Evidence-based Focused Review of Platelet Transfusions for Critically Ill Patients with Thrombocytopenia

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Case #1. A 48-year-old male is admitted to the intensive care unit (ICU) with worsening multi-organ system failure due to bacteremia from an abdominal wound. His platelet count was 160x10⁹/L 5 days ago, and today he has severe thrombocytopenia, (platelet count = 33x10⁹/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 re-ventilation. 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. She develops severe thrombocytopenia (platelet count = 33x10⁹/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 150x10⁹/L) was present in 8.3%-67.6% of adult patients on admission to the intensive care unit (ICU) and acquired by 13%-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%-50% of critically ill neonates develop thrombocytopenia, including 5%-10% with platelet counts less than 50x10^9/L.\textsuperscript{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 for ICU-associated thrombocytopenia is to treat the underlying cause.

Platelet transfusions are often used to treat thrombocytopenia in the ICU\textsuperscript{4} despite the lack of high quality published evidence suggesting benefit. Local clinical guidelines and recommendations regarding 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 non-bleeding critically ill neonates, children, and adults with severe (platelet count <50x10^9/L)\textsuperscript{1} thrombocytopenia.
Methods

Our research team was composed of transfusion medicine specialists including one adult hematologist, three pediatric hematologists and two methodologists. Investigators had experience in platelet transfusion studies and research in ICU-associated thrombocytopenia. We also elicited feedback from three adult, one pediatric and one neonatal ICU physician, 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). 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 who received platelet transfusions and 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 ICUs only; fewer than 10 patients; review articles; redundant publications; abstract-only publications; and non-English language articles. One author screened titles for
relevance and a second author assessed abstract and full texts for eligibility. Six reviewers independently performed the data abstraction.

**Quality assessments**

The methodological quality of individual studies was evaluated using criteria established for the reporting of randomized and non-randomized studies. Each article was assessed independently by all six investigators 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. We added applicability to our assessment of overall study quality to gauge the extent to which the study addressed our research question. Methodological quality of all studies was re-examined 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 (GRADE) which incorporates the quality of the evidence, benefits and risks, and resource utilization. Grade 1 recommendations are considered
strong; Grade 2 recommendations are weak. A, B, and C denotes high, moderate
or low quality of evidence, respectively. Once our systematic review was
complete, it became evident that there was insufficient evidence upon which to
base evidence-based recommendations for or against platelet transfusions in this
setting. Our conclusions were reached by consensus.

Results

Our initial literature search yielded 1,471 citations, of which 1,361 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 five 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 one RCT in 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 two studies, one
platelet transfusion resulted in a median increase in the platelet count of
15x10^9/L although results varied considerably across patients.4,9 Sustained
correction of thrombocytopenia to a platelet count above $100 \times 10^9$/L was rarely achieved with platelet transfusions.

**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). The use of platelet transfusions was not associated with improved survival; however, data were derived from observational studies of low methodological quality. Some studies reported an association between platelet count recovery (by transfusion or otherwise) and survival.

**Data synthesis**

Only one observational study of moderate quality addressed the impact of platelet transfusions on platelet count increment in critically ill adults. The other four studies indirectly addressed our research question. There was insufficient evidence to suggest a clinical benefit of platelet transfusions for patients with severe thrombocytopenia, and post-transfusion platelet count increments were modest.
Recommendation: For critically ill adults with severe thrombocytopenia and no evidence of bleeding, there is insufficient evidence to recommend for or against platelet transfusion.

Critically ill preterm neonates

Platelet count increment

Platelet counts increased by 50 – 95 x10⁹/L after a platelet transfusion in three 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% confidence interval, 8%-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 grams birthweight who were randomized within 72 hours of birth reported no difference in incidence or extension of intraventricular hemorrhage using platelet transfusion thresholds of 50x10⁹/L or 150x10⁹/L.⁸ Unadjusted analyses from four 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. In the only RCT, there was no difference in mortality with a platelet transfusion trigger of 50x10⁹/L or 150x10⁹/L.

Data synthesis

Of the 15 neonatal studies, four were directly applicable to our research question; however, study quality was graded as low. The findings from one RCT showed no difference in intraventricular hemorrhage with a platelet transfusion threshold of 50x10⁹/L or 150x10⁹/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.
Recommendation: *For critically ill preterm neonates with severe thrombocytopenia and no evidence of bleeding, there is insufficient evidence to recommend for or against platelet transfusion.*

Critically ill children

We identified one prospective cohort study of critically ill children (n= 138), which reported no difference in mortality between transfused and non-transfused children in adjusted analyses\(^2^8\).

