Indications and effects of plasma transfusions in critically ill children

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Contribution: OK, PH, SS and MT initiated and designed the study. OK, PD, AS, PH, SS and MT contributed to the acquisition of the data. All authors contributed to the data analysis, the writing of the manuscript and approved the final version. The CCCTG and the BloodNet helped improve the study design and reviewed the manuscript. The PlasmaTV investigators collected the data and approved the final manuscript.

Funding: This study was funded by the Groupe Francophone de Réanimation et Urgences Pédiatriques (GFRUP) and the Marisa Sophie Research Foundation for Critically Ill Children.

Running Title: Plasma transfusions in critically ill children

Descriptor number: 4.11 Pediatric Critical Care

Number of words: Manuscript: 3049 words

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 a third of transfused patients were not bleeding and had no planned procedure. Furthermore, plasma transfusion only corrected coagulation tests for patients with severe coagulopathy.
Abstract

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

Objective: To identify patient characteristics and 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 six pre-defined weeks. All critically ill children admitted to a participating unit were included if they received at least one plasma transfusion.

Main results: During the six study weeks, 13192 children were eligible among whom 443 (3.4%) receiving at least one plasma transfusion 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 post-operative bleeding in 10.6%. No bleeding or planned procedures were reported in 34.1%. Prior to 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 >2.5.

Conclusions: A third of transfused patients were not bleeding and had no planned procedure. Additionally, 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.

Abstract: 250 words
Introduction

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 US 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 ten 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 et al
have shown that abnormal coagulation tests are not associated with increased risk of bleeding in most procedures (17). In 2007, Lauzier et al 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 et al reported that half of the plasma transfused in the UK was given to non-bleeding 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 a significant waste, especially as blood availability is already a major concern.

There are few published reports of the reasons for plasma transfusion in children. A recent pediatric international survey showed an 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 non-bleeding 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 a 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 carried out 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 UK 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 one-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 weeks 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 prior to that transfusion. We only considered plasma transfusions, but not cryoprecipitate, albumin, or infusions of specific coagulation factors.

Clinical indications were categorized as follows:
A) **Critical bleeding:** massive bleeding (transfusion of all blood products > 80 ml/kg within 24 hours), bleeding in specific sites (intra-cranial, intra-ocular, retroperitoneal, intra-spinal, pericardial, non-traumatic intra-articular); or bleeding requiring a surgical intervention or drainage (e.g. hemothorax requiring drainage) (21)

B) **Minor bleeding:** minor surgical bleeding (wound, drain, etc.) or minor non-surgical bleeding (endotracheal tube secretions, nasogastric tube, urine, etc.)

C) **Planned surgery or procedures** (central venous catheter, pleural drain, etc.)

D) **High risk of post-operative bleeding** (as defined by the intensivist)

E) **No bleeding, no planned procedure** (hypovolemia, abnormal coagulation tests, factor or component replacement, at high risk of bleeding due to non-surgical 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 (FFP), Frozen Plasma (FP), Mirasol-treated Plasma, Solvent/Detergent Plasma (SD plasma)] (22), the rate and volume of the transfusion. Description and clinical outcome of the population was studied using 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 in Denmark, Italy and Norway) required to obtain individual patient written consent. 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 they were non-bleeding and without planned invasive procedures. The estimated proportion was 34%, based on previously reported data in critically ill adults (18). Based on 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 ± standard deviation (SD), median and interquartile range (IQR), or proportions with their 95%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 a one-way ANOVA test for continuous variables. We assessed the difference between coagulation test results drawn before and after plasma transfusion using the Wilcoxon signed rank test. Coagulation test cut-offs were determined incrementally, using the Wilcoxon signed rank test, by steps of 0.5 and 5 for 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 using
a one-way ANOVA, after categorizing the doses. Correlations between non-normally
distributed variables were assessed with Spearman’s correlation test.
All tests were 2-sided, with an alpha level of 0.05. All statistical analyses were
performed with SPSS version 20 for Mac (SPSS, Chicago, IL, USA).

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 prior to 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. 43%
were males. The median PELOD-2 score was 7 (IQR 5-10).
The center which included the largest number of patients contributed 11.1% of the
results. Fifteen centers (15/101, 14.8%) did not transfuse plasma during their six
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 17.7-25.3), planned surgery or procedure in 11.7% (95% CI 9.1-15.7), and high risk of post-operative 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) (Fig.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 on Extracorporeal Life Support (ECLS); 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 prior to 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 < 1.5.

Thromboelastography (TEG) was performed in seven centers (located in three countries: Denmark, United Kingdom and USA) on 13 (2.9%) patients. Rotational
Thromboelastometry (ROTEM) was performed in four centers (located in Belgium, France, Italy, and Switzerland) on 7 (1.6%).

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 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 (Fig. 2).

