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Authors

Russell, Robert
Bauer, David F
Goobie, Susan M
et al.

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Plasma and platelet transfusion strategies in critically ill children following severe trauma, traumatic brain injury and/or intracranial hemorrhage: From the Transfusion and Anemia Expertise Initiative – Control/Avoidance of Bleeding (TAXI-CAB)

Robert Russell, MD, MPH¹, David F. Bauer, MD, MPH², Susan M. Goobie, MD, FRCPC³, Thorsten Haas, MD⁴, Marianne E. Nellis, MD, MS⁵, Daniel K. Nishijima, MD, MAS⁶, Adam M. Vogel, MD⁷, Lacroix Jacques, MD, FRCPC⁸, Transfusion and Anemia Expertise Initiative Control/Avoidance of Bleeding (TAXI-CAB), Pediatric Critical Care Blood Research Network (BloodNet), Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

¹ Chair, group on Trauma; Associate Professor of Surgery, Pediatric General Surgery; Director of Trauma, Children's of Alabama, Birmingham, USA.

² Associate Professor, Pediatric Neurosurgery, Baylor College of Medicine, Texas Children's Hospital, Houston, USA.

³ Associate Professor of Anaesthesiology, Harvard Medical School. Senior Associate in Perioperative Anesthesia, Boston Children's Hospital, Dept. of Anesthesiology, Critical Care & Pain Medicine, Boston Children's Hospital, Boston, USA.

⁴ Professor of Anesthesiology, Department of Pediatric Anesthesia, Zurich University Children's Hospital, Zurich, Switzerland.

⁵ Associate Professor of Pediatrics, Division of Pediatric Critical Care Medicine, Weill Cornell Medicine, New York, USA.

⁶ Associate Professor of Emergency Medicine, Vice Chair of Research, Associate Research Director, Department of Emergency Medicine, Medical Director for the CTSC Clinical Research Center and Trial Innovation Network, University of California Davis School of Medicine, Sacramento, USA.

⁷ Associate Professor, Surgery and Pediatrics. Texas Children's Hospital and Baylor College of Medicine, Houston, Texas, USA.

⁸ Chair, group on traumatic brain injury and intracranial injury; Professor of Pediatrics, Division of Pediatric Critical Care, Department of Pediatrics, Sainte-Justine Hospital, Université de Montréal, Montreal, Canada.

Address Correspondence to: Dr. Jacques Lacroix, Sainte-Justine Hospital, room 3737, 3175 Côte Sainte-Catherine, Montreal (Quebec), Canada H3T 1C5, Telephone: (514) 345 4931, extension 5549, Fax: (514) 345 7731, jlacroix052@gmail.com.

Conflicts: Dr Thorsten Haas is consultant for Octapharma. Dr Daniel Nishijima is consultant for Bristol-Myers-Squibb. The other authors did not report any conflicts of interest.

Transfusion and Anemia Expertise Initiative – Control/Avoidance of Bleeding (TAXI-CAB) Members are listed in Appendix 1
Social media tweet

#Bleeding caused by #coagulopathy or low #platelet count should guide plasma and platelet #transfusion in severe pediatric trauma, brain injury or intracranial hemorrhage.

Abstract

Objectives: To present consensus statements and supporting literature for plasma and platelet transfusions in critically ill children with severe trauma, traumatic brain injury (TBI) and/or intracranial hemorrhage (ICH) from the Transfusion and Anemia EXpertise Initiative – Control/Avoidance of Bleeding (TAXI-CAB).

Design: Systematic review and consensus conference of international, multidisciplinary experts in platelet and plasma transfusion management of critically ill children.

Setting: Not applicable.

Patients: Critically ill neonates and children with severe trauma, traumatic brain injury (TBI) and/or intracranial hemorrhage (ICH).

Interventions: None

Measurements and Main Results: A panel of 8 experts developed expert based statements for plasma and platelet transfusions in critically ill neonates and children with severe trauma, TBI and/or ICH. These statements were reviewed and ratified by the 29 TAXI-CAB experts. A systematic review was conducted using MEDLINE, EMBASE, and Cochrane Library databases, from inception to December 2020. Consensus was obtained using the Research and Development/University of California, Los Angeles (UCLA) Appropriateness Method. Results were summarized using the Grading of Recommendations Assessment, Development, and Evaluation method. We developed 1 good practice statement and 6 expert consensus statements.

Conclusions: The lack of evidence precludes proposing recommendations on monitoring of the coagulation system and on plasma and platelets transfusion in critically ill pediatric patients with severe trauma, severe TBI or non-traumatic ICH.