**Recommendation: For critically ill children with severe thrombocytopenia and no evidence of bleeding, there is insufficient evidence to recommend 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 despite the fact that this intervention is commonly used. 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 for or against the use of platelet transfusions using GRADE methodology; however the data were too weak to support evidence-based recommendation in this regard. 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 would essentially reflect opinion and may undermine the design of future randomized trials.

Platelet transfusions are commonly used in the ICU; 9-30% of critically ill patients receive a transfusion, approximately 59-68% 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 <20x10\(^9\)/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 and 50x10\(^9\)/L for stable neonates and 30-100x10\(^9\)/L for preterm infants.\(^21,34,35\)
Although thrombocytopenia has been independently linked to death in the ICU\textsuperscript{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 since patients who receive multiple platelet transfusions are often more severely ill. A platelet count below $30 \times 10^9$/L is commonly used to define very severe thrombocytopenia in critical illness;\textsuperscript{13} however, the use of a specific platelet count threshold may incorrectly convey that there are step-wise changes in bleeding risk or other outcomes. Critically ill patients are heterogeneous with respect to admission diagnoses, co-morbidities, 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 non-bleeding critically ill patients with platelet counts below $10 – 20 \times 10^9$/L\textsuperscript{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 serious bleeding could be reduced with platelet transfusions when the platelet count is below $10 \times 10^9$/L.\textsuperscript{30,36} However these data may not be generalizable to critically ill patients who have frequent comorbidities and commonly require invasive procedures which add to
the overall bleeding risk. In addition to platelet count, the decision to transfuse platelets will depend on age, weight, other hemostatic parameters and the need for invasive procedures.

Strengths of this review were the methodology used to identify studies and assess study quality, and our conservative approach used to formulate 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\textsuperscript{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.
Acknowledgements:

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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.B. performed the article search, reviewed the articles, performed data extraction and quality assessments, analyzed the data and wrote the manuscript; N.S. reviewed the articles, performed data extraction and quality assessments, developed the outcome tables, analyzed the data and wrote the manuscript; S.S. performed data extraction and quality assessments, analyzed the data and wrote the manuscript, N.H. conceived the study, performed data extraction and quality assessments, analyzed the data and wrote the manuscript; 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 statement: None of the authors has any conflict of interest to disclose.
REFERENCES


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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Population</th>
<th>Study design</th>
<th>Results</th>
<th>Study Quality*</th>
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</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
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<tr>
<td>Stanworth 2013³</td>
<td>1923</td>
<td>Adults; medical ICU</td>
<td>Prospective cohort</td>
<td>Median increase was 15x10⁹/L (IQR, 2-35x10⁹/L).</td>
<td>Low</td>
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<tr>
<td>Thomas 2009¹²</td>
<td>350</td>
<td>Adults; dengue fever</td>
<td>Prospective cohort</td>
<td>Median PLT count yield† was 12.4% higher than baseline after transfusion (range, -3.9% – 67.1%).</td>
<td>Low</td>
</tr>
<tr>
<td>Arnold 2006⁹</td>
<td>216</td>
<td>Adults; medical/surgical ICU</td>
<td>Retrospective cohort</td>
<td>Median increase after single PLT transfusion was 14x10⁹/L (IQR, -2 – 30x10⁹/L).</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stephan 1999¹¹</td>
<td>147</td>
<td>Adults; surgical ICU</td>
<td>Prospective cohort</td>
<td>PLT count rose above 40-50x10⁹/L (but never above 100x10⁹/L) after transfusion.</td>
<td>Low</td>
</tr>
<tr>
<td>Stephan 1999¹⁰</td>
<td>72</td>
<td>Adults; surgical ICU</td>
<td>Case-control study</td>
<td>Platelet transfusion led to sustained correction of thrombocytopenia in 8/16 patients, the remainder had only transient improvement.</td>
<td>Low</td>
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<td>Neonates</td>
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<tr>
<td>Von Lindern 2011¹⁵</td>
<td>422</td>
<td>Premature neonates</td>
<td>Retrospective cohort study</td>
<td>Platelet transfusion resulted in good, but less sustained rise in platelet count for neonates with severe thrombocytopenia (data not shown).</td>
<td>Low</td>
</tr>
<tr>
<td>Stanworth 2009¹⁴</td>
<td>194</td>
<td>Neonates</td>
<td>Prospective cohort</td>
<td>59% of transfusions increased counts &gt;40x10⁹/L; 8% of transfusions increased counts &lt;20x10⁹/L; median platelet count increase from 27x10⁹/L (IQR, 19-36x10⁹/L) to 79x10⁹/L (IQR, 47-126x10⁹/L).</td>
<td>Moderate</td>
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<tr>
<td>Andrew 1993⁸</td>
<td>152</td>
<td>Premature neonates</td>
<td>Randomized controlled trial</td>
<td>Significant increase by 95x10⁹/L in the intervention group (PLT transfusions for platelets below 150x10⁹/L).</td>
<td>Low</td>
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</table>

