Platelet Transfusion Practices in Critically Ill Children

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Abstract: OBJECTIVES Little is known about platelet transfusions in pediatric critical illness. We sought to describe the epidemiology, indications, and outcomes of platelet transfusions among critically ill children. DESIGN Prospective cohort study. SETTING Multicenter (82 PICUs), international (16 countries) from September 2016 to April 2017. PATIENTS Children ages 3 days to 16 years prescribed a platelet transfusion in the ICU during screening days. INTERVENTIONS None. MEASUREMENTS AND MAIN RESULTS Over 6 weeks, 16,934 patients were eligible, and 559 received at least one platelet transfusion (prevalence, 3.3%). The indications for transfusion included prophylaxis (67%), minor bleeding (21%), and major bleeding (12%). Thirty-four percent of prophylactic platelet transfusions were prescribed when the platelet count was greater than or equal to 50×10 cells/L. The median (interquartile range) change in platelet count post transfusion was 48×10 cells/L ($17\text{-}82 \times 10$ cells/L) for major bleeding, 42×10 cells/L ($16\text{-}80 \times 10$ cells/L) for prophylactic transfusions to meet a defined threshold, 38×10 cells/L ($17\text{-}72 \times 10$ cells/L) for minor bleeding, and 25×10 cells/L ($10\text{-}47 \times 10$ cells/L) for prophylaxis in patients at risk of bleeding from a device. Overall ICU mortality was 25% but varied from 18% to 35% based on indication for transfusion. Upon adjusted analysis, total administered platelet dose was independently associated with increased ICU mortality (odds ratio for each additional 1 mL/kg platelets transfused, 1.002; 95% CI, 1.001-1.003; p = 0.005). CONCLUSIONS The majority of platelet transfusions are given as prophylaxis to nonbleeding children, and significant variation in platelet thresholds exists. Studies are needed to clarify appropriate indications, with focus on prophylactic transfusions.

Platelet Transfusion Practices in Critically Ill Children

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Interventions: None.

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Conclusions: The majority of platelet transfusions are given as prophylaxis to nonbleeding children, and significant variation in platelet thresholds exists. Studies are needed to clarify appropriate indications, with focus on prophylactic transfusions. (*Crit Care Med* 2018; 46:1309–1317)

Key Words: critical care; pediatrics; platelet transfusions; thrombocytopenia

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Platelet transfusions are commonly prescribed in critical illness, but uncertainty remains regarding their efficacy and safety for all indications. In 2015, an American Association of Blood Banks (AABB) survey reported that 48,000 children in the United States received 165,000 apheresis platelet units (1). Unfortunately, there is no information regarding

the epidemiology, indications, and outcomes for critically ill children receiving platelet transfusions.

Evidence-based guidelines for pediatric platelet transfusions are generally lacking and based primarily on expert opinion. Recommendations published by the AABB state that pediatric platelet transfusions are indicated for 1) total platelet count (TPC) less than 10×10^9 cells/L due to hypoproliferative thrombocytopenia, 2) active bleeding in association with qualitative platelet defects, 3) unexplained excessive bleeding when undergoing cardiopulmonary bypass, or 4) patients undergoing extracorporeal membrane oxygenation (ECMO) with TPC less than 100×10^9 cells/L (2).

Little is known about the practice of platelet transfusion in pediatric critical illness. In order to evaluate platelet transfusion strategies in critically ill children and guide platelet transfusion practices, it is important to understand the epidemiology. The primary objective of the study was to describe patterns of platelet transfusions among critically ill children, including transfusion thresholds, indications, posttransfusion platelet count increment, and outcomes. The international nature supports its generalizability.

METHODS

Study Population

This point prevalence study was an exploratory, international, prospective, cross-sectional design. PICUs were recruited through the Pediatric Critical Care Blood Research Network, Pediatric Acute Lung Injury and Sepsis Investigators network, several international critical care societies, and sites who previously participated in an epidemiologic study of plasma transfusions (3). Sites were encouraged to recruit across all pediatric critical care areas, including specialized pediatric cardiac critical care units, but were not required to do so. Each site was assigned 6 random weeks (between September 2016 and April 2017) and screened all 7 days of each week. A child was considered eligible if admitted to the PICU during one of the screening days and between 3 days and 16 years old. A potential subject was enrolled if he/she received a platelet transfusion prescribed by the intensive care team during one of the screening days. Patients were excluded if life expectancy was less than 24 hours, gestational age was less than 37 weeks, or the patient was previously enrolled. The study was approved by the Institutional Review Board at each site, except for the United Kingdom where it was approved by the Health Research Authority of the National Health Service. Waiver of consent was granted at all sites except one in Italy that required written consent. Sites in Switzerland required a description of the study to be posted with an opt-out possibility for families.

