Indications and Effects of Plasma Transfusions in Critically Ill Children

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Abstract

Rationale: Plasma transfusions are frequently prescribed for critically ill children, although their indications lack a strong evidence base. Plasma transfusions are largely driven by physician conceptions of need, and these are poorly documented in pediatric intensive care patients.

Objectives: To identify patient characteristics and to characterize indications leading to plasma transfusions in critically ill children, and to assess the effect of plasma transfusions on coagulation tests.

Methods: Point-prevalence study in 101 pediatric intensive care units in 21 countries, on 6 predefined weeks. All critically ill children admitted to a participating unit were included if they received at least one plasma transfusion.

Measurements and Main Results: During the 6 study weeks, 13,192 children were eligible. Among these, 443 (3.4%) received at least one plasma transfusion and were included. The primary indications for plasma transfusion were critical bleeding in 22.3%, minor bleeding in 21.2%, planned surgery or procedure in 11.7%, and high risk of postoperative bleeding in 10.6%. No bleeding or planned procedures were reported in 34.1%. Before plasma transfusion, the median international normalized ratio (INR) and activated partial thromboplastin time (aPTT) values were 1.5 and 48, respectively. After plasma transfusion, the median INR and aPTT changes were −0.2 and −5, respectively. Plasma transfusion significantly improved INR only in patients with a baseline INR greater than 2.5.

Conclusions: One-third of transfused patients were not bleeding and had no planned procedure. In addition, in most patients, coagulation tests are not sensitive to increases in coagulation factors resulting from plasma transfusion. Studies assessing appropriate plasma transfusion strategies are urgently needed.

Keywords: plasma; blood transfusion; child; critical illness; blood coagulation tests

At a Glance Commentary

Scientific Knowledge on the Subject: Plasma transfusions are frequently prescribed for critically ill children, although most clinical uses of plasma are not evidence based.

What This Study Adds to the Field: Our data indicate that one-third of transfused patients were not bleeding and had no planned procedure. Furthermore, plasma transfusion corrected coagulation tests only for patients with severe coagulopathy.

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*A complete list of members may be found before the beginning of the References.

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Although plasma transfusions are frequently prescribed worldwide, the indications for their use remain unclear. In 2011, 3,882,000 plasma units were transfused in the United States in adults and children (1). According to U.S. pediatric health information administrative databases, nearly 3% of all recorded pediatric admissions receive a plasma transfusion during their hospital stay (2). In France, administration of plasma has increased by more than 40% over the last 10 years, often in clinical situations where the biological and/or clinical criteria do not seem to justify its use (3). Experts recommend plasma transfusions mainly in the context of massive transfusion and in case of bleeding associated with documented abnormal coagulation tests (4, 5).

In massively bleeding patients, observational data suggest that early use of plasma and platelets seems to be associated with improved outcomes in patients with life-threatening bleeding (6). However, in a less critical clinical context, adult and pediatric epidemiological studies have shown an independent association between plasma transfusion and development of nosocomial infections (7, 8), acute respiratory distress syndrome (9–11), multiple organ failure (8, 11), and mortality (12). Therefore, it might seem important to determine when the benefits outweigh the side effects, especially as previous studies have already shown that plasma transfusions failed to correct mildly abnormal coagulation tests (13–15). There is no specific pediatric data on this issue. However, the increased morbidity associated with plasma transfusions in observational studies might be due to unrecognized biases, as plasma might be given to sicker patients.

Plasma transfusions are frequently administered to correct abnormal coagulation tests (16), which are often viewed as predicting a risk of bleeding although Segal and colleagues have shown that abnormal coagulation tests are not associated with increased risk of bleeding in most procedures (17). In 2007, Lauzier and colleagues reported that plasma transfusions were often administered to critically ill adults who were not bleeding and who did not require an invasive procedure/surgery (18). In 2011, Stanworth and colleagues reported that half of the plasma transfused in the United Kingdom was given to nonbleeding patients (15). These practices are not in accordance with the guidelines for the use of frozen plasma published by expert committees (4, 5). This might lead to significant waste, especially as blood availability is already a major concern.

There are few published reports of the reasons for plasma transfusion in children. One pediatric international survey showed important heterogeneity in plasma transfusion thresholds and strategies (19), with two-thirds of responding pediatric critical care physicians stating that they prescribe plasma transfusions for nonbleeding critically ill children. This marked heterogeneity in plasma transfusion patterns might be due to the absence of randomized controlled trials (RCTs) that could guide plasma transfusion strategies (20).

