Received Date : 07-Sep-2016

Revised Date : 23-Dec-2016

Accepted Date : 28-Dec-2016

Article type : Original Article

Factors influencing plasma transfusion practices in paediatric intensive care units around the world

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¹⁰PlasmaTV investigators are listed in the acknowledgments

Short Title: Factors influencing plasma transfusion practices

Funding: none

Competing interests: Dr Spinella is a consultant for Octapharma, Cerus and TerumoBCT. The other authors have no competing interests to disclose.

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/vox.12490](https://doi.org/10.1111/vox.12490)

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Number of words in abstract: 236

Number of words in manuscript: 2854

Abstract

Background and Objectives: Plasma transfusions are a frequent treatment worldwide, but many studies have reported a wide variation in the indications to transfuse. Recently, an international pediatric study also showed wide variation in frequency in the use of plasma transfusions: 25% of the centres transfused plasma to > 5% of their patients, whereas another 25% transfused plasma to < 1% of their patients. The objective of this study was to explore the factors associated with different plasma transfusions practices in these centers.

Materials and Methods: Online survey sent to the local investigators of the 101 participating centres, in February 2016. Four areas were explored: beliefs regarding plasma transfusion, patients' case-mix in each unit, unit's characteristics, and local blood product transfusion policies and processes.

Results: The response rate was 82% (83/101). 43% of the respondents believed that plasma transfusions can arrest bleeding, whereas 27% believe that plasma transfusion can prevent bleeding. Centres with the highest plasma transfusion rate were more likely to think that hypovolemia and mildly abnormal coagulation tests are appropriate indications for plasma transfusions ($p=0.02$ and $p=0.04$, respectively). Case-mix, centre characteristics, or local transfusion services were not identified as significant relevant factors.

Conclusion: Factors influencing plasma transfusion practices reflect beliefs about indications and the efficacy of transfusion in the prevention and management of bleeding as well as effects on coagulation tests. Educational and other initiatives to target these beliefs should be the focus of research.

Key words: Blood Component Transfusion; Plasma; Child; Critical Illness.

Introduction

Plasma transfusions continue to be commonly prescribed worldwide, in both adults and children, often in the emergency department, in the operating room, and in critical care units [1, 2]. But there is recognition that little quality evidence-based data exists to guide clinicians with regard to appropriate indications for plasma transfusion [3].

This lack of evidence seems to have led to a wide variation in plasma transfusions practices. A national epidemiological study in UK adult critical care reported a wide range in plasma indications as well an important variation in plasma dose [4]. A scenario-based survey of 187 pediatric critical care physicians also showed a wide variation in the indications to plasma transfusions [5]. There is also an important variation in plasma transfusion practices among different countries, as plasma represents 17.5% of all transfusions in the United States of America [6], but only 12.5% in France [7] and 12.3% in Switzerland [8]. Furthermore, over the last 5 years, the consumption has been stable in the United States of America (from 17.4% in 2008 to 17.5% in 2013), whereas it has slightly increased in France (from 11.4% in 2008 to 12.5% in 2013) and has decreased in Switzerland (from 16.2% in 2008 to 12.3% in 2013). We recently conducted an observational study on plasma transfusions in 101 centres from 21 countries [9]. We reported significant heterogeneity in plasma use: whereas a 25% of the centres transfused plasma to > 5% of their patients, another 25% transfused plasma to < 1% of their patients. Therefore, there seems to be a wide variation in the utilisation of plasma transfusions, but there is no information on the reasons for this observation.

Consequently, the objective of this study was to explore a range of factors and beliefs associated with plasma transfusion for critically ill children at all centres, and to compare the results for the different practices of plasma transfusion between those centres with the highest and the lowest rate of plasma transfusions.

Material and Methods

Study Design: This survey used an online questionnaire.

Study Population: The questionnaire was mailed to 101 paediatric critical care physicians from 21 countries, practicing in academic (PICUs) and who had participated in [a large international point-prevalence study on plasma transfusions](#) [9]. The latter study's objectives were to identify patient characteristics and to characterize indications leading to plasma transfusions in critically ill children as well as to assess the effect of plasma transfusions on coagulation tests. This point-prevalence study showed that 34% of transfused patients were not bleeding and had no planned procedure. Additionally, in most patients, coagulation tests were not sensitive to increased coagulation factor content resulting from plasma transfusion.

