICU	Retrospective cohort	Median increase after single PLT transfusion was 14 $\times$ 10^9/L (IQR, −2-30 $\times$ 10^9/L)	Moderate
11	147	Surgical ICU	Prospective cohort	PLT count rose above 40-50 $\times$ 10^9/L (but never >100 $\times$ 10^9/L) after transfusion	Low
10	72	Surgical ICU	Case-control study	Platelet transfusion led to sustained correction of thrombocytopenia in 8/16 patients; the remainder had only transient improvement	Low
Neonates					
15	422	Preterm neonates	Retrospective cohort study	Platelet transfusion resulted in good, but less sustained, rise in platelet count for neonates with severe thrombocytopenia (data not shown)	Low
14	194	Neonates	Prospective cohort	Fifty-nine percent of transfusions increased counts >40 $\times$ 10^9/L; 8% of transfusions increased counts <20 $\times$ 10^9/L; median platelet count increase from 27 $\times$ 10^9/L (IQR, 19-36 $\times$ 10^9/L) to 79 $\times$ 10^9/L (IQR, 47-126 $\times$ 10^9/L)	Moderate
8	152	Preterm neonates	RCT	Significant increase by 95 $\times$ 10^9/L in the intervention group (PLT transfusions for platelets <150 $\times$ 10^9/L)	Low

IQR, interquartile range; PLT, platelet.
*Study quality included applicability to the research question.
†PLT yield is the platelet count increase after transfusion corrected for body weight and platelet dose.

including 5% to 10% with platelet counts <50 $\times$ 10^9/L.[3] In contrast to patients with chemotherapy-induced thrombocytopenia, ICU-associated thrombocytopenia is multifactorial and develops as a result of infection, inflammation, and coagulation factor consumption. Platelet turnover is often increased in critical illness, which may pose less of a hemostatic risk than patients with bone marrow failure; conversely, complex comorbidities may add to the overall risk of bleeding. The principal treatment of ICU-associated thrombocytopenia is to treat the underlying cause.

Platelet transfusions are often used to treat thrombocytopenia in the ICU[4] despite the lack of high-quality published evidence suggesting benefit. Local clinical guidelines and recommendations for platelet transfusion thresholds for critically ill patients vary and are based largely on expert opinion. The benefits of platelet transfusions on clinical outcomes such as bleeding avoidance and survival are uncertain. The objectives of this focused review were to systematically review the literature on the effect of platelet transfusions on platelet count increment, bleeding, and mortality and to formulate recommendations for or against the use of platelet transfusions for nonbleeding critically ill neonates, children, and adults with severe (platelet count <50 $\times$ 10^9/L)[1] thrombocytopenia.

Methods

Our research team was composed of transfusion medicine specialists including 1 adult hematologist, 3 pediatric hematologists, and 2 methodologists. Investigators had experience in platelet transfusion studies and research in ICU-associated thrombocytopenia. We also elicited feedback from 3 adult, 1 pediatric, and 1 neonatal ICU physicians, all with experience in research methodology.

Search strategy and study selection

We searched Medline and Embase for relevant articles published until November 2012 using the keywords "critical illness," "thrombocytopenia," and "platelet transfusions" (supplemental Appendix A; see the *Blood* Web site). We manually searched reference lists of primary articles and relevant reviews and solicited additional articles from authors. Studies were eligible if the study population was critically ill patients of any age who had thrombocytopenia and received platelet transfusions and if at least one of the following was reported as a study outcome: platelet count increment, bleeding, or mortality. We included all experimental and observational study designs. We excluded studies of specific thrombocytopenic syndromes such as drug-induced immune thrombocytopenia, primary immune thrombocytopenia, or neonatal alloimmune thrombocytopenia; cardiac ICU studies only; studies with fewer than 10 patients; review articles; redundant publications; abstract-only publications; and non-English-language articles. One reviewer screened titles for relevance, and a second reviewer assessed abstract and full texts for eligibility. Six reviewers independently performed the data abstraction.