PLT = platelet; IQR= interquartile range; †PLT yield is the platelet count increase after transfusion corrected for body weight and platelet dose. *Study quality includes applicability to the research question.
Table 2. The impact of platelet transfusions on mortality in critically ill patients with thrombocytopenia.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Population</th>
<th>Study design</th>
<th>Results</th>
<th>Study Quality*</th>
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<tbody>
<tr>
<td>Adults</td>
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<tr>
<td>Thomas 2009&lt;sup&gt;12&lt;/sup&gt;</td>
<td>350</td>
<td>Adults; dengue fever</td>
<td>Prospective cohort</td>
<td>In patients with PLT counts &lt;50x10^9/L, 2 transfused patients died vs. 1 non-transfused patient; deaths were not related to bleeding.</td>
<td>Low</td>
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<tr>
<td>Stephan 1999&lt;sup&gt;11&lt;/sup&gt;</td>
<td>147</td>
<td>Adults; surgical ICU</td>
<td>Prospective cohort</td>
<td>Transfusion was not associated with an increased risk of death in univariate analysis.</td>
<td>Low</td>
</tr>
<tr>
<td>Stephan 1999&lt;sup&gt;10&lt;/sup&gt;</td>
<td>72</td>
<td>Adults; surgical ICU</td>
<td>Case-control study</td>
<td>In patients with PLTs &lt;50x10^9/L, there was no difference in mortality between transfused and non-transfused patients (50% and 45%, respectively).</td>
<td>Low</td>
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<tr>
<td>Neonates</td>
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<tr>
<td>Del Vecchio 2001&lt;sup&gt;26&lt;/sup&gt;</td>
<td>1389</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>33% mortality in transfused group vs. 3% mortality in the non-transfused group (p=0.0001). OR for death (p=0.0001): 10.4 with 1 PLT transfusion; 9.4 with 2-4 PLT transfusions; 29.9 with &gt;4 transfusions.</td>
<td>Low</td>
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<tr>
<td>Baer 2007&lt;sup&gt;23&lt;/sup&gt;</td>
<td>494</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>Risk of death increased with additional transfusions (OR=1.14 per transfusion): 2% in non-transfused; 11% with 1-2 transfusions; 20% with 3-10 transfusions; 35% with &gt;10 transfusions.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Christensen 2006&lt;sup&gt;25&lt;/sup&gt;</td>
<td>284</td>
<td>ELBW neonates</td>
<td>Retrospective cohort</td>
<td>Overall mortality 23% in transfused neonates. Risk of death increased with additional transfusions: 9% in non-transfused; 20% for 1-5 transfusions; 29% for &gt;5 transfusions.</td>
<td>Low</td>
</tr>
<tr>
<td>Baer 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>273</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>Unadjusted mortality increased with additional transfusions: 0% in non-transfused; 4% for 1 transfusion; 14% for 2-5 transfusions; 24% for 6-10 transfusions; 36% for 11-20 transfusions; 50% for &gt;20 transfusions.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stanworth 2009&lt;sup&gt;14&lt;/sup&gt;</td>
<td>194</td>
<td>Neonates</td>
<td>Prospective cohort</td>
<td>33% mortality in 31 neonates (≥5 transfusions) vs. 2% in 53 non-transfused patients.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Gupta 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>182</td>
<td>Neonates</td>
<td>Prospective observational</td>
<td>61 (33.5%) of 182 thrombocytopenic neonates died, of whom 96.5% received PLTs. Bleeding was not the primary cause of death for any patient.</td>
<td>Low</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Population</td>
<td>Study Design</td>
<td>Findings</td>
<td>Quality</td>
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<tr>
<td>Bonifacio 2007&lt;sup&gt;16&lt;/sup&gt;</td>
<td>164</td>
<td>Premature neonates</td>
<td>Case control</td>
<td>Case control (94 cases, 70 controls)</td>
<td>Low</td>
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<td></td>
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<td>Mortality 48.3% in transfused neonates and 18.2% in non-transfused neonates.</td>
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<tr>
<td>Andrew 1993&lt;sup&gt;8&lt;/sup&gt;</td>
<td>152</td>
<td>Preterm neonates</td>
<td>Randomized controlled trial</td>
<td>16 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)</td>
<td>Low</td>
</tr>
<tr>
<td>Garcia 2001&lt;sup&gt;18&lt;/sup&gt;</td>
<td>61</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>Unadjusted mortality did not correlate with number of transfusions: 42.8% with 1 transfusion; 15.3% with 2-4 transfusions; 28.5% with &gt;4 transfusions.</td>
<td>Low</td>
</tr>
<tr>
<td>Dohner 2009&lt;sup&gt;17&lt;/sup&gt;</td>
<td>45</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>48.8% mortality in patients given ≥ 20 PLT transfusions.</td>
<td>Low</td>
</tr>
<tr>
<td>Murray 2002&lt;sup&gt;21&lt;/sup&gt;</td>
<td>44</td>
<td>Preterm Neonates</td>
<td>Retrospective review</td>
<td>5 deaths in the transfused group (n=25) vs. no deaths in the non-transfused group (n=19) in neonates with PLTs&lt;50x10&lt;sup&gt;9&lt;/sup&gt;/L.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Gerday 2009&lt;sup&gt;19&lt;/sup&gt;</td>
<td>NR</td>
<td>Neonates</td>
<td>Prospective cohort</td>
<td>No difference in mortality in patients transfused based on count versus mass (0.9% vs. 0.4%, respectively; p=0.10); no deaths ascribed to bleeding.</td>
<td>Low</td>
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<tr>
<td>Children</td>
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<tr>
<td>Agrawal 2008&lt;sup&gt;28&lt;/sup&gt;</td>
<td>138</td>
<td>Children; medical and surgical ICU</td>
<td>Prospective cohort</td>
<td>Transfusion was not a significant contributor to mortality in adjusted analysis. Unadjusted OR for death: 3.8 (95% CI, 1.25-11.5; p=0.01) transfused vs. non-transfused. ‘Transfusion’ was not specified but assumed to be PLT transfusion.</td>
<td>Low</td>
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</tbody>
</table>