Development of Questionnaire: Determinants potentially affecting transfusion practices were first identified through consultation with eight experts in paediatric critical care, haematology, and transfusion practice, and all members of the study steering committee. Four different areas were recognized and addressed in the survey: a) beliefs regarding the efficacy of plasma transfusion (ability to prevent or stop bleeding, ability to improve abnormal coagulation tests, risks relating to nosocomial infections and acute lung injury, etc.); b) patient case-mix at each unit (proportion of surgical, cardiac or trauma patients, proportion of trauma patients, proportion of patients on extracorporeal support, predicted and observed mortality, etc.); c) characteristics of each unit (number of beds, number of critical care physicians, open versus closed unit model (prescriptions done by primary physicians versus only by critical care physicians), in-house critical care physician attendance at night, etc.); and d) support from the local transfusion service (involvement of a blood banker or haematologist in reviewing the decision to transfuse, computerized ordering process requiring the physician to justify the transfusion, etc.).

We [decided to](#) define mild, moderate and severe coagulopathy as an international normalized ratio (INR) below 1.5, between 1.5 and 2.5, and above 2.5, respectively, and/or activated partial thromboplastin time (aPTT) below 60, between 60 and 80, and above 80, respectively.

Formatting and Pretesting of Questionnaire: The survey instrument was developed in English by two authors (OK and SS) and was formatted using a website (www.surveymonkey.com). We first ensured the clarity of the questionnaire, its relevance, its completeness, and its accuracy by testing it on five co-authors who were not directly involved in the phrasing of the questions (PD, AS, PCS, MT, and SL). Some modifications were suggested and changes were made. [The survey is available as an online supplemental file.](#)

Administration of the Questionnaire: The survey administration was carried out according to the principles of Dillman [10] and the recommendation of Burns [11]. The first email was sent in February 2016, and two reminder mails were sent 2 and 4 weeks later.

Statistical Analysis: Binary and multiple choice results are presented as proportions. Results from the 7-point Lickert scale were categorized into “disagree” or “decreases the likelihood” (1 and 2), “intermediate opinion” (3, 4, and 5), and “agree” or “increases the likelihood” (6 and 7). [Continuous results are presented as median and interquartile range \(IQR\).](#)

The participating centres were categorized as having high, intermediate, and low rates of plasma transfusion according to the proportion of transfused patients in the observational study, i.e. > 75th percentile, between the 25th and 75th percentile, and < the 25th percentile, respectively. Differences between the centres with high and low rates of plasma transfusion were evaluated using the Mann-Whitney test. Differences between the centres from Europe, North America, and rest of the world were evaluated using the Kruskal-Wallis test. Differences were considered statistically significant when a two-sided α level was < 0.05. No adjustments were made for multiple comparisons, as the different questions are not independent and as this would increase the risk of type II errors. All statistical analyses were performed with SPSS version 22 for Mac (SPSS, Chicago, IL, USA).

Results

The participation rate was 82% (83/101). Respondents were from 21 countries: 57% from Europe, 34% from North America, and 9% from the rest of the world (Australia, Chile, Japan, New Zealand, and Saudi Arabia). The median size of the participating PICUs was 13 beds (IQR 10-23). The median number of admissions per year was 700 (IQR 400-1025). The median mortality rate was 4 (IQR 2-5). 36% of the centres did not offer ECMO, 29% had < 10 ECMO runs per year, and 35% had > 10 ECMO runs per year. 68% of the centres treated patients with liver failure and/or liver transplants. However, the median number of these liver patients with liver failure and/or liver transplants was only 4 per year (IQR 2-10).

Overall beliefs on the benefits and harm of plasma transfusions

Whilst only 27% of the respondents agreed that plasma transfusions can prevent bleeding, 43% agreed that they can stop bleeding. 29% agreed that they can improve moderately abnormal coagulation tests (Figure 1). 95% of the respondents agreed that plasma transfusions should not be used as volume expanders.

37% of the respondents thought that plasma transfusions are associated with increased risk of adverse reactions, such as increased risk of acute respiratory distress syndrome (ARDS), circulatory overload, and nosocomial infection.

Indications for plasma transfusion

When coagulation tests are only mildly abnormal (INR < 1.5 and aPTT < 40), even significant bleeding (3ml/kg through a thoracocentesis drain) would not prompt plasma transfusion for 62% of the respondents, and a 29% would wait until the INR is > 2.5 to transfuse plasma (Table 1).