Quality assessments

The methodologic quality of individual studies was evaluated using criteria established for the reporting of randomized controlled trials (RCTs) and nonrandomized studies.[5,6] Each article was assessed independently by all 6 reviewers and then discussed as a team. During the discussion, we refined the quality assessment criteria to suit the topic by adding a criterion (adjustment of confounding) and providing explicit definitions of appropriateness of patient selection, outcome, exposure, and follow-up pertinent to platelet transfusion studies. For RCTs, the adequacy of randomization, allocation concealment, blinding, follow-up, outcome assessment, and analysis were assessed.[5] We added applicability to our assessment of overall study quality to gauge the extent to which the study addressed our research question. The methodologic quality of all studies was reexamined in pairs and determined by consensus (supplemental Appendix B).

GRADE recommendations

Our intent was to formulate recommendations for or against the use of platelet transfusions using Grading of Recommendations Assessment, Development, and Evaluation, which incorporates the quality of the evidence, benefits and risks, and resource utilization.[7] Grade 1 recommendations are considered strong; grade 2 recommendations are weak. A, B, and C denote high, moderate, or low quality of evidence, respectively. Once our systematic review was

Table 2. The impact of platelet transfusions on mortality in critically ill patients with thrombocytopenia

Reference	N	Population	Study design	Results	Study quality*
Adults					
12	350	Dengue fever	Prospective cohort	In patients with PLT counts $<50 \times 10^9$/L, 2 transfused patients died vs 1 nontransfused patient; deaths were not related to bleeding	Low
11	147	Surgical ICU	Prospective cohort	Transfusion was not associated with an increased risk of death in univariate analysis	Low
10	72	Surgical ICU	Case-control study	In patients with PLTs $<50 \times 10^9$/L, there was no difference in mortality between transfused and nontransfused patients (50% and 45%, respectively)	Low
Neonates					
26	1389	Neonates	Retrospective cohort	Thirty-three percent mortality in transfused group vs 3% mortality in the nontransfused group ($P = .0001$). OR for death ($P < .0001$): 10.4 with 1 PLT transfusion; 9.4 with 2-4 PLT transfusions; 29.9 with >4 transfusions.	Low
23	494	Neonates	Retrospective cohort	Risk of death increased with additional transfusions (OR = 1.14 per transfusion): 2% in nontransfused; 11% with 1-2 transfusions; 20% with 3-10 transfusions; 35% with >10 transfusions	Moderate
25	284	ELBW neonates	Retrospective cohort	Overall mortality was 23% in transfused neonates. Risk of death increased with additional transfusions: 9% in nontransfused; 20% for 1-5 transfusions; 29% for >5 transfusions.	Low
24	273	Neonates	Retrospective cohort	Unadjusted mortality increased with additional transfusions: 0% in nontransfused; 4% for 1 transfusion; 14% for 2-5 transfusions; 24% for 6-10 transfusions; 36% for 11-20 transfusions; 50% for >20 transfusions	Moderate
14	194	Neonates	Prospective cohort	Thirty-three percent mortality in 31 neonates (≥5 transfusions) vs 2% in 53 nontransfused patients	Moderate
27	182	Neonates	Prospective observational	Sixty-one (33.5%) of 182 thrombocytopenic neonates died, of whom 96.5% received PLTs. Bleeding was not the primary cause of death for any patient.	Low
16	164	Preterm neonates	Case control (94 cases, 70 controls)	Mortality was 48.3% in transfused neonates and 18.2% in nontransfused neonates	Low
8	152	Preterm neonates	RCT	Sixteen deaths (20.5%) in the intervention group (n = 78) vs 11 deaths (14.9%) in the control group (n = 74) (statistical test of significance not provided)	Low
18	61	Neonates	Retrospective cohort	Unadjusted mortality did not correlate with number of transfusions: 42.8% with 1 transfusion; 15.3% with 2-4 transfusions; 28.5% with >4 transfusions	Low
17	45	Neonates	Retrospective cohort	Mortality was 48.8% in patients given ≥20 PLT transfusions	Low
21	44	Preterm neonates	Retrospective review	Five deaths in the transfused group (n = 25) vs no deaths in the nontransfused group (n = 19) in neonates with PLTs $<50 \times 10^9$/L	Moderate
19	NR	Neonates	Prospective cohort	No difference in mortality in patients transfused based on count vs mass (0.9% vs 0.4%, respectively; $P = .10$); no deaths ascribed to bleeding	Low
Children					
28	138	Medical and surgical ICU	Prospective cohort	Transfusion was not a significant contributor to mortality in adjusted analysis. Unadjusted OR for death: 3.8 (95% CI, 1.25-11.5; $P = .01$) transfused vs nontransfused. "Transfusion" was not specified but assumed to be PLT transfusion.	Low