This point-prevalence study is part of a larger undertaking that aims to design an RCT to address optimal plasma transfusion strategies in critically ill children (8, 19, 20). Our primary objectives were to identify the characteristics and clinical situations resulting in plasma transfusion and to evaluate changes in coagulation laboratory values resulting from the initial plasma transfusion in critically ill children.

Methods

Study Sites and Population

This point-prevalence study is an international multicenter cross-sectional observational study performed in 101 pediatric intensive care units (PICUs) in 21 countries. Clinical sites were recruited through several research networks including BloodNet of the Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI), the Canadian Critical Care Trials Group (CCCTG), the European Society of Pediatric Neonatal Intensive Care (ESPNIC), the U.K. Pediatric Intensive Care Society (PICS), the Groupe Francophone de Réanimation et Urgences Pédiatriques (GFRUP), and the Australian and New Zealand Intensive Care Society (ANZICS), as well as through personal contacts made by the study investigators. For each study site, six 1-week periods were randomly predefined over six consecutive months (April to September 2014). Within each week, screening was done and data were collected on 5 days (Monday to Friday, from midnight to midnight).

All critically ill children aged 3 days to 16 years old admitted to a participating PICU on one of the 30 study days were considered eligible. Any eligible patient for whom at least one plasma transfusion was administered on any study day was included unless one of the exclusion criteria (i.e., plasmapheresis and gestational age less than 37 wk at the time of PICU admission) was present. If a patient was readmitted within 24 hours of PICU discharge, this was considered part of the same admission.

Outcome Definitions

The primary outcome was the primary indication for the first plasma transfusion and the coagulation tests before that transfusion. We considered only plasma transfusions, not cryoprecipitate, albumin, or infusions of specific coagulation factors.

Clinical indications were categorized as follows:

1. *Critical bleeding*: Massive bleeding (transfusion of all blood products > 80 ml/kg within 24 h), bleeding in specific sites (intracranial, intraocular, retroperitoneal, intraspinal, pericardial, nontraumatic intraarticular), or bleeding requiring a surgical intervention or drainage (e.g., hemothorax requiring drainage) (21)
2. *Minor bleeding*: Minor surgical bleeding (wound, drain, etc.) or minor nonsurgical bleeding (endotracheal tube secretions, nasogastric tube, urine, etc.)
3. *Planned surgery or procedures* (central venous catheter, pleural drain, etc.)
4. *High risk of postoperative bleeding* (as defined by the intensivist)
5. *No bleeding, no planned procedure* (hypovolemia, abnormal coagulation tests, factor or component replacement, at high risk of bleeding due to nonsurgical reasons, etc.)

The secondary outcome was the changes in coagulation tests that occurred after the first plasma transfusion.

We also collected data on the transfusion itself, such as the product that had been used (fresh-frozen plasma, frozen plasma, Mirasol-treated plasma, solvent/detergent plasma) (22), and on the rate and volume of the transfusion.

A description of the population, and of the clinical outcome, was based on the daily Pediatric Logistic Organ Dysfunction (PELOD)-2 score (23), length of mechanical ventilation, PICU length of stay, and PICU

mortality. Because the PELOD-2 score is predictive of mortality when measured on certain specific days, we collected patient data on Days 1 (first transfusion), 2, 5, 8, and 12 of PICU stay (24). Length of mechanical ventilation, PICU length of stay, and PICU mortality were censored 28 days after the end of the enrollment period.

Ethics Approval

This study was approved by ethics committees or boards at all sites. Five centers (two in Canada, one each in Denmark, Italy, and Norway) required that individual patient written consent be obtained. French and Belgian sites provided study information in the PICU waiting room, with an opt-out (or passive) consent. The ethics committees or boards of all other sites did not require individual consent.

Sample Size

The sample size was calculated to attain a precision of ±5% of the proportion of patients in whom plasma was transfused despite the fact that they were nonbleeding and without planned invasive procedures. The estimated proportion was 34%, based on previously reported data in critically ill adults (18). On the basis of these assumptions, the study aimed to enroll 339 critically ill children who received at least one plasma transfusion.

Statistical Analysis

Descriptive statistics are reported as mean ± SD, median and interquartile range (IQR), or proportions with their 95% confidence interval (CI).