When coagulation tests are severely abnormal (INR > 2.5 and/or aPTT > 80), significant bleeding would prompt plasma transfusion for 71% of the respondents, but only 17% would transfuse plasma if the bleeding was minor.

Moderate and critical bleeding, as well as an INR > 2.5, were reported to increase the likelihood of plasma transfusion, whereas an INR < 1.5 and a previous reaction to plasma transfusion were reported to decrease the likelihood of plasma transfusion (Figure 2). Hypovolemia, mild bleeding, thrombocytopenia, anaemia, and hypoxemia were reported not to affect the likelihood of plasma transfusion.

Beliefs on predictive value of coagulation tests

Altogether, 30% of the respondents believed that coagulation tests could reliably predict bleeding, although there were differences among the stated predictability of different tests: 37% of the respondents believed that INR could predict bleeding, 34 % thromboelastographic (TEG) or thromboelastometric (ROTEM) tests, 29 % aPTT, 27% Prothrombin Time (PT), and 22% fibrinogen ($p=0.01$, Figure 3).

Respondents who believed that INR predicted bleeding were more likely to think that plasma transfusions can prevent bleeding ($p=0.01$), plasma transfusions can stop bleeding ($p=0.02$), plasma transfusions can improve mildly abnormal coagulation tests ($p=0.001$), plasma transfusions are an appropriate treatment for patients at risk of post-op bleeding and with mild coagulopathy ($p=0.02$), and that plasma transfusions do not induce acute respiratory failure ($p<0.001$). However, there was no association between beliefs on predictive value of coagulation tests and physicians' or centres' demographics.

Local transfusion service and policies

48% of the centres allowed only their physicians trained in critical care to prescribe plasma transfusions.

However, other centres also allowed anaesthesiologists (31%), surgeons (29%), cardiac surgeons (28%), and haematologists (24%) to directly prescribe plasma transfusion for patients in the PICU. 60% of the centres required junior physicians (residents or fellows) to seek supervision by board-certified critical care physicians in order to prescribe plasma transfusion.

Only 12% of the centres had a written protocol to guide plasma transfusions among which 50% did not update their protocol within a two-year period. 90% of the protocols used INR as an indicator to plasma transfusion, 30% used PT, 60% used aPTT, and 40% also used TEG or ROTEM.

66% of the centres had to justify plasma prescription to the Blood Bank or Transfusion Services, while ordering the plasma unit. However, these individuals rarely seemed to challenge a request for plasma which was reported in < 6% of the centres.

75% of the centres did not carry out any retrospective review regarding the use of plasma transfusions in their centre. Of those centres that undertook regular audit, 50% had this review at least every three months. Blood bank staff or transfusion services were involved in 71% of the reviews, haematologists in 42%, critical care physicians in 33%, quality officers in 19%, and anaesthesiologists in 5%.

Comparison between centres with higher and lower rates of plasma transfusions

Hypovolemia and mildly abnormal coagulation tests were more frequently believed to be appropriate indications to plasma transfusions in centres with a higher rate of plasma transfusions (24% versus 14%, $p=0.02$ and 5% versus 0%, $p=0.04$, respectively). These centres were more frequently situated in Europe (30% versus 19%, $p=0.04$).

There were no other statistically significant differences between centres with high and low rates of plasma transfusions, in terms of case-mix (proportion of cardiac surgery, extracorporeal life support, etc.), PICU characteristics (number of beds, number of admissions per year, etc.), or plasma transfusion policies (Table 2). However, the centres with lower plasma transfusion rates tended to have less positive views on plasma transfusions (lower ability to stop bleeding, higher risk of transfusion associated nosocomial infections and acute respiratory failure), and more doubts that coagulation tests could predict bleeding. Furthermore, the centres with lower plasma transfusion rates tended to be larger and have fewer cardiac surgery admissions. Finally, there was a trend suggesting that PICUs with senior physicians attending during the night-time and supervision of prescriptions by junior physicians have lower plasma transfusion rates.

Barriers to changing plasma transfusion practices

A majority of the respondents reported that the lack of high quality data to motivate practice change was the most important barrier to changing plasma transfusion practices (Table 3).

Discussion

The results of this survey highlight several issues pertaining to plasma transfusion practices and emphasize the very divergent views on the benefits and harms of plasma transfusion.