CI, confidence interval; ELBW, extremely low birth weight (<1000 g); NR, not reported; OR, odds ratio. Other abbreviations are explained in Table 1.
*Study quality included applicability to the research question.

complete, it became evident that there was insufficient evidence to develop recommendations for or against platelet transfusions in this setting. Our conclusions were reached by consensus.

Results

Our initial literature search yielded 1471 citations, of which 1361 were excluded after screening titles. An additional 47 articles were excluded after abstract review, and 45 were excluded after full text review. Three articles were added after reviewing reference lists and authors' suggestions. Finally, 21 studies in neonates (n = 15), adults (n = 5), and children (n = 1) were included. Only 5 studies directly addressed the research question; the other 16 were indirectly applicable and often considered platelet transfusions as an outcome, rather than the intervention. Our search identified only 1 RCT which was done in preterm neonates.[8]

Critically ill adults

Platelet count increment. Five observational studies addressed the effect of platelet transfusions on platelet-count increment in critically ill adults (Table 1).[4,9-12] In 2 studies, 1 platelet transfusion resulted in a median increase in the platelet count of 15×10^9/L, although results varied considerably across patients.[4,9] Sustained correction of thrombocytopenia to a platelet count above 100×10^9/L was rarely achieved with platelet transfusions.

Table 3. The impact of platelet transfusions on bleeding in critically ill neonates with thrombocytopenia

Reference	N	Population	Study design	Results	Study quality*
20	1283	VLBW neonates	Prospective observational	Institution with fewest PLT transfusions had least number of IVH cases. Infants with a greater incidence of IVH were more likely to have received PLT transfusions on days 1 and 3 (OR, 3.6; 95% CI, 1.5-8.3).	Low
14	194	Neonates	Prospective cohort	Major hemorrhage occurred in 40% of 31 transfused neonates (≥5 transfusions) vs 5% in 53 nontransfused neonates	Moderate
22	168	Neonates	Prospective observational	Twenty-one percent (95% CI, 8%-31%) reduction in minor bleeds during the 12 h period after PLT transfusion compared with 12 h before PLT transfusion	High
16	164	Preterm neonates	Case control (94 cases, 70 controls)	Overall 37/60 (61.7%) transfused neonates had IVH vs 7/22 (31.8%) nontransfused neonates (similar across gestational age groups)	Low
8	152	Preterm neonates	RCT	Major bleeding: 22/78 (28.2%) in the intervention group vs 19/74 (25.7%) in controls (PLT transfusions for platelets below 50×10^9/L); $P = .73$	Low
18	61	Neonates	Retrospective cohort	Bleeding incidence: 60% with 1 transfusion; 42.3% with 2-4 transfusions; 35.7% with >4 transfusions	Low
17	45	Neonates	Retrospective cohort	Nineteen percent bleeding incidence in patients who received ≥20 PLT transfusions	Low
21	44	Preterm neonates	Retrospective review	No patient (25 transfused, 19 nontransfused) developed new or extended IVH	Moderate
19	NR	Neonates	Prospective cohort	Transfusion protocol based on PLT mass (PLT count × mean PLT volume) was associated with fewer grade 3 and 4 IVHs compared with a PLT-count based transfusion protocol (1.8 vs 0.4%, $P = .01$)	Low

VLBW, very low birth weight. Other abbreviations are explained in Table 1.
*Study quality included applicability to the research question.

Bleeding. No study reported the impact of platelet transfusions on bleeding avoidance in critically ill adults.