After plasma transfusions, TEG and ROTEM were performed in 7 (1.6%) and 4 (0.9%) patients, respectively.

Changes in INR and aPPT values compared to 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 < 2.5 and -1.1 (IQR -2.0 to -0.4) for 55 children (17%) with a baseline INR value ≥ 2.5 (p<.0001). The median aPTT change after transfusion was -2 (IQR -7 to -3) for 249 children (62%) with a baseline aPTT
value < 60 sec and -22 (IQR -44 to -5) for 151 children (38%) with a baseline aPTT value ≥ 60 sec (p<.0001).

4 Effect of plasma dose

5 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 ≥ 2.5 (Spearman’s Rho coefficient -0.47, p<0.001).

Clinical outcome

9 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% (119/443, 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 prepared for a procedure, whereas only 22% receive plasma for critical bleeding. Clinically significant decrease in INR and aPTT values were only noted for INR values > 2.5 or aPTT values > 60 sec. 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 et al 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 et al also showed that plasma transfusions were often administered to critically ill adults who were not bleeding; 33.7% of plasma orders were for non-bleeding patients with no planned invasive procedures (18). Our study shows very 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 et al showed that plasma transfusion did not correct INR levels < 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 et al (15).

Our study shows that only severely abnormal coagulation tests are improved by plasma transfusions and that this association was non-linear. 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 non-bleeding 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 due to increasing demand in certain patient populations (26) which in turn justifies the
rationalization of blood product (including plasma) transfusions. More specifically, in
order to ensure the best use of blood products and to reduce unnecessary
transfusion, it is important to ascertain whether transfusing critically ill but non-
bleeding patients with a baseline INR < 2.5 is appropriate. Indeed, it is possible that
there are some benefits, which are not measured by coagulation tests. Furthermore,
these cut-offs are based on observational data, and might not truly reflect the efficacy
of plasma transfusions, which could only be tested in a randomized 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 utilization 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 patients were enrolled. Definitive conclusions cannot be drawn but
meaningful hypotheses have been generated. Our findings reveal certain very
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 to 4 (2-7) and 6.0% in a large PICU population
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 themselves, as some sites with specific transfusion strategies might have been less keen to participate. The limited data collected did not include information on co-interventions, 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 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 non-bleeding 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.
Acknowledgments

We would like to thank all of the PlasmaTV investigators for their tremendous work. We would also like to thank the Plateforme de Recherche Clinique of the Department of Pediatrics, Geneva University Hospital, for their help with this study. We are also grateful to Alan Tinmouth, Daniel Levin, Douglas Willson, Kusum Menon and Neil Blumberg for their very helpful comments on the manuscript.

PlasmaTV investigators: Australia: Warwick Butt, Carmel Delzoppo, Kym Bain (Royal Childrens Hospital, Melbourne); Simon Erickson, Nathan Smalley (Princess Margaret Hospital for Children, Perth); Tavey Dorofaeff, Debbie Long (Royal Childrens Hospital, Brisbane); Nathan Smalley, Greg Wiseman (Townsville Hospital, Townsville). Belgium: Stéphan Clément de Cléty, Caroline Berghe (Cliniques universitaires Saint-Luc, Brussels); Annick de Jaeger (Princess Elisabeth Children's University Hospital, Ghent); Pierre Demaret, Marc Trippaerts (CHC-CHR, Liège); Ariane Willems, Shancy Rooze (Hôpital universitaire des enfants Reine Fabiola, Brussels); Jozef De Dooy (Antwerp University Hospital, Edegem). Canada: Elaine Gilfoyle, Lynette Wohlgemuth (Alberta Children's Hospital, Calgary, AB); Marisa Tucci, Mariana Dumitrascu (CHU Sainte-Justine, Montréal, QC); Davinia Withington, Julia Hickey (Montreal Children's Hospital, Montreal, QC); Karen Choong, Lois Sanders (McMaster Children's Hospital, Hamilton, ON); Gavin Morrison (IWK Health Centre, Halifax, NS); Janice Tijssen (Children's Hospital, London Health Sciences Centre, London, ON); David Wensley, Gordon Krahn (British Columbia Children's Hospital, Vancouver, BC); Marc-André Dugas, Louise Gosselin (Centre Mère Enfant Soleil, CHU de Québec, Québec, QC); Miriam Santschi (CHUS, Sherbrooke, QC).