Our survey showed that many respondents believe that plasma transfusions can both prevent and stop bleeding as well as correct mildly abnormal coagulation tests. However, there are only a few large randomized controlled trials, in very specific clinical settings, that have evaluated the effectiveness of plasma to prevent or stop bleeding. In the first trial, the Northern Neonatal Nursing Initiative (NNNI) Trial Group randomised 776 neonates to plasma or to volume expanders (gelofusin or dextrose-saline) and did not show any differences in the prevention of intra-ventricular haemorrhage [12]. More recently, the PROPPR trial recruited adults with severe trauma and major bleeding, and did not identify that mortality was affected by higher doses of plasma and platelet transfusions [13]. Etemadrezai et al randomized 90 adults with severe closed head injury to receive plasma transfusions versus normal saline and of note reported that new intracerebral hematomas in follow-up CT scans were more common in the plasma transfusion group versus the normal saline group [14]. Recently, Müller et al randomized critically ill adults with INR between 1.5 and 3.0 and who required a procedure to receive prophylactic plasma transfusion versus normal saline [15]. The rate of bleeding events was similar in both groups, supporting the view that plasma transfusion does not prevent bleeding events, although the study failed to recruit to target. In general, data from both adult and paediatric populations indicate that plasma transfusions fail to correct mildly abnormal coagulation tests ($\text{INR} < 2.5$) [9, 16, 17]. Therefore, most of the perceived benefits of plasma transfusions are not based on solid evidence.

In our study, 30% of the respondents believe that routinely used coagulation tests can predict bleeding. These physicians were more like to also believe that plasma transfusions could prevent or stop bleeding. However, many studies show that abnormal coagulation tests are not associated with increased risk of bleeding in association with various procedures (angiography, bronchoscopy, direct and transjugular liver biopsy, and thoracocentesis) [18]. A recent randomized controlled trial, conducted in critically ill adults with INR between 1.5 and 3 undergoing invasive procedures, has shown that coagulation tests and individual coagulation factor levels were similar in patients regardless of whether bleeding occurred [19]. Given that 41% of the respondents identified the lack of accurate tests to predict bleeding as a major barrier to improving plasma transfusion practices, one avenue of research should evaluate the development of new and reliable strategies to improve the identification of patients at risk of bleeding as a priority.

Our survey indicates that only 37% of the respondents believe that plasma transfusions are associated with adverse effects, and that by implication plasma transfusion is a very safe intervention. However, observational data in both adults and children indicate that plasma transfusions are associated with more nosocomial infections [20], more respiratory failure [21-23], more multiple organ dysfunction [20, 23], increased PICU length of stay [20], and higher mortality [24]. These associations could be due to indication bias and may not actually reflect

increased risk with plasma transfusion. Hemovigilance studies also show that plasma transfusions are frequently associated with transfusion related acute lung injury (TRALI), an eight-fold increased risk compared to that associated with red cell transfusion [25].

Overall the survey was not able to identify factors associated with high versus low plasma transfusion rates although this may have been influenced by demographic factors. Centres transfusing more frequently tend to be located in Europe, and were more often inclined to believe that hypovolemia and mildly abnormal coagulation tests were appropriate indications for plasma transfusion. Although the patient case-mix and PICU characteristics were not significantly different between centres with high and low plasma transfusion rates, there were trends that suggested that larger PICUs with senior physicians attending during the night-time and supervision of prescriptions by junior physicians might be important elements that favour more restrictive plasma transfusion. However, this might also suggest that other factors not captured by this survey could be relevant; these might include multidisciplinary training on blood transfusion issues or unofficial policies affecting local practice. It is also possible that there is an association between the PICU characteristics (number of beds, in-house senior physicians) are different in Europe and in North America. Due to the small sample size, this was not evaluated in a multiple regression model.

Certain limitations associated with the conduct of this survey must be recognized. Firstly, the small sample size and the substantial heterogeneity of the replies received may explain the fact that there were few statistically significant differences between centres with high and low transfusion rates. Secondly, a selection bias may have occurred given that the participating centres represented a small proportion of the PICUs existing worldwide who were willing to participate in the original observational study. Therefore, it is not known if the answers obtained from those sites who participated can be generalized to other centres.

Our results suggest that there are very divergent views on the benefits and harms of plasma transfusions. The next step should focus on educational and training objectives that would lead to more evidence based practice in paediatric critical care. These interventions should certainly be scientifically evaluated.