Data Collection

For each enrolled subject, the site chose from the following indications for the transfusion (more than one could be selected): 1) TPC less than 10×10^9 cells/L with failure of platelet production; 2) TPC less than 30×10^9 cells/L in neonate with failure of platelet production; 3) major bleeding as defined by a) bleeding requiring massive transfusion; b) intracranial, intraocular, retroperitoneal, intraspinal, or nontraumatic intra-articular bleeding; or c) bleeding requiring surgical intervention (i.e., hemothorax requiring drainage); 4) minor bleeding (surgical or nonsurgical) as defined by any bleeding not meeting criteria for major bleeding; 5) preparation for surgery; 6) preparation for invasive procedure; 7) known qualitative platelet defect with risk of bleeding; or 8) at risk of bleeding from device. Indications 1, 2, 5, 6, 7, and 8 were all categorized as "prophylactic" transfusions. When sites were unsure of indication, the record was reviewed by the study principal investigator (PI), and an assignment was made after discussion with the local PI.

Data collected included patient demographics, reason for admission, any prior platelet transfusions, attributes of the platelet product (dose, source, and processing), any adverse reactions to the transfusion, and laboratory assays assessed before and after transfusion. All laboratory data were collected at the discretion of the medical team and recorded by the research team up to 24 hours prior to and 36 hours following the transfusion of interest. Major clinical outcome data, including length of stay, length of mechanical ventilation, mortality, and degree of organ dysfunction, as measured by PELOD-2 score (4) were collected. Study data were managed using Research Electronic Data Capture electronic data capture tools hosted at Weill Cornell Medicine.

Statistical Approach

Demographic and clinical characteristics were described as n (%) or mean ± SD or median and interquartile range (IQR), as appropriate. Categorical data were compared by Fisher exact/chi-square tests. Continuous variables were compared by analysis of variance/Kruskal-Wallis tests or t test/Wilcoxon Rank-Sum for parametric/nonparametric data, respectively. All p values were two sided with statistical significance evaluated at the 0.05 alpha level. All analyses for descriptive statistics were performed in R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

To assess the independent association between total administered platelet dose and mortality, a multivariable logistic regression model was developed. Candidate variables with a p value of less than 0.1 on unadjusted analyses were included. These were full days since PICU admission, ECMO, PELOD-2 score on day of transfusion, bleeding as indication for transfusion, postoperative status at admission to PICU, and lowest platelet count on day of admission. Multicollinearity between variables was assessed and determined not to be an issue. The regression was performed using a backward, stepwise model. All analyses for outcomes data were conducted using SPSS version 25 (IBM Corp, Armonk, NY).

RESULTS

Prevalence

Eighty-two sites from 16 countries participated. The majority of sites were urban (97%), academic (98%), trauma centers