Keywords

child; critical care; evidence-based; guidelines; intensive care; intracranial hemorrhage; pediatrics; plasma; platelet; transfusion; trauma; traumatic brain injury

INTRODUCTION

Plasma transfusions are frequently prescribed to treat or to prevent bleeding caused by a coagulation disorder. Likewise, platelets are transfused to treat or to prevent bleeding caused by thrombocytopenia or platelet dysfunction. Among 356,583 pediatric trauma patients recorded in the American College of Surgeons National Trauma Databank (2010–2012), 1072 (7.6%) received at least one plasma transfusion, 886 (6.3%) received at least one platelet transfusion, 96 (0.7%) received whole blood, and 173 (0.04%) received a massive transfusion (MT) [1].

In 2013, the Joint Commission and the American Medical Association Convened Physician Consortium National Summit ranked transfusion of blood products second among five overused treatments that may affect patient safety [1, 2]. The transfusion of plasma and platelets can be life-saving, but may also cause clinically significant adverse effects, such as acute respiratory distress syndrome and circulatory overload [3]. In national audits

conducted in the United Kingdom, about 20% of blood product usage is outside guideline recommendations [4]. Clearly, clinical decision-making can be improved to best guide plasma and platelet transfusion practice in patients admitted to pediatric intensive care units (PICU). This sentiment is also true for critically ill pediatric patients with severe trauma, moderate to severe traumatic brain injury (TBI) or non-traumatic intracranial hemorrhage (ICH).

There is some evidence that protocols or guidelines can improve clinical practice in the ICU environment [5–12]. The purpose of “Transfusion and Anemia Expertise Initiative - Control/Avoidance of Bleeding” (TAXI-CAB) was to use structured and systematic methods to help practitioners in their decision-making when considering plasma and platelet transfusion in critically ill children. In this paper, we report our assessment of the literature on plasma and platelet transfusion in pediatric patients with severe trauma, moderate to severe TBI or non-traumatic ICH admitted to the pediatric intensive care unit (PICU), i.e., by definition experiencing critical illness.

METHODS

The search strategy, item selection and recommendation generation used to identify and select references for systematic review and to develop recommendation are detailed in the general manuscript of TAXI-CAB [13]. Briefly, we searched Ovid MEDLINE®, Ovid EMBASE, and Cochrane Library (Wiley) from inception through December 2020 using a combination of medical subject heading terms and text words to define concepts of plasma or platelet transfusion, transfusion triggers, laboratory tests to assess efficacy of transfusion in children admitted to the PICU with severe trauma, severe TBI and/or ICH. For articles selected for inclusion, reference lists and citing articles were selected from Scopus (Elsevier) and screened. Two reviewers independently reviewed all citations and performed data extraction and assessments of bias. Literature was reviewed for relevance to this subgroup. Research Electronic Data Capture (REDCap) hosted at Weill Cornell Medicine was used for standardized data extraction. We used a standardized data extraction form to construct evidence tables and graded the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [14].

Eight experts participated in the development of recommendations from this subgroup (five for severe trauma and three for TBI and/or ICH). A panel of 29 experts convened in an on-line format over 18 months to develop good practice statements, recommendations and, when evidence was lacking, expert consensus statements. Good practice statements are those in which there is high-level of certainty that the practice will do more good than harm, but there is little in the way of supporting literature evidence. Expert consensus statements are based on the expert opinion of the group, but in areas where research is likely needed. All statements from each subgroup were reviewed by the full panel of experts and voted on using the Research and Development/University of California, Los Angeles (UCLA) Appropriateness Method. Agreement was defined a priori as >80% of all experts. The recommendations and statements are intended to apply to infants, children and adolescents. Prophylactic transfusions are those prescribed to patients at risk of bleeding, whereas therapeutic transfusions are given to those with active bleeding.

Definitions

Severe trauma —Acute body injury caused by any kind of physical accidental and non-accidental trauma, including blunt and penetrating trauma (e.g., significant hemorrhagic trauma to the torso). In this study, we did not consider severe burn as traumatic cases.

Traumatic brain injury (TBI) —Acute brain injury caused by any kind of physical accidental and non-accidental trauma, including blunt and penetrating trauma. We did not consider as TBI cases of hypoxic brain injury caused by near-drowning, strangulation or acute respiratory insufficiency, nor cases of intoxication.

Intracranial hemorrhage (ICH) —Acute intracranial venous or arterial hematoma or intracerebral bleeding caused by a traumatic injury or by the rupture of an intracranial blood vessel.

Deteriorating neurologic function —Was considered to be present if the patient had clinical deterioration in examination with worsening neurologic deficit, decreasing Glasgow coma scale (GCS) score, or change in pupillary light reflex. This finding could be caused by elevated intracranial pressure over 20 mmHg or expanding cerebral hematoma.