We assessed the association between the indication for plasma transfusion and the different variables (demographic data, coagulation tests, clinical outcome measures) with a Pearson chi-square test (for dichotomous variables) and one-way analysis of variance (ANOVA) for continuous variables. We assessed the difference between coagulation test results drawn before and after plasma transfusion by Wilcoxon signed-rank test. Coagulation test cutoffs were determined incrementally, using the Wilcoxon signed-rank test, by steps of 0.5 and 5 for the international normalized ratio (INR) and activated partial thromboplastin time (aPTT), respectively. We also assessed the association between plasma transfusion dose and change in coagulation tests by one-way ANOVA, after categorizing the doses. Correlations between nonnormally distributed variables were assessed by Spearman correlation test.

All tests were two-sided, with an α level of 0.05. All statistical analyses were performed with SPSS version 20 for the Mac (SPSS, Chicago, IL).

Results

Frequency and Description of the Population

One hundred and one PICUs from 21 countries participated in this study, from April to September 2014. Fifty-six centers were in Europe, 35 in North America, 5 in Oceania, 3 in Asia, and 2 in South America. The median number of beds per PICU was 13 (IQR, 10–22).

Over the 30 study days, 13,192 patients were admitted and hence eligible. Per PICU, the median number of patients already admitted at the beginning of a study week was 9 (IQR, 5–13) and the median number of new admissions on each study day was 2 (IQR, 1–3).

Only one patient was not enrolled, because written consent was not obtained. Plasma transfusions were observed in 443 patients (3.4%; 95% CI, 3.1–3.7). The median length of PICU stay before the first plasma transfusion was 1 day (IQR, 0–5).

Table 1 describes the baseline characteristics of included patients. The median age and weight were 1 year (IQR, 0.2–6.4) and 9.1 kg (IQR, 4.0–21.0), respectively. Forty-three percent were males. The median PELOD-2 score was 7 (IQR, 5–10).

The center that included the largest number of patients contributed 11.1% of the results. Fifteen centers (15 of 101, 14.8%) did not transfuse plasma during their 6 study weeks.

Indications for Plasma Transfusion

The primary indication for plasma transfusion was critical bleeding in 22.3% of patients (95% CI, 18.7–26.5), minor bleeding in 21.2% (95% CI, 17.8–25.3), planned surgery or procedure in 11.7% (95% CI, 9.1–15.7), and high risk of postoperative bleeding in 10.6% (95% CI, 8.0–14.0). No bleeding or planned procedures were reported in 34.1% of patients (95% CI, 29.8–38.6) (Figure 1). Among the latter, 68.3% (95% CI, 60.4–75.1) were transfused to correct abnormal coagulation tests, 13.2% (95% CI, 8.7–19.6) were considered at high risk of bleeding due to their medical condition, 12.6% (95% CI, 8.2–18.8) were transfused to treat hypovolemia, and 6.0% (95% CI, 3.2–10.9) were transfused to replace losses (ascites, chylothorax, or antithrombin deficiency).

Forty-eight patients received plasma while receiving extracorporeal life support; 12 of these (25%) received plasma for critical bleeding. Six (13%) received plasma as part of an ongoing trial (NCT01903863).

Coagulation Tests before Plasma Transfusion

Coagulation tests were performed before the first plasma transfusion in 96.4% of the patients. Prothrombin time (PT) was measured in seconds and in percentage in 59.1 and 23.3% of the patients, respectively. INR and aPTT were measured in 74.0 and 90.3% of patients, respectively. The median time between sampling for coagulation tests and initiation of plasma transfusion was 3.5 hours (IQR, 1.7–6.5).

The median results for INR and aPTT were 1.5 (IQR, 1.3–2.0) and 48 (IQR, 36–75), respectively. Thirty percent of patients transfused were not bleeding, had no planned procedure, and had an INR less than 1.5.

Thromboelastography was performed in seven centers (located in three countries: Denmark, the United Kingdom, and the United States) on 13 (2.9%) patients. Rotational thromboelastometry was performed in four centers (located in Belgium, France, Italy, and Switzerland) on seven (1.6%) patients.

Plasma Transfusions

At the time of the first plasma transfusion, fresh-frozen plasma was given to 75% of the patients, whereas solvent/detergent plasma and frozen plasma were given in 14 and 6%, respectively. Physicians were not aware of the type of plasma in 5% of transfusions. The median dose of plasma was 11 ml/kg (IQR, 9.7–15.1). Plasma was transfused over a median time of 60 minutes (IQR, 30–104). The median dose and median transfusion rate were not significantly higher for patients with critical bleeding ($P = 0.10$).