Mortality. Three studies addressed the relationship between platelet transfusions and mortality (Table 2).[10-12] The use of platelet transfusions was not associated with improved survival; however, data were derived from observational studies of low methodological quality. Some studies[11,13] reported an association between platelet count recovery (by transfusion or otherwise) and survival.

Data synthesis. Only 1 observational study of moderate quality addressed the impact of platelet transfusions on platelet count increment in critically ill adults.[9] The other 4 studies indirectly addressed our research question.[4,10-12] There was insufficient evidence to suggest a clinical benefit of platelet transfusions for patients with severe thrombocytopenia, and posttransfusion platelet count increments were modest.

Recommendation: For critically ill adults with severe thrombocytopenia and no evidence of bleeding, there is insufficient evidence to make a recommendation for or against platelet transfusion.

Critically ill preterm neonates

Platelet count increment. Platelet counts increased by 50-95 × 10^9/L after a platelet transfusion in 3 studies (Table 1). Platelet doses and number of transfusions were not consistently reported.[8,14,15]

Bleeding. Nine studies reported the effect of platelet transfusions on bleeding in neonates (Table 3).[8,14,16-22] One study reported a 21% reduction (95% CI, 8% to 31%) in minor bleeds in the 12-hour period after platelet transfusion compared with the 12-hour period before transfusion.[22] One RCT in preterm infants of <1500 g birth weight who were randomized within 72 hours of birth reported no difference in the incidence or extension of intraventricular hemorrhage (IVH) using platelet transfusion thresholds of 50×10^9/L or 150×10^9/L.[8] Unadjusted analyses from 4 observational studies reported a higher incidence of bleeding events with additional platelet transfusions.[14,16,18,20]

Mortality. Twelve studies examined the association between platelet transfusions and mortality in neonates (Table 2). In unadjusted analyses, the risk of death was highest among neonates who received the most platelet transfusions.[8,14,16-19,21,23-27] In the only RCT, there was no difference in mortality with a platelet transfusion trigger of 50×10^9/L or 150×10^9/L.[8]

Data synthesis. Of the 15 studies in neonates, 4 were directly applicable to our research question; however, study quality was graded as low. The findings from 1 RCT showed no difference in IVH with a platelet transfusion threshold of 50×10^9/L or 150×10^9/L in preterm neonates immediately after birth; however, a description of the randomization procedure was not provided, allocation concealment was uncertain, bleeding assessments were not validated, and infants who developed thrombocytopenia after 72 hours were not included. Other studies in neonates could not exclude the possibility of harm with platelet transfusions.[8]

Recommendation: For critically ill preterm neonates with severe thrombocytopenia and no evidence of bleeding, there is insufficient evidence to make a recommendation for or against platelet transfusion.

Critically ill children

We identified 1 prospective cohort study of critically ill children (n = 138), which reported no difference in mortality between transfused and nontransfused children in adjusted analyses.[28]

Recommendation: For critically ill children with severe thrombocytopenia and no evidence of bleeding, there is insufficient evidence to make a recommendation for or against platelet transfusion.

Discussion

The key finding from this focused review is the lack of evidence underpinning a very common medical intervention in critically ill patients with thrombocytopenia. High-quality data to support or refute the need for prophylactic platelet transfusion in the ICU are lacking. There is a pressing need for research on the efficacy and safety of this intervention.

Our intention was to synthesize the literature and provide recommendations using Grading of Recommendations Assessment, Development, and Evaluation methodology; however, the evidence for or against platelet transfusions in these patient groups was too weak. In fact, there were no RCTs addressing platelet count thresholds in critically ill adults or children, and the only RCT in neonates was published 20 years ago and evaluated platelet transfusion thresholds that may not be as relevant to current practice. Thus, we felt it was more prudent to avoid recommendations altogether, which may potentially undermine the design of future randomized trials.