In conclusion, this survey assessed the beliefs of paediatric critical care physicians on plasma transfusions. The most striking observation resulting from this survey is the great diversity of opinion existing among paediatric physicians with regard to the potential benefits and risks of plasma. This clearly highlights the importance of implementing educational initiatives and the need for stronger evidence from future randomized controlled trials.

Acknowledgments

We would like to thank all of the PlasmaTV investigators.

PlasmaTV investigators: **Australia:** Warwick Butt, Carmel Elope, Kym Bain (Royal Children's Hospital, Melbourne); Simon Erickson, Nathan Smalley (Princess Margaret Hospital for Children, Perth; Tavey Dorofaeff, Debbie Long (Royal Children's 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, ShancyRooze (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-Andre Dugas, Louise Gosselin (Centre Mère Enfant Soleil, CHU de Québec, Québec, QC) ; Miriam Santschi (CHUS, Sherbrooke, QC). **Chile:** Bettina Von Dessauer, Nadia Ordenes (Hospital De Niños Roberto Del Río, Santiago). **Denmark:** Arash Afshari, Lasse Hoegh Andersen, Jens Christian Nilsson, Mathias Johansen, Anne-Mette Baek Jensen (Rigshospitalet, University of Copenhagen, Copenhagen). **Ecuador:** Santiago Campos Mino, Michelle Grunauer (Hospital de los Valles, Universidad San Francisco de Quito, Quito). **France:** Nicolas Joram (Hôpital mère enfant, Nantes) ; Nicolas Rouillet-Renoleau (Hôpital Gatién de Clocheville, CHU Tours, Tours) ; Etienne Javouhey, Fleur Cour-Andlauer, Aurélie Portefaix (Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Lyon) ; Olivier Brissaud, Julie Guichoux (Hôpital des Enfants, Bordeaux) ; Valérie Payen (CHU Grenoble, Grenoble) ; Pierre-Louis Léger (Hôpital Armand-Trousseau, Paris) ; Mickael Afanetti (Hopitaux Pédiatriques CHU Lenval, Nice) ; Guillaume Mortamet (Hopital Necker, Paris) ; Matthieu Maria (Hôpital d'Enfants CHRU de Nancy, Nancy) ; Audrey Breining (Hopitaux Universitaires de Strasbourg, Strasbourg) ; Pierre Tissieres (Hôpital Kremlin-Bicêtre, Paris) ; Aimée Dorkenoo (CHRU Lille, Lille) ; Anna Deho (Hopital Robert Debré, Paris). **Germany:** Harry Steinherr (Medizinische Hochschule Hannover, Hannover). **Greece:** Filippia Nikolaou (Athens Children Hospital P&A Kyriakou, Athens). **Italy:** Anna Camporesi (Children Hospital Vittore Buzzi, Milano) ; Federica Mario (Department of Women's and Children's Health, Padua). **Japan:** Tatsuya Kawasaki, Shinya Miura (Shizuoka Children's Hospital, Shizuoka City). **New Zealand:** John Beca, Miriam Rea, Claire Sherring, Tracey Bushell (Starship Children's Hospital, Auckland). **Norway:** Gunnar Bentsen (Oslo University Hospital – Rikshospitalet, Oslo). **Portugal:** Alexandra Dinis (Hospital Pediátrico – CHUC, Coimbra) ; Gabriela Pereira (UCIP Hospital Dona Estefânia, Lisbon) ; Marisa Vieira (Hospital de Santa Maria, Lisbon) ; Marta Moniz (Hospital Prof. Dr Fernando Fonseca, Amadora). **Saudi Arabia:** Saleh Alshehri (King Saud Medical City, Riyadh) ; Manal Alasnag, Ahmad Rajab (King Fahd Armed Forces Hospital, Jeddah). **Slovakia:** Maria Pisarcikova (DFN Kosice, Kosice). **Spain:** Iolanda Jordan (Hospital Sant Joan de Déu, Barcelona) ; Joan Balcells (Hospital Vall d'Hebron, Barcelona) ; Antonio Perez-Ferrer, Jesús de Vicente Sánchez, Marta Vazquez Moyano (La Paz University Hospital, Madrid) ; Antonio Morales Martinez (Malaga Regional University Hospital, Malaga) ; Jesus Lopez-Herce, Maria Jose Solana (Hospital General Universitario Gregorio Marañón, Madrid) ; Jose Carlos Flores González (Puerta del Mar University Hospital, Cadiz) ; Maria Teresa Alonso (Hospital Virgen del Rocío, Sevilla) ; Manuel Nieto Faza (Hospital Universitario Cruces, Bilbao). **Switzerland:** Marie-Hélène Perez, Vivianne Amiet (CHUV, Lausanne) ; Carsten Doell (Kinderspital Zürich, Zürich) ; Alice Bordessoule (Geneva University Hospital, Geneva). **The Netherlands:** Suzan Cochijs-den Otter, Berber Kapitein (Erasmus MC – Sophia Children's Hospital, Rotterdam) ; Martin Kneyber (Beatrix Children's Hospital, Groningen). **United Kingdom:** Joe Brierley, Vanessa Rea, Stephen McKeever (Great Ormond Street, London) ; Andrea Kelleher (Royal Brompton Hospital, London) ; Barney Scholefield, Anke Top, Nicola Kelly, SatnamVirdee (Birmingham Children's Hospital, Birmingham) ; Peter Davis, Susan George (Bristol Royal Hospital for Children, Bristol) ; Kay C Hawkins, Katie McCall, Victoria Brown (Royal Manchester Children's Hospital, Manchester) ; Kim Sykes (University Hospital Southampton, Southampton) ; Richard Levin, Isobel MacLeod (Yorkhill Children's Hospital, Glasgow) ; Marie Horan, Petr Jirasek (Alder Hey Children's hospital,