Coagulation Tests after Plasma Transfusion

Coagulation tests were performed after the first plasma transfusion in 89.4% of patients. The median time between the end of the

Table 1. Demographic Data according to Primary Indication for Plasma Transfusion

	Critical Bleeding (*n* = 99)	Minor Bleeding (*n* = 94)	Planned Procedure (*n* = 52)	High Risk of Postoperative Bleeding (*n* = 47)	No Bleeding, No Procedure (*n* = 151)	*P* Value
Sex (male), n (%)	40 (40%)	39 (41%)	20 (38%)	15 (32%)	75 (50%)	0.21
Age (yr), median (IQR)	4.0 (0.25–11.1)	1.7 (0.25–7.6)	2.0 (0.5–6.1)	0.5 (0.1–1.9)	0.5 (0.1–4.4)	<0.001
Weight (kg), median (IQR)	15.1 (4.7–35.0)	9.7 (4.5–20.0)	12.0 (6.0–27.8)	6.1 (3.6–11.9)	6.9 (3.5–17.5)	0.001
Reasons for PICU admission*, n (%)						
Respiratory	35 (35%)	21 (22%)	18 (35%)	8 (17%)	61 (40%)	0.006
Septic shock	5 (5%)	9 (10%)	11 (21%)	1 (2%)	39 (26%)	<0.001
Hemorrhagic shock	26 (26%)	2 (2%)	4 (8%)	0 (0%)	4 (3%)	<0.001
Other shock	9 (9%)	4 (4%)	4 (8%)	6 (13%)	11 (7%)	0.46
Trauma	19 (19%)	3 (3%)	1 (2%)	0 (0%)	6 (4%)	<0.001
Traumatic brain injury	15 (15%)	1 (1%)	2 (4%)	0 (0%)	8 (5%)	<0.001
Burn	0 (0%)	1 (1%)	1 (2%)	1 (2%)	2 (1%)	0.75
Cardiac surgery (bypass)	30 (30%)	47 (50%)	1 (2%)	19 (40%)	36 (24%)	<0.001
Cardiac surgery (no bypass)	0 (0%)	3 (3%)	1 (2%)	7 (15%)	6 (4%)	<0.001
Cardiac nonsurgical	7 (7%)	10 (11%)	7 (14%)	3 (6%)	23 (15%)	0.24
Emergency surgery	29 (29%)	2 (2%)	6 (12%)	9 (19%)	13 (9%)	<0.001
Elective surgery	16 (16%)	47 (50%)	3 (6%)	22 (47%)	19 (13%)	<0.001
Seizure	5 (5%)	2 (2%)	4 (8%)	1 (2%)	11 (7%)	0.32
Encephalopathy	6 (6%)	5 (5%)	3 (6%)	0 (0%)	9 (6%)	0.57
Meningitis	2 (2%)	0 (0%)	2 (4%)	0 (0%)	5 (3%)	0.29
Renal failure	8 (8%)	10 (11%)	10 (19%)	1 (2%)	16 (11%)	0.07
Hepatic failure	10 (10%)	5 (5%)	11 (21%)	1 (2%)	18 (12%)	0.01
Postoperative liver transplantation	2 (2%)	0 (0%)	2 (4%)	4 (9%)	3 (2%)	0.04
Other reason†	11 (11%)	2 (2%)	8 (15%)	9 (19%)	17 (11%)	0.24
Severity at inclusion (plasma transfusion), median (IQR)						
PELOD-2 score	8 (6–11)	7 (5–8)	7 (4–11)	7 (5–9)	7 (5–10)	0.05
Worst lactate	3.2 (1.6–5.3)	2.4 (1.7–4.1)	2.2 (1.2–4.9)	2.7 (1.9–5.4)	2.1 (1.4–5.1)	0.54
Support, n (%)						
Mechanical ventilation	87 (88%)	82 (87%)	38 (73%)	42 (89%)	122 (81%)	0.08
ECLS	12 (12%)	7 (7%)	1 (2%)	11 (23%)	17 (11%)	0.1
CRRT	5 (5%)	7 (7%)	6 (12%)	5 (11%)	12 (8%)	0.63
MARS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Intermittent dialysis	1 (1%)	1 (1%)	1 (2%)	0 (0%)	2 (1%)	0.92

Definition of abbreviations: CRRT = continuous renal replacement therapy; ECLS = extracorporeal life support; IQR = interquartile range; MARS = molecular adsorbent recirculating system; PELOD-2 = Pediatric Logistic Organ Dysfunction-2 (23); PICU = pediatric intensive care unit.
*Some patients had more than one reason for admission.
†The main other reasons for admission were oncologic–hematologic disease (19 patients), neurosurgery (5 patients), and metabolic disorders (4 patients).

plasma transfusion and sampling for coagulation tests was 4.0 hours (IQR, 1.7–8.2).