TABLE 1. Demographics of Subjects

Variables	Major Bleeding (n = 64)	Minor Bleeding (n = 115)	Prophylactic Transfusions in Patients on Devices (n = 79)	Prophylactic Transfusions to Meet Threshold (n = 278)	p
Age (yr), median (IQR)	3 (0–11)	4 (0–10)	0 (0–3)	5 (1–11)	< 0.001
Sex (male), n (%)	33 (52)	66 (57)	44 (56)	152 (55)	0.897
Weight (kg), median (IQR)	13.7 (5.9–36.5)	16.0 (8.5- 28.5)	6.4 (3.5–18.8)	19.1 (8.6–38.1)	< 0.001
Days since admission, median (IQR)	1 (0–3)	2 (0–8.8)	5 (2–13)	2 (0–6)	< 0.001
Mechanical ventilation, n (%)	48 (75)	82 (71)	74 (94)	141 (51)	< 0.001
Underlying oncologic diagnosis, n (%)	21 (34)	35 (31)	9 (12)	155 (59)	< 0.001
Reason for PICU admission, n (%)					
Respiratory	15 (23)	51 (44)	48 (61)	96 (35)	< 0.001
Septic shock	4 (6)	22 (19)	9 (11)	85 (31)	< 0.001
Hemorrhagic shock	16 (25)	5 (4)	2 (3)	6 (2)	< 0.001
Other Shock	4 (6)	5 (4)	4 (5)	11 (4)	0.810
Trauma	4 (6)	7 (6)	1 (1)	2 (1)	0.002
Traumatic brain injury	3 (5)	2 (2)	0 (0)	3 (1)	0.114
Burn	0 (0)	1 (1)	0 (0)	1 (0)	0.731
Cardiac surgery—bypass	14 (22)	17 (15)	13 (16)	21 (8)	0.004
Cardiac surgery—no bypass	1 (2)	4 (3)	1 (1)	3 (1)	0.366
Cardiac—nonsurgical	3 (5)	10 (9)	12 (15)	16 (6)	0.047
Emergency surgery	4 (6)	1 (1)	3 (4)	6 (2)	0.131
Elective surgery	3 (5)	7 (6)	5 (6)	8 (3)	0.312
Seizure	1 (2)	6 (5)	0 (0)	8 (3)	0.181
Encephalopathy	6 (9)	15 (13)	4 (5)	16 (6)	0.078
Meningitis	0 (0)	1 (1)	2 (3)	2 (1)	0.390
Renal failure	3 (5)	15 (13)	8 (10)	29 (10)	0.371
Hepatic failure	3 (5)	8 (7)	2 (3)	13 (5)	0.576
Postoperative liver transplant	2 (3)	3 (3)	1 (1)	7 (3)	0.879
Other	23 (36)	27 (23)	15 (19)	92 (33)	0.026
PELOD-2 score prior to transfusion, median (IQR)	7 (5.5–10.5)	7 (6–11)	8 (7–11)	7 (4–9)	0.001

IQR = interquartile range.
Of the 559 patients transfused and enrolled, 536 had reported data.

(85%), and ECMO centers (80%). Of the participating sites, 48 of 82 (58%) were located in North America, 23 of 82 (28%) in Europe, four of 82 (5%) in Oceania, four of 82 (5%) in the Middle East, and three of 82 (4%) in Asia.

During the 6 weeks of screening, 16,934 patients were eligible. Of those, 559 received platelet transfusions and were enrolled yielding a platelet transfusion prevalence of 3.3% per patient. There were nine of 82 sites (11%) that did not transfuse platelets during the entire study period. The sites that did not transfuse any eligible subjects were limited to North America and Europe.

Subjects

Subject demographics are summarized in **Table 1** and categorized according to indication for platelet transfusion. The median (IQR) age was 4.1 years (0.5–10.8 yr), and 55% were male. The three most common reasons for admission were respiratory insufficiency/failure (39%), septic shock (22%), and cardiac surgery involving bypass (12%). Nearly half the subjects (44%) had an underlying oncologic diagnosis. The majority were mechanically ventilated at time of transfusion (64.4%) and admitted to the PICU for a median (IQR) length of 2 days (2–7 d) before enrollment. The median (IQR)
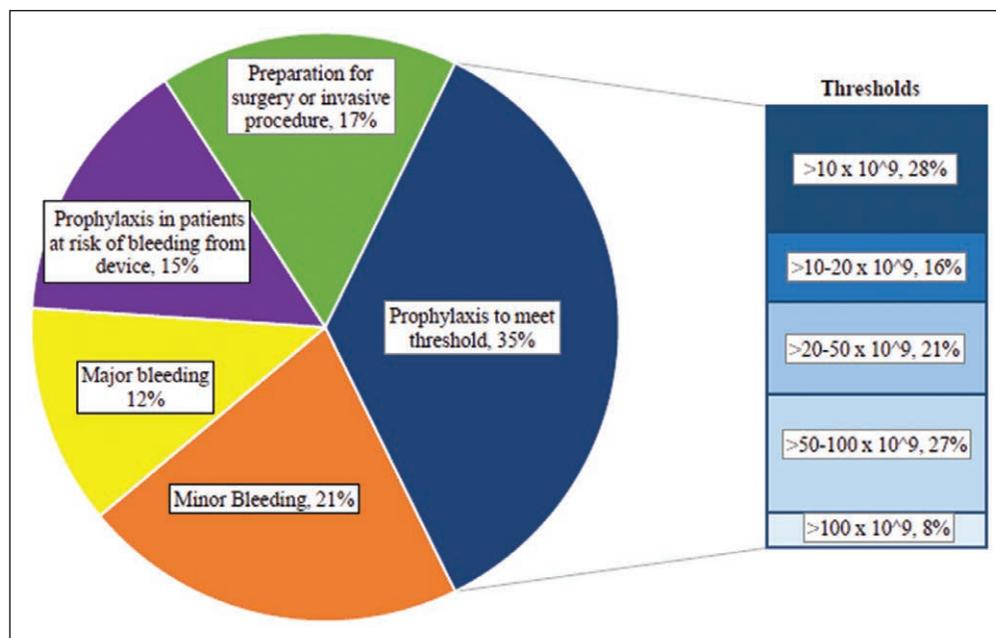
Figure 1. Indications for platelet transfusions.