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### Table 1: Demographic data according to primary indication for plasma transfusion

<table>
<thead>
<tr>
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<th>Critical bleeding (n=99)</th>
<th>Minor bleeding (n=94)</th>
<th>Planned procedure (n=52)</th>
<th>High risk of post-operative bleeding (n=47)</th>
<th>No bleeding, no procedure (n=151)</th>
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<td>Gender [male], n (%)</td>
<td>40 (40%)</td>
<td>39 (41%)</td>
<td>20 (38%)</td>
<td>15 (32%)</td>
<td>75 (50%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Age [years], median (IQR)</td>
<td>4.0 (0.25-11.1)</td>
<td>1.7 (0.25-7.6)</td>
<td>2.0 (0.5-6.1)</td>
<td>0.5 (0.1-1.9)</td>
<td>0.5 (0.1-4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight [kg], median (IQR)</td>
<td>15.1 (4.7-35.0)</td>
<td>9.7 (4.5-20.0)</td>
<td>12.0 (6.0-27.8)</td>
<td>6.1 (3.6-11.9)</td>
<td>6.9 (3.5-17.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Reasons for PICU admission* (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiratory</td>
<td>35 (35%)</td>
<td>21 (22%)</td>
<td>18 (35%)</td>
<td>8 (17%)</td>
<td>61 (40%)</td>
<td>0.006</td>
</tr>
<tr>
<td>septic shock</td>
<td>5 (5%)</td>
<td>9 (10%)</td>
<td>11 (21%)</td>
<td>1 (2%)</td>
<td>39 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hemorrhagic shock</td>
<td>26 (26%)</td>
<td>2 (2%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td>4 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>other shock</td>
<td>9 (9%)</td>
<td>4 (4%)</td>
<td>4 (8%)</td>
<td>6 (13%)</td>
<td>11 (7%)</td>
<td>0.46</td>
</tr>
<tr>
<td>trauma</td>
<td>19 (19%)</td>
<td>3 (3%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>6 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>traumatic brain injury</td>
<td>15 (15%)</td>
<td>1 (1%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
<td>8 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>burn</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
<td>0.75</td>
</tr>
<tr>
<td>cardiac surgery (bypass)</td>
<td>30 (30%)</td>
<td>47 (50%)</td>
<td>1 (2%)</td>
<td>19 (40%)</td>
<td>36 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cardiac surgery (no bypass)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td>1 (2%)</td>
<td>7 (15%)</td>
<td>6 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cardiac non-surgical</td>
<td>7 (7%)</td>
<td>10 (11%)</td>
<td>7 (14%)</td>
<td>3 (6%)</td>
<td>23 (15%)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>emergency</td>
<td>elective surgery</td>
<td>seizure</td>
<td>encephalopathy</td>
<td>meningitis</td>
<td>renal failure</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>n, (%)</td>
<td>29 (29%)</td>
<td>16 (16%)</td>
<td>5 (5%)</td>
<td>6 (6%)</td>
<td>2 (2%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>n, (%)</td>
<td>2 (2%)</td>
<td>47 (50%)</td>
<td>2 (2%)</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>n, (%)</td>
<td>6 (12%)</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>n, (%)</td>
<td>9 (19%)</td>
<td>22 (47%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>n, (%)</td>
<td>13 (9%)</td>
<td>19 (13%)</td>
<td>11 (7%)</td>
<td>9 (6%)</td>
<td>5 (3%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>0.57</td>
<td>0.29</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Severity at inclusion (plasma transfusion) (median, IQR)

<table>
<thead>
<tr>
<th></th>
<th>PELOD-2 score</th>
<th>Worst lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, %</td>
<td>8 (6-11)</td>
<td>2.2 (1.2-4.1)</td>
</tr>
<tr>
<td>n, %</td>
<td>7 (5-8)</td>
<td>2.4 (1.7-6.1)</td>
</tr>
<tr>
<td>n, %</td>
<td>7 (4-11)</td>
<td>2.7 (1.9-5.4)</td>
</tr>
<tr>
<td>n, %</td>
<td>7 (5-9)</td>
<td>2.1 (1.4-4.1)</td>
</tr>
<tr>
<td>n, %</td>
<td>7 (5-10)</td>
<td>5.1</td>
</tr>
<tr>
<td>p-value</td>
<td>0.05</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Support (n, %)

<table>
<thead>
<tr>
<th></th>
<th>Mechanical ventilation</th>
<th>ECLS</th>
<th>CRRT</th>
<th>MARS</th>
<th>Intermittent dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, %</td>
<td>87 (88%)</td>
<td>12 (12%)</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>n, %</td>
<td>82 (87%)</td>
<td>7 (7%)</td>
<td>7 (7%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>n, %</td>
<td>38 (73%)</td>
<td>1 (2%)</td>
<td>6 (12%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>n, %</td>
<td>42 (89%)</td>
<td>11 (23%)</td>
<td>5 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>n, %</td>
<td>122 (81%)</td>
<td>17 (11%)</td>
<td>12 (8%)</td>
<td>2 (1%)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.08</td>
<td>0.1</td>
<td>0.63</td>
<td>-</td>
<td>0.92</td>
</tr>
</tbody>
</table>

1 Some patients had more than one reason for admission.

2 The main other reasons for admission were oncologic-hematologic disease (19 patients), neurosurgery (5 patients), and metabolic disorders (4 patients).