The median results for INR and aPTT were 1.4 (IQR, 1.2–1.7) and 41 (IQR, 33–59), respectively. The median INR and aPTT changes were −0.2 (IQR, −0.4 to 0; n = 281; $P < 0.001$) and −5 (IQR, −17 to 2; n = 356; $P < 0.001$), respectively (Figure 2).

After plasma transfusions, thromboelastography and rotational thromboelastometry were performed in seven (1.6%) and four (0.9%) patients, respectively.

Changes in INR and aPPT values compared with baseline are shown in Figures 3A and 3B. The median INR change after transfusion was −0.1 (IQR, −0.3 to 0) for 273 children (83%) with a baseline INR value less than 2.5 and −1.1 (IQR, −2.0 to −0.4) for 55 children (17%) with a baseline INR value of at least 2.5 ($P < 0.0001$). The median aPTT change after transfusion was −2 (IQR, −7 to 3) for 249 children (62%) with a baseline aPTT value less than 60 seconds and −22 (IQR, −44 to −5) for 151 children (38%) with a baseline aPTT value of at least 60 seconds ($P < 0.0001$).

Effect of Plasma Dose

Figure 4 shows how the plasma dose transfused modified INR and aPTT values according to baseline. A dose–response relationship was observed only in children with a baseline INR of at least 2.5 (Spearman's ρ coefficient, −0.47; $P < 0.001$).

Clinical Outcome

Median length of mechanical ventilation was 5 days (IQR, 1–16) and median PICU length of stay was 10 days (IQR, 4–24) in our study population. Table 2 shows that there were no statistically significant variations according to the primary indication for plasma transfusion. PICU mortality was 26.9% (119 of 443; 95% CI, 23–31).

Discussion

In this large international observational study, we examined the indications of plasma transfusions in critically ill children and their effects on coagulation tests. We found that 34% of patients who receive plasma were neither bleeding nor being

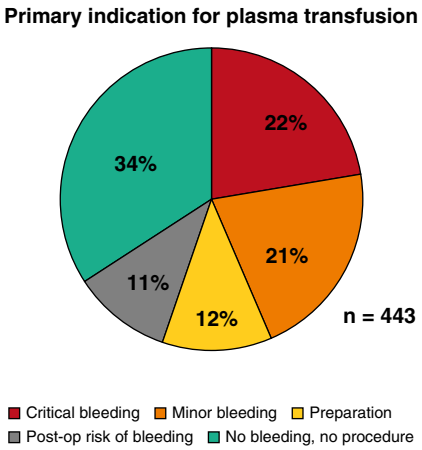

Figure 1. Proportions of the various primary indications for plasma transfusion. The indications were categorized as critical bleeding (massive bleeding, bleeding in specific sites, or bleeding requiring a surgical intervention or drainage; *red*), minor bleeding (*orange*), preparation for surgery or procedures (*yellow*), at high risk of postoperative bleeding (*gray*), and no bleeding, no planned procedure (*green*).

prepared for a procedure, whereas only 22% receive plasma for critical bleeding.

Clinically significant decreases in INR and aPTT values were noted only for INR values greater than 2.5 or aPTT values greater than 60 seconds. These findings underscore that when the INR is only mildly prolonged, the assay is not sensitive to the increase in coagulation factors resulting from transfusion. It must be recognized that coagulation tests may not be the most appropriate measure of plasma transfusion efficacy, as they fail to predict bleeding (17). Unfortunately, alternative laboratory measures to better ascertain this do not exist at the present time.

In 2004, Dzik and Rao reported that the most common purpose of plasma transfusion in adults was to "prepare" a patient with an elevated INR for invasive procedures (16). In 2007, Lauzier and colleagues also showed that plasma transfusions were often administered to critically ill adults who were not bleeding; 33.7% of plasma orders were for nonbleeding patients with no planned invasive procedures (18). Our study shows similar results; 34.1% of patients transfused with plasma were not bleeding and had no planned invasive procedures.