Reported adverse reactions were uncommon. In the 515 transfusions in which this data were entered, there were a total of 32 reactions (6%). A new fever or increase in temperature by 1°C, if already febrile, occurred most frequently (3%), followed by hypotension (3%), urticaria (0.6%), and bronchospasm (0.2%). There were no hemolytic reactions or confirmed septic reactions.

Laboratory Assays

The TPC was known prior to transfusion in the vast majority of cases (99%). The median (IQR) TPC prior to transfusion was 40×10^9 cells/L ($20–66 \times 10^9$ cells/L). Thirty-four percent of transfusions were prescribed when the TPC was greater than or equal to 50×10^9 cells/L. Of the 278 prophylactic transfusions prescribed to meet a threshold, 46 (17%) were given to surgical patients. The median (IQR) TPC prior to transfusion in patients with surgical indications for PICU admission was 48×10^9 cells/L ($30–81 \times 10^9$ cells/L). This differed significantly ($p < 0.001$) from medical patients whose median (IQR) TPC prior to transfusion was 26×10^9 cells/L ($15–42 \times 10^9$ cells/L) (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D564; legend: Comparison of medical and surgical patients receiving prophylactic transfusions to meet a defined threshold.).

Viscoelastic testing, such as thromboelastography and rotational thromboelastometry (ROTEM), was uncommonly analyzed prior to transfusion (5% and 2%, respectively).

Figure 2 depicts the change in TPC following transfusion at various times and for various indications corrected for transfusion dose. The median change in TPC varied across groups based on indication ($p = 0.03$). For every 10 mL/kg of platelets transfused, the median (IQR) change in TPC was 48×10^9 cells/L ($17–82 \times 10^9$ cells/L) for patients with major bleeding, 42×10^9 cells/L ($16–80 \times 10^9$ cells/L) for prophylactic transfusions to meet a threshold, 38×10^9 cells/L ($17–72 \times 10^9$ cells/L) for patients with minor bleeding, and 25×10^9 cells/L ($10–47 \times 10^9$ cells/L) for prophylactic transfusions in patients at risk of bleeding from a device. The incremental change in TPC did not vary between those who had an underlying oncologic diagnosis and those who did not ($p = 0.57$).