Liverpool) ; David Inwald, Amina Abdulla, Sophie Raghunanan (Imperial College Healthcare, London) ; Bob Taylor (Royal Belfast Hospital for Sick Children, Belfast) ; Alison Shefler, Hannah Sparkes (Oxford University Hospitals, Oxford). **USA:** Sheila Hanson, Katherine Woods, David Triscari, Kathy Murkowski (Children's Hospital of Wisconsin, Milwaukee, WI) ; Caroline Ozment (Duke University, Durham, NC) ; Marie Steiner, Dan Nerheim, Amanda Galster (University of Minneapolis, Minneapolis, MN) ; Renee Higgerson, LeeAnn Christie (Dell Children's Medical Center, Austin, TX) ; Phil Spinella, Daniel Martin, Liz Rourke (Washington University in St. Louis, Saint Louis, MO) ; Jennifer Muszynski, Lisa Steele, (Nationwide Children's Hospital, Columbus, OH) ; Samuel Ajizian, Michael C McCrory (Wake Forest School of Medicine, Winston-Salem, NC) ; Kevin O'Brien, Christopher Babbitt, Erin Felkel, Glenn Levine (Miller Children's Hospital Long Beach, Long Beach, CA) ; Edward J Truemper, Mabelle Zink (Children's Hospital and Medical Center, Omaha, NE) ; Marianne Nellis (NYPH - Weill Cornell Medical College, New York, NY) ; Neal J Thomas, Debbie Spear (Penn State Hershey Children's Hospital, Hershey, PA) ; Barry Markovitz, Jeff Terry, Rica Morzov (Children's Hospital Los Angeles, Los Angeles, CA) ; Vicki Montgomery, Andrew Michael, Melissa Thomas (University of Louisville and Kosair Children's Hospital, Louisville, KY) ; Marcy Singleton, Dean Jarvis, Sholeen Nett (Dartmouth Hitchcock Medical Center, Lebanon, NH) ; Douglas Willson, Michelle Hoot (Virginia Commonwealth University, Richmond, VA) ; Melania Bembea, Alvin Yiu (Johns Hopkins University, Baltimore, MD) ; David McKinley, Elizabeth Scarlett, Jennifer Sankey, Minal Parikh (Geisinger, Danville, PA) ; E. Vincent S. Faustino (Yale School of Medicine, New Haven, CT) ; Kelly Michelson, Jay Riling, Laura Campbell (Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL) ; Shira Gertz (Hackensack University Medical Center, Hackensack, NJ) ; Jill M. Cholette (University of Rochester, Rochester, NY) ; Asumthia Jeyapalan (Holtz Children's Hospital-Jackson Memorial Hospital, Miami, FL) ; Margaret Parker (Stony Brook University, Stony Brook, NY) ; Scot Bateman, Amanda Johnson (UMass Memorial Children's Medical Center, Worcester, MA).

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Tables

Table 1: Indications for plasma transfusion according to clinical situation, in critically ill children with an INR between 1.5 and 2.5 and/or an aPTT between 60 and 80 sec.