The effect of plasma transfusions on coagulation tests has been described in adults. In 121 patients with moderately abnormal coagulation tests (INR < 1.85), the post-transfusion INR value decreased to below 1.1 in only 0.8% of this mixed surgical and medical intensive care patient population (13). In another study, Holland and Brooks showed that plasma transfusion did not correct INR levels less than 2.0–2.5 in 103 adult patients who received 174 transfusions (14). These studies demonstrate the inability of the INR to document the effect of plasma infusions at INR values commonly encountered in critical care patients. Similar results have also been reported by Stanworth and colleagues (15). Our study shows that only severely abnormal coagulation tests are improved by plasma transfusions and that this association was nonlinear. This is likely due to the exponential relationship between coagulation factor concentration and coagulation test results (25). Our results suggest that a mild to moderate elevation of the INR in a nonbleeding patient is not a worthwhile target for intervention.

Despite improvements in the management of blood products, some modeling suggests that blood availability could become a major concern in the next 5–10 years because of increasing demand in certain patient populations (26), which in turn justifies the rationalization of blood product (including plasma) transfusions. More specifically, to ensure the best use of blood products and to reduce unnecessary transfusion, it is important to ascertain whether transfusing critically ill but nonbleeding patients with a baseline INR less than 2.5 is appropriate. Indeed, it is possible that there are some benefits, which are not measured by coagulation tests. Furthermore, these cutoffs are based on observational data, and might not truly reflect the efficacy of plasma transfusions, which could be tested only in a randomized

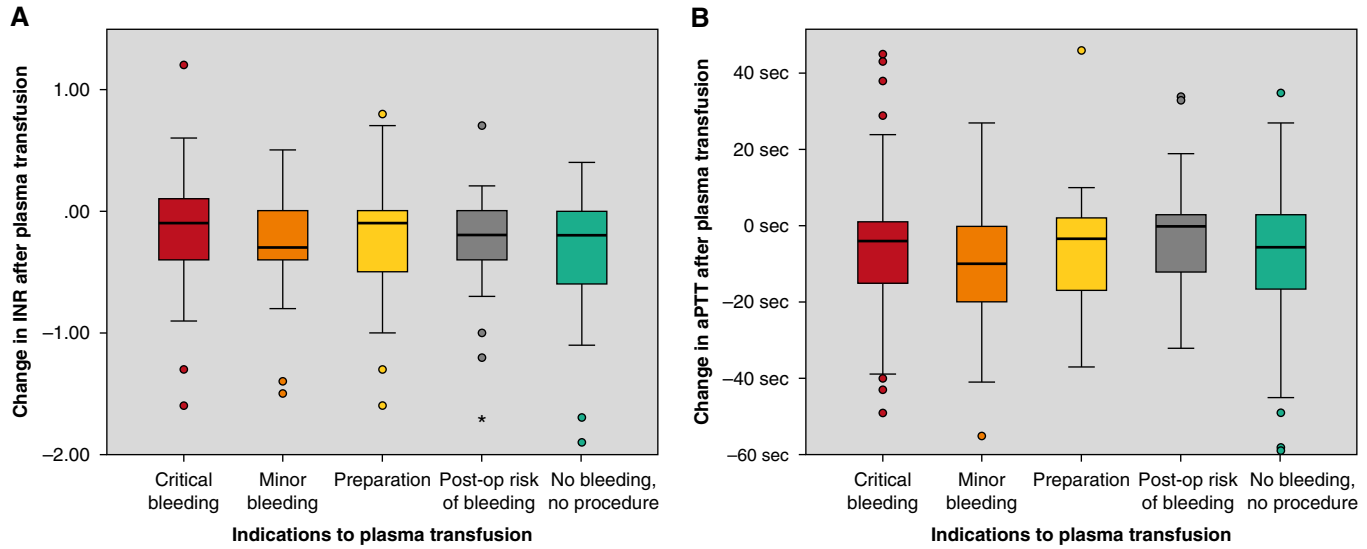

Figure 2. (*A*) Changes in international normalized ratio (INR) and (*B*) changes in activated partial thromboplastin time (aPTT) after plasma transfusion, according to the indications for transfusion: critical bleeding (*red*), minor bleeding (*orange*), preparation for surgery or procedures (*yellow*), at high risk of postoperative bleeding (*gray*), and no bleeding, no planned procedure (*green*). The median INR change was −0.2 (interquartile range [IQR], −0.4 to 0; n = 281 pairs of tests) and the median aPTT change was −5 (IQR, −17 to 2). Mild outliers (<1.5 IQR) and extreme outliers (>1.5 IQR) are marked with *circles* and an *asterisk*, respectively.