3 CRRT: Continuous Renal Replacement Therapy; ECLS: Extracorporeal Life Support; MARS: Molecular Adsorbent Recirculating System; PELOD-2 score: Pediatric Logistic Organ Dysfunction 2 score (23); PICU: Pediatric Intensive Care Unit.
**Table 2: Patient outcomes according to primary indication for plasma transfusion**

<table>
<thead>
<tr>
<th></th>
<th>Critical bleeding (n=99)</th>
<th>Minor bleeding (n=94)</th>
<th>Planned procedure (n=52)</th>
<th>High risk of post-operative bleeding (n=47)</th>
<th>No bleeding, no procedure (n=151)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PELOD-2 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2* (n=402)</td>
<td>8 (5-10)</td>
<td>6 (5-8)</td>
<td>8 (4-11)</td>
<td>8 (5-9)</td>
<td>8 (5-10)</td>
<td>0.37</td>
</tr>
<tr>
<td>Day 5* (n=296)</td>
<td>7 (5-9)</td>
<td>6 (3-9)</td>
<td>8 (4-10)</td>
<td>7 (4-10)</td>
<td>8 (4-10)</td>
<td>0.43</td>
</tr>
<tr>
<td>Day 8* (n=227)</td>
<td>6 (4-9)</td>
<td>5 (3-9)</td>
<td>8 (4-10)</td>
<td>7 (5-9)</td>
<td>6 (3-9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Day 12* (n=162)</td>
<td>6 (3-7)</td>
<td>6 (2-9)</td>
<td>7 (3-10)</td>
<td>6 (3-8)</td>
<td>7 (3-9)</td>
<td>0.79</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>5 (1-15)</td>
<td>2 (1:8)</td>
<td>9 (2-25)</td>
<td>7 (3-13)</td>
<td>6 (2-17)</td>
<td>0.20</td>
</tr>
<tr>
<td>PICU length of stay (days)</td>
<td>11 (3-23)</td>
<td>7 (3-14)</td>
<td>18 (5-32)</td>
<td>11 (6-25)</td>
<td>12 (4-26)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>34 (35%)</td>
<td>14 (16%)</td>
<td>16 (32%)</td>
<td>9 (19%)</td>
<td>46 (31%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

1 Results are provided as median and interquartile range (IQR), except for mortality.
2 * Days after the first plasma transfusion.
3 PELOD-2 score: Pediatric Logistic Organ Dysfunction 2 score (23); PICU: Pediatric Intensive Care Unit.

---

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Figure legends

Figure 1: Proportion of the different primary indications to plasma transfusion. The indications were categorized as critical bleeding (massive bleeding, bleeding in specific sites, or bleeding requiring a surgical intervention or drainage, in red), minor bleeding (in orange), preparation for surgery or procedures (in yellow), at high risk of post-operative bleeding (in gray), and no bleeding, no planned procedure (in green).

Figure 2: Changes in International Normalized Ratio (INR, panel A) and activated Partial Thromboplastin Time (aPTT, panel B) after plasma transfusion, according to the indications for transfusion: critical bleeding (in red), minor bleeding (in orange), preparation for surgery or procedures (in yellow), at high risk of post-operative bleeding (in gray), and no bleeding, no planned procedure (in green). The median INR change was -0.2 (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 a circle (O) and asterisk (*) on the boxplot.

Figure 3: Boxplot of the changes in International Normalized Ratio (INR, panel A) and activated Partial Thromboplastin Time (aPTT, panel B) after plasma transfusion, according to the coagulation test prior to transfusion (n=281 and n=360 pairs of INR and aPTT, respectively). Mild outliers (< 1.5 * IQR) and extreme outliers (> 1.5 * IQR) are marked with a circle (O) and asterisk (*) on the boxplot.

Figure 4: Boxplot of the changes in International Normalized Ratio (INR, panel A) and activated Partial Thromboplastin Time (aPTT, panel B) after plasma transfusion, according to the dose of plasma transfusion in ml/kg and according to the baseline coagulation test (n=281 and n=360 pairs of INR and aPTT, respectively). Mild outliers
(< 1.5 * IQR) and extreme outliers (> 1.5 * IQR) are marked with a circle (O) and asterisk (*) on the boxplot.
Primary indication to plasma transfusion

- Critical bleeding: 22%
- Minor bleeding: 11%
- Preparation: 12%
- Post-op risk of bleeding: 34%
- No bleeding, no procedure: 12%

n = 443
A) Change in INR after plasma transfusion

B) Change in aPTT after plasma transfusion

Indications to plasma transfusion:
- Critical bleeding
- Minor bleeding
- Preparation
- Post-op risk of bleeding
- No bleeding, no procedure