	Plasma transfusion is		
	Not indicated	Intermediate opinion	Indicated
Clinically significant bleeding	2%	27%	71%
Minor bleeding	31%	52%	17%
Before a procedure	23%	45%	32%
At risk of bleeding after surgery	19%	54%	27%
At risk of bleeding due to medical condition	29%	51%	20%
INR, international normalized ratio; aPTT, activated partial thromboplastin time.			

Table 2: Variables according to rate of plasma transfusion.

Variable	Low rate (n=21)	Intermediate rate (n=41)	High rate (n=21)	p value ^a
<i>Respondents' beliefs (proportion of agreement with the statement)</i>				
Plasma transfusions can prevent bleeding.	19%	29%	28%	0.83
Plasma transfusions can stop bleeding.	24%	49%	52%	0.08
Plasma transfusions can improve moderately abnormal coagulation tests.	38%	22%	33%	0.99
Plasma transfusion should be used as volume expansion.	0%	0%	0%	0.57
Plasma is appropriate for a patient with mildly abnormal coagulation tests who is mildly bleeding.	0%	5%	5%	0.04
Plasma is appropriate for a patient with severely abnormal coagulation tests with clinically significant bleeding.	81%	93%	100%	0.06
Hypovolemia increases the likelihood of plasma transfusion.	14%	25%	24%	0.02
Plasma transfusions are associated with increased risk of nosocomial infections.	19%	36%	43%	0.50
Plasma transfusions are associated with increased risk of acute respiratory failure.	19%	39%	52%	0.17
Plasma transfusions are associated with increased risk of circulatory overload.	14%	41%	17%	0.15
PT can predict bleeding.	24%	29%	24%	0.45
INR can predict bleeding.	24%	36%	52%	0.57
aPTT can predict bleeding.	14%	34%	33%	0.40
Fibrinogen level can predict bleeding.	24%	24%	14%	0.56

ROTEM or TEG can predict bleeding.	10%	49%	24%	0.58
<i>PICU characteristics</i>				
Median number of PICU beds	14	18	12	0.14
Median number of PICU admissions per year	700	775	600	0.42
Median proportion of admissions for post-op general surgery	20%	20%	20%	0.55
Median proportion of admissions for post-op cardiac surgery	15%	20%	30%	0.30
Median proportion of admissions for post-op neurosurgery	20%	20%	20%	0.26
Median proportion of admissions for trauma	20%	20%	10%	0.44
Median ECMO runs per year	3	7	5	0.90
Median number of liver patients per year	2	3	2	0.38
<i>Prescription process and policies</i>				
Junior physicians can prescribe plasma transfusions without supervision.	30%	28%	42%	0.25
In-house board-certified critical care physician at night.	60%	55%	33%	0.11
Blood bank or transfusion services challenge some plasma prescription.	35%	42%	33%	0.77

Plasma transfusion rates were categorized as low (< 1% of the PICU patients receiving plasma transfusions), intermediate (between 1% and 5%), and high (> 5%).

^a Mann-Whitney test to compare units with lower versus higher plasma transfusion rates.

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; ROTEM, rotational thromboelastometry; TEG, thromboelastography; ECMO, extracorporeal membrane oxygenation; PICU, paediatric intensive care unit.

Table 3: Barriers to changing plasma transfusion practices.

	Very important	Intermediate opinion	Unimportant
Lack of high quality data to motivate practice change	59%	27%	14%
Absence of reliable tests to predict bleeding	41%	45%	12%
Absence of international recommendations	41%	36%	23%
Colleagues' opinions	27%	42%	31%
Plasma transfusions are beneficial and do not cause harm	16%	33%	51%
Protocols are not easily updated	11%	25%	64%

Figure legends

Figure 1: Beliefs regarding plasma transfusion.

Figure 2: Likelihood of different indications to increase or decrease plasma transfusion.

INR, international normalized ratio.

Figure 3: Beliefs regarding the ability of coagulation tests to predict bleeding.

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time;

ROTEM, rotational thromboelastometry; TEG, thromboelastography.

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Title:

Factors influencing plasma transfusion practices in paediatric intensive care units around the world

Date:

2017-02-01

Citation:

Karam, O., Demaret, P., Duhamel, A., Shefler, A., Spinella, P. C., Tucci, M., Leteurtre, S. & Stanworth, S. J. (2017). Factors influencing plasma transfusion practices in paediatric intensive care units around the world. VOX SANGUINIS, 112 (2), pp.140-149. <https://doi.org/10.1111/vox.12490>.

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