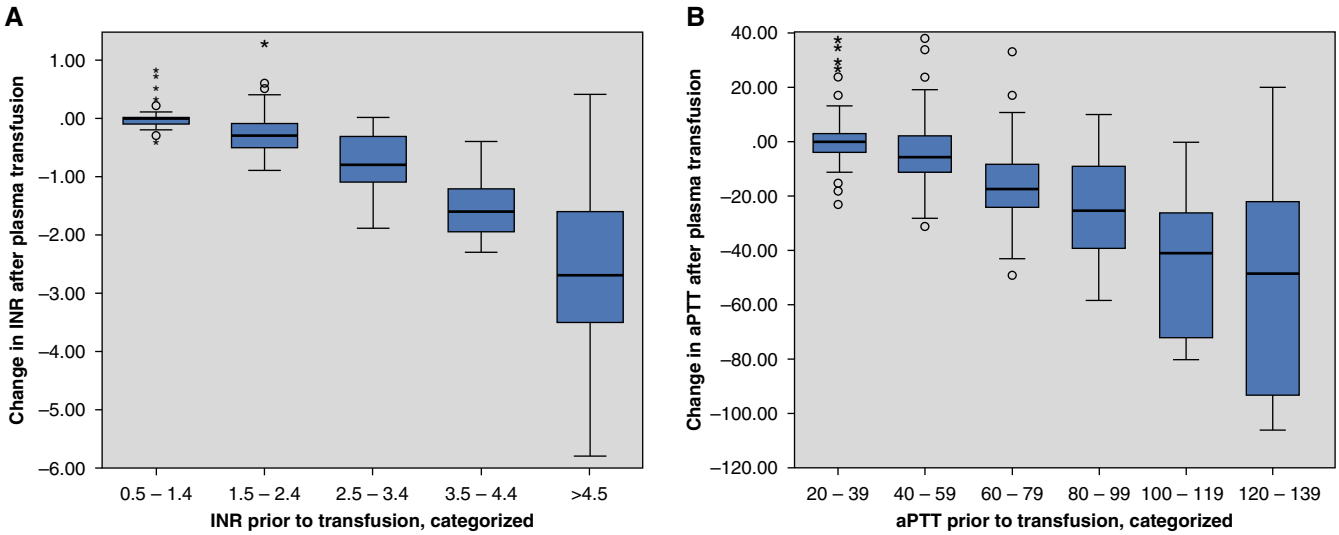

Figure 3. (*A*) Changes in international normalized ratio (INR) and (*B*) changes in activated partial thromboplastin time (aPTT) after plasma transfusion, according to the coagulation test before transfusion (n = 281 and n = 360 pairs of INR and aPTT tests, respectively). Mild outliers (<1.5 interquartile range [IQR]) and extreme outliers (>1.5 IQR) are marked with *circles* and *asterisks*, respectively.

controlled trial. Nonetheless, it seems obvious that a more restrictive transfusion strategy could considerably reduce the unnecessary use of plasma, which would allow for more appropriate resource use where truly needed.

This is the largest prospective observational study on plasma transfusions in critically ill children, both in terms of number of patients and in terms of PICUs. Worldwide enrollment enhances external validity. This study also avoided selection bias, as all but one eligible patient were enrolled. Definitive conclusions cannot be drawn, but meaningful hypotheses have been generated. Our findings reveal certain striking observations that suggest overuse of plasma in certain clinical contexts. The data will allow us to design a future RCT to evaluate these hypotheses.

Some limitations must be recognized. The design of our study does not permit comparison between patients transfused and not transfused with plasma. This was not the purpose of our study as data collection was limited only to patients who received plasma (prevalent cases) and not to the much larger group of patients who did not receive plasma. The patients in our study were sicker than those in a general PICU population, as our median PELOD-2 score and mortality rate were 7 (IQR, 5–10) and 26.6%, respectively, compared with 4 (2–7) and 6.0% in a large PICU population (23). This may reflect the fact that plasma was given mainly to sicker patients. Although we enrolled virtually all patients admitted in the participating PICUs, there might have been a selection bias for centers