Outcomes

Outcome data were available for 532 of the 559 enrolled patients. The median (IQR) length of stay in the PICU was 13 days (6–29 d). The median (IQR) number of ventilator-free days was 4 (1–9). The mortality rate for all children was 25%. Outcomes based on indication are summarized in **Table 2**.
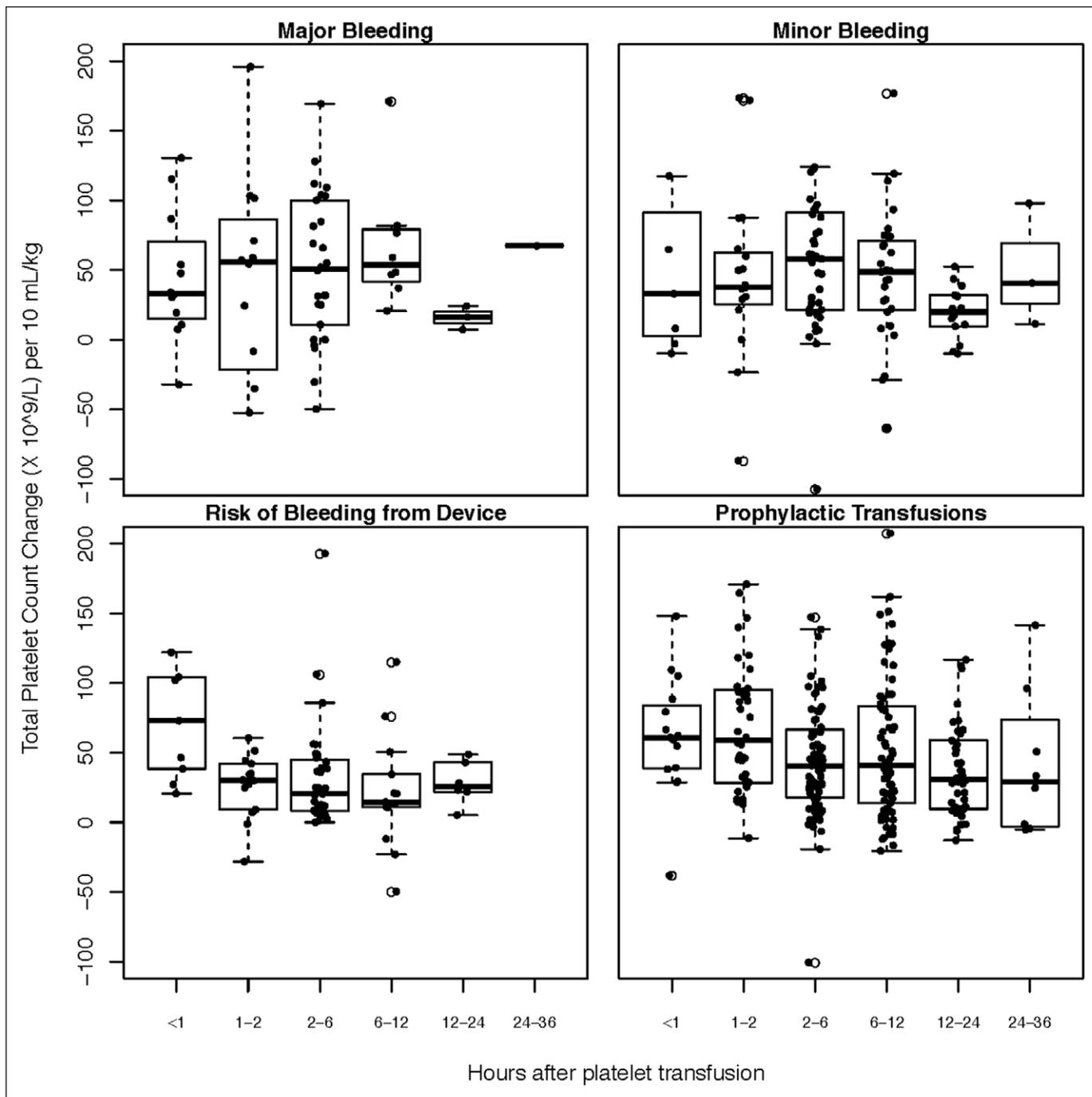
PELOD-2 score at enrollment was 7 (5–10). The frequency of subjects receiving medications that may affect platelet function was milrinone (17%), aspirin (3%), and nonsteroidal anti-inflammatories (2%). Subjects were supported by the following devices at time of platelet transfusion: ECMO (17%), continuous renal replacement therapy (CRRT) (11%), intermittent hemodialysis (1%), and molecular adsorbent recirculation system (1%). Approximately one third of the children (36%) had received at least one other platelet transfusion in the PICU during the admission prior to enrollment.

Indications

The indications for each platelet transfusion are summarized in **Figure 1**. The majority (67%) of transfusions were prophylactic; major or minor bleeding was the indication in only one third of transfusions (33%). Of the 79 patients who received prophylactic transfusions while on mechanical circulatory devices, 67 (85%) were supported by ECMO, and 12 (15%) were supported with CRRT.

Blood Product/Transfusion Event

The majority of platelets transfused were collected by apheresis (87%) or whole blood derived (13%). The transfusions were commonly leukoreduced (93%) and irradiated (80%). They were infrequently volume reduced (8%), pathogen inactivated (5%), or human leukocyte antigen matched (1%). The median (IQR) administered platelet dose per transfusion event was 9.4 mL/kg (5.5–13.1 mL/kg). Subjects received a median (IQR) 4 (2–11) platelet transfusion events during their PICU course for a total median (IQR) administered dose of 32.4 mL/kg (14.0–91.4 mL/kg). The total number of transfusions that the 559 enrolled subjects received over their PICU admissions was 6,090.