Bleeding —Was defined as severe or moderate according to the Bleeding Assessment Scale in Critically Ill Children (BASIC) [15].

Hemorrhagic shock —Defined as hemodynamic instability caused by a severe bleeding.

RESULTS

Study selection

Searching studies for (1) severe trauma and (2) TBI and/or ICH identified 3885 and 2565 abstracts, respectively. After duplicates were removed, a total of 3434 and 2215 were screened. Then, out of 105 and 93 full text manuscripts about (1) severe trauma and (2) TBI and/or ICH, respectively, we selected 29 and 1 paper for detailed review (see Figures 1 and 2). These papers underwent data extraction and assessment of bias in order to generate statements (see Supplemental Data Tables 1 and 2); one good practice statement and six expert consensus statements were produced. The voting data, including the number of voting experts and median score, are provided for each statement.

Good practice statement

- 1. In critically ill pediatric patients with severe trauma, moderate to severe TBI or non-traumatic ICH, we suggest close monitoring of bleeding, including evaluation of potential expansion of ICH, and serial evaluation of the coagulation system. 83% Agreement (n=24), Median 8 (IQR 7–9).**

Rationale —Clinically significant coagulopathy is frequent in children with severe trauma. It can cause major hemorrhage and/or hemorrhagic shock. Severe TBI by itself

can cause a clinically significant coagulation disorder [16]. Miner et al. [17] reported that 71% of children with severe head trauma show some alteration of the coagulation system (platelets, prothrombin time, fibrinogen, etc.), including evidence of disseminated intravascular coagulopathy (DIC) in some cases. While, the pathophysiology of trauma-induced coagulopathy is debated, an imbalance between procoagulant factors, anticoagulant factors, platelets, endothelium and fibrinolysis is present [18]. Additionally, hypothermia, acidosis and resuscitation with hypocoagulable fluids (i.e., hemodilution) can worsen trauma-induced coagulopathy.

There is an absence of high-quality data to guide best plasma and platelet transfusion strategies in pediatric patients with severe trauma, moderate to severe TBI or non-traumatic ICH. Nevertheless, given the available data, we suggest serial evaluation of the coagulation system, including standard coagulation tests - prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen and/or platelet count - in pediatric patients with severe trauma, moderate to severe TBI or non-traumatic ICH. In patients who are having active resuscitation for hemorrhagic shock, serial monitoring of the blood volume and coagulation system is suggested while active resuscitation is ongoing. The frequency of the monitoring is at the discretion of the provider. Once bleeding stops (either by medical or surgical interventions), liberalization of the monitoring can be considered until values trend toward normal. In some instances, viscoelastic testing (VET) (thromboelastometry, TEG, or rotational thromboelastometry, ROTEM) can be considered to help decision-making (see statement #4).

Expert consensus statements

2. **In critically pediatric patients with severe trauma, moderate to severe traumatic TBI or in critically ill children with non-traumatic ICH, there is insufficient evidence to make any recommendation regarding specific indications or transfusion strategies to direct plasma or platelet transfusion.** *83% Agreement (n=24), Median 8 (IQR 7–9).*

Rationale —There is insufficient strong high-quality evidence needed in order to make any recommendations regarding indications for plasma or platelet transfusion in pediatric patients with severe trauma, severe traumatic ICH or in critically ill children with non-traumatic ICH.

3. **In critically injured pediatric patients in hemorrhagic shock following trauma, a resuscitation strategy of red blood cells (RBCs), plasma, and platelets in ratios between 2:1:1 to 1:1:1 might be considered.** *90% Agreement (n=21), Median 8 (IQR 7.5–9).*

Rationale —MT may be required in critically injured pediatric patients in hemorrhagic shock following trauma. While there are many definitions of MT, each differ in timeframe and volume of blood products administered. For example, giving >10% of blood volume per minute, >50% within 3 hours, >100% of total blood volume or >10 RBC units in adults within 24 hours are considered as MT by different investigators [19]. Neff et al. [20] defined MT as the transfusion of 40 ml/kg of blood products over 24 hours because this

volume/day reliably identifies critically injured children at high risk for early in-hospital death. The incidence rate of MT, when defined as 40 mL/kg/24 h, among 356,583 pediatric civilian trauma patients was 0.04% [1]. MT is rarely required in pediatric trauma, but it is potentially life-saving in patients with hemorrhagic shock.