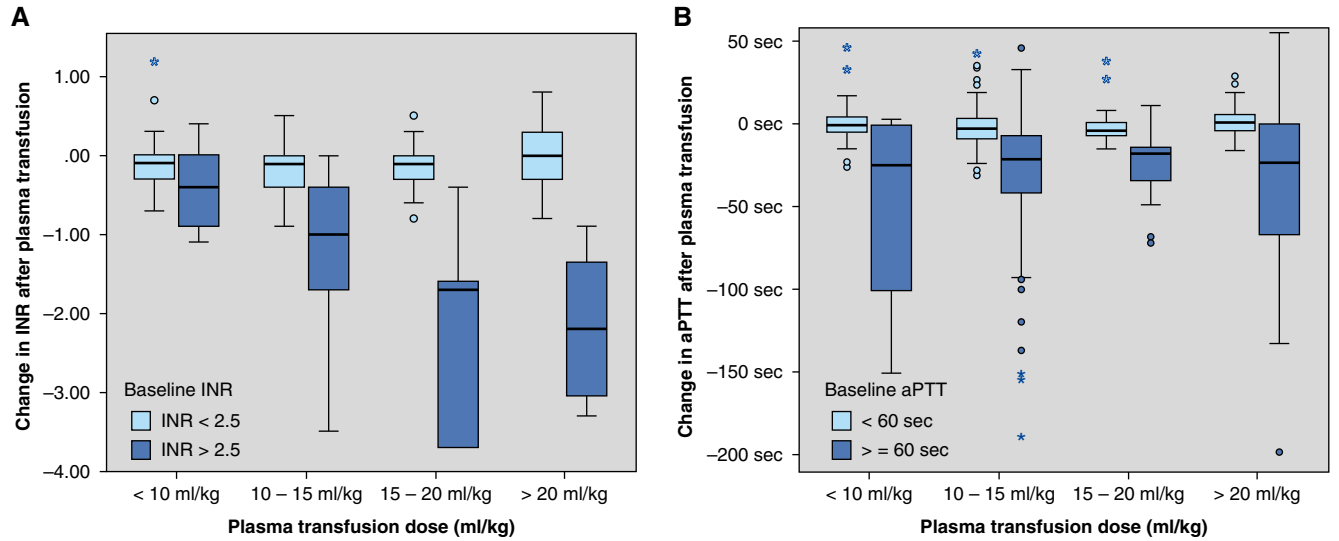

Figure 4. (*A*) Changes in international normalized ratio (INR) and (*B*) changes in activated partial thromboplastin time (aPTT) after plasma transfusion, according to the dose of plasma transfusion (ml/kg) and according to the baseline coagulation test (n = 281 and n = 360 pairs of INR and aPTT tests, respectively). Mild outliers (<1.5 interquartile range [IQR]) and extreme outliers (>1.5 IQR) are marked with *circles* and *asterisks*, respectively.

Table 2. Patient Outcomes according to Primary Indication for Plasma Transfusion

	Critical Bleeding (*n* = 99)	Minor Bleeding (*n* = 94)	Planned Procedure (*n* = 52)	High Risk of Postoperative Bleeding (*n* = 47)	No Bleeding, No Procedure (*n* = 151)	*P* Value
PELOD-2 score						
Day 2* (n = 402)	8 (5–10)	6 (5–8)	8 (4–11)	8 (5–9)	8 (5–10)	0.37
Day 5* (n = 296)	7 (5–9)	6 (3–9)	8 (4–10)	7 (4–10)	8 (4–10)	0.43
Day 8* (n = 227)	6 (4–9)	5 (3–9)	8 (4–10)	7 (5–9)	6 (3–9)	0.69
Day 12* (n = 162)	6 (3–7)	6 (2–9)	7 (3–10)	6 (3–8)	7 (3–9)	0.79
Duration of mechanical ventilation, d	5 (1–15)	2 (1–8)	9 (2–25)	7 (3–13)	6 (2–17)	0.20
PICU length of stay, d	11 (3–23)	7 (3–14)	18 (5–32)	11 (6–25)	12 (4–26)	0.46
Mortality, n (%)	34 (35%)	14 (16%)	16 (32%)	9 (19%)	46 (31%)	0.01

Definition of abbreviations: PELOD-2 = Pediatric Logistic Organ Dysfunction-2 (23); PICU = pediatric intensive care unit.
Results are provided as median (interquartile range), except for mortality.
*Days after the first plasma transfusion.

themselves, as some sites with specific transfusion strategies might have been less inclined to participate. The limited data collected did not include information on cointerventions, such as heparin, antithrombin, coagulation factor concentrates, vitamin K, or platelet administration. Finally, mortality was higher than anticipated in our patient cohort. It is therefore possible that we underestimated the burden of rapidly fatal disease, as we did not measure ventilator-free days but only the length of mechanical ventilation.

This international observational study shows that nonbleeding patients represent more than half of the critically ill children receiving plasma transfusions. Commonly used coagulation tests are not sensitive to the effects of plasma transfusion for the majority of patients transfused. Studies assessing appropriate plasma transfusion strategies are urgently needed. ■

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