Figure 2. Change in platelet count following transfusion by indication.

Variables associated with ICU mortality by univariate regression analysis are described in **Supplemental Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/D565). In the unadjusted model, each additional 1 mL/kg of platelets transfused was associated with an increase in mortality of 0.3% (odds ratio, 1.003; 95% CI, 1.002–1.004; $p < 0.001$). Multivariable logistic regression showed a 2% increase in mortality for every additional standard dose (10 mL/kg) of platelets administered after adjustment for confounding variables (odds ratio for each additional 1 mL/kg transfused of 1.002; 95% CI, 1.001–1.003; $p = 0.005$), shown in **Table 3**.

DISCUSSION

This international point prevalence study is the first published analysis of the epidemiology, indications, and outcomes of critically ill children transfused platelets. Approximately two thirds of platelet transfusions were prescribed in a prophylactic manner to nonbleeding children. Thirty-four percent of prophylactic transfusions were prescribed when the TPC was greater than or equal to 50×10^9 cells/L. Although the observed rise in TPC following transfusion varied based on indication, those at risk of bleeding from a circulatory device had the smallest increase. Mortality in patients who receive platelet

TABLE 2. Outcomes by Diagnosis

Variables	Major Bleeding (n = 64)	Minor Bleeding (n = 113)	Prophylactic Transfusions in Patients on Devices (n = 77)	Prophylactic Transfusions to Meet Threshold (n = 278)	p
PICU length of stay (d), median (IQR)	10 (4–27)	14 (7–27)	25 (12–50)	11.5 (5–26)	< 0.001
Mechanical ventilator-free days, median (IQR)	2 (0–8)	3 (0–9)	2 (0–7)	5 (1–10)	< 0.001
Total platelet dose (mL/kg), median (IQR)	30.9 (13.5–67.3)	27.3 (10.4–62.1)	97.7 (40.0–243.0)	28.6 (12.3–79.8)	< 0.001
Mortality, n (%)	18 (28.1)	40 (35.4)	27 (35.1)	48 (17.3)	< 0.001

IQR = interquartile range.

Of the 559 patients transfused and enrolled, 532 had reported outcome data.

transfusions was high, ranging from 17% to 35% according to indication. There was an independent association between administered platelet dose and mortality.

Platelet transfusion practices observed in this study resemble those published in adults. In one large observational study of critically ill adults in the United Kingdom, wide variation in platelet use was reported (5). The prevalence of platelet transfusion was 9%. More than half of platelet units were given as "prophylactic transfusions" in patients with no documented bleeding. One third of transfusions were given when the TPC greater than 50×10^9 cells/L. Similar findings were seen in a retrospective study from three adult ICUs in Canada; the median TPC reported prior to platelet transfusion was 87×10^9 cells/L (6). In these same two studies, the median (IQR) increment in TPC following transfusion was modest, 15×10^9 cells/L ($2–36 \times 10^9$ cells/L) and 23×10^9 cells/L ($7–44 \times 10^9$ cells/L) (5, 6).

Pediatric data from a single-center prospective study reported the prevalence of critically ill children receiving at least one platelet transfusion to be 7.2% (7). The average TPC was $49 \pm 34 \times 10^9$ cells/L prior to transfusion, similar to thresholds reported here. They reported a wide range of incremental changes in TPC following transfusion (from 30 to nearly 100×10^9 cells/L), based on indication for transfusion. The variation in TPC noted in our study is likely not only due to differences in the indication for transfusion but

also due to differences in patient characteristics or etiology of thrombocytopenia. For example, change in TPC is expected to be different between patients transfused prophylactically in preparation for neurosurgery compared with a bleeding patient with an oncologic disorder. Of note, the incremental change in TPC we report did not vary with the presence or absence of an underlying oncologic diagnosis. The incremental change in TPC in critically ill children following platelet transfusion may be higher than that observed in critically ill adults because of better ABO compatibility, which was implicated in improved posttransfusion platelet increment in adults with hematologic malignancies (8). The incremental change in TPC we report also varied by indication for transfusion. The smallest incremental change was seen in those at risk of bleeding from a device, which may be theoretically explained by alloimmunization and consumption related to the device itself. Children with major bleeding had a greater median rise in TPC than those with minor or no bleeding. Variations in platelet products, including storage solution, age, and temperature, may have impacted the median change in TPC post transfusion. Differences in storage solution affect posttransfusion platelet count at 1 and 24 hours and may have played a role (9, 10). In addition, differences in age of the platelets transfused has been related to clinical complications in trauma patients (11). Platelets stored at