Platelet transfusions are commonly used in the ICU; 9% to 30% of critically ill patients receive a transfusion, the majority of which are used to prevent, rather than to treat, bleeding.[9,29,30] Despite the high utilization of platelet products, platelet transfusion practices in the ICU are variable.[31,32] The use of platelet transfusions in patients with sepsis was addressed in the 2012 Surviving Sepsis Campaign.[33] This guideline recommended platelet transfusions for adults with platelet counts $<20 \times 10^9$/L who were considered to be at significant risk of bleeding. This was a weak recommendation reflecting consensus opinion and informed by data derived from other patient groups. Similar weak recommendations for platelet transfusions were made for pediatric patients. For neonates, most published guidelines, which are also largely opinion-based, have recommended platelet transfusion thresholds between 20×10^9/L and 50×10^9/L for stable neonates and between 30×10^9/L and 100×10^9/L for preterm infants.[21,34,35]

Although thrombocytopenia has been independently linked to death in the ICU,[1] the association between low platelet counts and poor clinical outcomes does not establish causality, nor does it provide adequate evidence to support correcting the thrombocytopenia with platelet transfusions. These studies are subject to confounding by indication because patients who receive multiple platelet transfusions are often more severely ill. A platelet count below 30×10^9/L is commonly used to define very severe thrombocytopenia in critical illness[13]; however, the use of a specific platelet count threshold may incorrectly convey that there are stepwise changes in bleeding risk or other outcomes. Critically ill patients are heterogeneous with respect to admission diagnoses, comorbidities, medications, dynamic changes in coagulation parameters, and the need for invasive procedures, which may individually or cumulatively influence the risk of bleeding. Current data do not yet allow for the stratification of bleeding risk, which may be more informative than platelet count alone.

For the nonbleeding critically ill patients with platelet counts below 10-20 $\times 10^9$/L,[33] prophylactic platelet transfusions may be reasonable. This suggestion is supported by data from randomized trials in patients with chemotherapy-associated thrombocytopenia, which showed that platelet transfusions reduce the risk of serious bleeding when the platelet count is below 10×10^9/L.[30,36] However, these data may not be generalizable to critically ill patients who have frequent comorbidities and commonly require invasive procedures. In addition to platelet count, the decision to transfuse platelets will depend on age, weight, and other hemostatic parameters.

Strengths of this review were the methodology used to identify studies and assess study quality and our conservative approach to formulating conclusions. Our team is experienced in guideline development and transfusion medicine research, and our conclusions were informed by feedback from broad range of critical care specialists. Limitations were the inability to make specific recommendations for or against platelet transfusions in critically ill patients given the lack of data.

The clinical benefits of platelet transfusions on bleeding avoidance and mortality in thrombocytopenic critically ill patients remain unknown. Given that platelet transfusions are associated with risks including bacterial infection, severe allergic reactions, transfusion-related acute lung injury, and thrombosis,[37] clinical equipoise exists as to the overall benefit of this intervention. A randomized trial could be designed to evaluate the impact of a conservative vs liberal platelet transfusion strategy, or platelet transfusions vs no platelet transfusions on bleeding and mortality. Patients could be stratified by bleeding risk, incorporating patient characteristics and context in addition to the platelet count.

Acknowledgments

We thank Deborah Cook, Maureen Meade, Francois Lauzier, Karen Choong, and Paul Clarke for reviewing the manuscript and the recommendations. We thank Mrs Elizabeth Uleryk for her help performing the literature search.

Funding for the McMaster Transfusion Research program is provided in part by Canadian Blood Services and Health Canada.

Authorship

Contribution: L.L. designed the study, performed the article search, reviewed the articles, performed data extraction and quality assessments, analyzed the data, and wrote the manuscript; R.S.B. performed the article search, reviewed the articles, performed data extraction and quality assessments, analyzed the data, and wrote the manuscript; N.S.S. reviewed the articles, performed data extraction and quality assessments, developed the outcome tables, analyzed the data, and wrote the manuscript; S.J.S. performed data extraction and quality assessments, analyzed the data, and wrote the manuscript; N.M.H. conceived the study, performed data extraction and quality assessments, analyzed the data, and wrote the manuscript; and D.M.A. conceived the study, designed the study, performed data extraction and quality assessment, analyzed the data, and wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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