NR= not reported; PLT = platelet; CI = confidence intervals; OR= Odds ratio; ELBW = extremely low birthweight (<1,000 g). *Study quality includes applicability to the research question.
Table 3. The impact of platelet transfusions on bleeding in critically ill neonates with thrombocytopenia.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Population</th>
<th>Study design</th>
<th>Results</th>
<th>Study Quality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn 2003</td>
<td>1283</td>
<td>VLBW neonates</td>
<td>Prospective observational</td>
<td>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).</td>
<td>Low</td>
</tr>
<tr>
<td>Stanworth 2009</td>
<td>194</td>
<td>Neonates</td>
<td>Prospective cohort</td>
<td>Major hemorrhage occurred in 40% of 31 transfused neonates (≥5 transfusions) vs. 5% in 53 non-transfused neonates.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Muthukumar 2012</td>
<td>168</td>
<td>Neonates</td>
<td>Prospective observational</td>
<td>21% (95% CI, 8%-31%) reduction in minor bleeds during the 12-hour period after PLT transfusion compared with 12 hours before PLT transfusion.</td>
<td>High</td>
</tr>
<tr>
<td>Bonifacio 2007</td>
<td>164</td>
<td>Preterm neonates</td>
<td>Case control (94 cases, 70 controls)</td>
<td>Overall 37/60 (61.7%) transfused neonates had IVH vs. 7/22 (31.8%) non-transfused neonates (similar across gestational age groups).</td>
<td>Low</td>
</tr>
<tr>
<td>Andrew 1993</td>
<td>152</td>
<td>Preterm neonates</td>
<td>Randomized controlled trial</td>
<td>Major bleeding: 22/78 (28.2%) in the intervention group vs. 19/74 (25.7%) in controls (PLT transfusions for platelets below 50x10^9/L); p=0.73.</td>
<td>Low</td>
</tr>
<tr>
<td>Garcia 2001</td>
<td>61</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>Bleeding incidence: 60% with 1 transfusion; 42.3% with 2-4 transfusions; 35.7% with &gt;4 transfusions.</td>
<td>Low</td>
</tr>
<tr>
<td>Dohner 2009</td>
<td>45</td>
<td>Neonates</td>
<td>Retrospective cohort</td>
<td>19% bleeding incidence in patients who received ≥20 PLT transfusions.</td>
<td>Low</td>
</tr>
<tr>
<td>Murray 2002</td>
<td>44</td>
<td>Preterm Neonates</td>
<td>Retrospective Review</td>
<td>No patient (25 transfused, 19 non-transfused) developed new or extended IVH.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Gerday 2009</td>
<td>NR</td>
<td>Neonates</td>
<td>Prospective cohort</td>
<td>Transfusion protocol based on PLT mass (PLT count x mean PLT volume) was associated with fewer Grade 3 and 4 IVH compared with a PLT-count based transfusion protocol (1.8 vs. 0.4%, p=0.01).</td>
<td>Low</td>
</tr>
</tbody>
</table>

NR= not reported; PLT = platelet; IVH= Intraventricular hemorrhage; VLBW= very low birth-weight. *Study quality includes applicability to the research question.
Evidence-based focused review of platelet transfusions for critically ill patients with thrombocytopenia

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