TABLE 3. Multiple Logistic Regression Model of Independent Variables and ICU Mortality

Candidate Independent Variables	OR (95% CI)	p
Full days since PICU admission	1.021 (1.006–1.036)	0.007
Postoperative at admission	1.676 (0.940–2.990)	0.080
Extracorporeal life support	3.256 (1.782–5.951)	< 0.001
Lowest platelet count at admission	0.995 (0.990–1.001)	0.089
PELOD score on day of transfusion	1.311 (1.220–1.408)	< 0.001
Indication for transfusion = major or minor bleeding	2.391 (1.463–3.906)	0.001
Total administered dose of platelets	1.002 (1.001–1.003)	0.005

OR = odds ratio.

Continuous renal replacement therapy and PELOD score at admission removed from model based on likelihood ratio test in backward stepwise model.

room temperature may be relatively inert and not consumed at a high enough rate to show reduced increments compared with nonbleeding patients. "Cold" platelets (stored at 4°C) have been shown to have increased hemostatic efficacy and increased safety relative to bacterial contamination (12–14).

Our study confirms that clinicians rely on few assays, other than TPC alone, to prescribe platelet transfusions. Whiting et al (15) suggest that viscoelastic testing is more effective than standard laboratory testing to guide transfusion therapy in adults undergoing cardiac surgery or following trauma. A recent Cochrane review analyzing the benefit of viscoelastic testing to monitor hemostatic treatment versus usual care in adults or children with bleeding reported that application of thromboelastography- or ROTEM-guided transfusion strategies may reduce the need for blood products and improve morbidity (16). The Effects of Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) trial, comparing different platelet doses in adults and children with hematologic malignancies, reported a poor relationship between degree of severity of thrombocytopenia and bleeding risk (17). More work needs to be done to define bleeding risk, other than isolated platelet counts, in critically ill children.

Given there are few evidence-based guidelines for platelet transfusion in critically ill children, it is not surprising that significant variation in prescribing practices exists. Randomized trials represent the goal for evidence-based practitioners, but we must recognize considerable challenges undertaking trials of platelet transfusions in critically ill children. Alternative designs, such as comparative effectiveness methods, need to be considered. Since nearly half the children in this cohort had an underlying oncologic diagnosis, this specific population should be investigated. Future studies should also focus on children supported by circulatory devices since they receive the highest exposure to platelet transfusions with high mortality.

This study represents the largest prospective study of platelet transfusions in critically ill children reported to date. Since the data were predominantly collected with waiver of consent, it is without selection bias. Given the number of international sites, results should be externally valid for PICUs with platelet transfusions readily available in their blood banks. The results, although primarily descriptive in nature, provide important preliminary data that identify at-risk patient populations and will facilitate the design of future trials.

Some limitations exist. Unfortunately, there is no validated bleeding assessment tool in critically ill children, so it was not included as an outcome. Data were not collected on transfusion of other hemostatic products, such as plasma, cryoprecipitate, or antifibrinolytics. Since we did not collect data on the 16,375 nontransfused patients, we cannot directly compare patients transfused and not transfused. The number of sites that did not transfuse any subjects were limited to North America and Europe and may represent different regional approaches to platelet transfusions. Data were not collected on platelet transfusions ordered by anesthesiologists or surgeons so only reflects practices of pediatric intensivists. Data on adverse events related to the transfusions were collected

passively. The population of children transfused had increased acuity compared with the general PICU population, in both median Pediatric Logistic Organ Dysfunction-2 scores (7 vs 4) and mortality (25% vs 3%) (18). Finally, the association between platelet dose and mortality must be interpreted with caution as patients who are sicker are often more heavily transfused, and this confounding cannot be removed entirely.

In conclusion, the majority of platelet transfusions prescribed in the PICU are given prophylactically to nonbleeding children, and significant variation in platelet thresholds exists. Studies are needed to clarify appropriate indications for platelet transfusion and subsequent responses in critically ill children according to their illness, with particular focus on prophylactic transfusions. Further work should investigate the association between administered platelet dose and mortality.

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