MT can be delivered by the transfusion of RBC, plasma and platelets altogether in a given ratio or with transfusion of whole blood. Kinslow et al [19] conducted a systematic review on the efficacy of different plasma/RBC ratios (note the sequence: not RBC/plasma ratios as listed in the statement) to decrease mortality in pediatric trauma patients who require a MT [21–26]. The definition of MT differed between all these studies. Three reported a significant improvement in 24-hour mortality with plasma/RBC ratio 1:1 [22, 23] or 1:2 [21]. Another study [27] reported no benefit with high plasma/RBC ratio in 364 combat-injured pediatric trauma patients who received a MT. Inaba et al. [28] also reported no improvement in survival with plasma transfusion (17.3% vs. 14.1%; $p = 0.30$) irrespective of plasma/RBC ratio. On the other hand, the risk of deep venous thrombosis was increased in severely injured children who received plasma/RBC and platelets/RBC ratio 2:1 [21]. The outcomes of these studies are inconsistent (3 positive, 5 negative), and it is difficult to ascertain specific effects of plasma or platelets as they are often given in tandem in an effort toward balanced resuscitation. No pediatric randomized controlled trial (RCT) demonstrated survival benefit with high or low ratios. Despite the lack of strong pediatric evidence, early replacement therapy with ratios between 1:1:1 or 2:1:1 for RBC/plasma/platelets is advocated by experts in pediatric intensive care medicine [29–31].

The Traumatic Hemostasis and Oxygenation Research (THOR) network suggests using whole blood rather than blood components to treat some cases of severe acute hemorrhage [31–33]. One clinical study supports the use of whole blood in pediatric trauma [33].

Even though there is a lack of evidence in pediatric patients, the TAXI-CAB experts concluded that a balanced resuscitation strategy/ratio for RBC/plasma/platelet of 1:1:1 or 2:1:1 in injured children with hemorrhagic shock or with life-threatening hemorrhage might be considered. This transfusion strategy can be stopped once the hemorrhage is controlled.

4. **In critically ill pediatric patients with severe trauma, moderate to severe TBI or non-traumatic ICH, viscoelastic testing (e.g., TEG, ROTEM) might be considered as an adjunct to standard laboratory hemostatic testing to inform decisions regarding the transfusion of plasma and/or platelets. 95% Agreement ($n=22$), Median 8.5 (IQR 7.75–9).**

Rationale —Within minutes of injury, a high percentage of severely injured patients with hemorrhagic shock develop a clotting abnormality termed Trauma Induced Coagulopathy (TIC). TIC was observed in 57% of 956 patients younger than 17 years of age with severe trauma [34]. In this study, coagulopathic children received more RBC and plasma transfusions and had fewer ICU ($p=0.042$) and ventilator-free days ($p=0.007$) and higher mortality ($p < 0.001$); the difference in mortality was also seen in those patients with severe TBI ($p=0.002$) [26]. Abnormal TEG, ROTEM, PT, aPTT and/or low platelet count are associated with a higher risk of mortality [35–38]. Leeper et al. [39] reported an association

between a higher INR and the risk of mortality in 776 pediatric trauma patients. Deng et al. [40] reported that a ROTEM-guided protocol improves the outcomes of pediatric trauma patients. Thus, close monitoring of the coagulation system might be considered in critically ill pediatric patients with severe trauma, moderate to severe TBI, and may also be beneficial in children with ICH.

However, the best and most appropriate testing strategy is still a matter of debate. Standard tests such as PT/INR, aPTT, platelet count and fibrinogen might be considered. Two systematic reviews suggest that using TEG or ROTEM to help with decision-making about transfusion strategy reduces the amount of bleeding in adults with MT [41, 42]. However, the pediatric data embedded in these systematic reviews were collected in two trials recruiting 131 cases of elective cardiac surgery with cardiopulmonary bypass, not in PICU patients with severe trauma, TBI and/or ICH [43, 44]. The best evidence that we have on which coagulation tests may be considered in trauma patients comes from the “Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (iTacTic)” RCT [45]. This large pragmatic trial aimed to determine whether augmenting major hemorrhage protocols (MHPs) with either point-of-care VET would improve outcomes compared to Conventional Coagulation Tests (CCTs). The RCT included 396 adults with trauma-related major hemorrhage activating a MT protocol. At 24 hours, there was no difference in the proportion of patients with the composite primary outcome of participants who were alive and free of MT (VET: 67%, CCT: 64%, Odds Ratio (OR) 1.15, 95% CI 0.76–1.73). Moreover, there was no difference in 28-day mortality (VET: 25%, CCT: 28%, OR 0.84, 95% CI 0.54–1.31), or in other secondary outcomes or serious adverse events. In the pre-specified subgroup of 74 patients with TBI, 64% were alive and free of MT at 24 h compared to 46% in the CCT arm (OR 2.12, 95% CI 0.84–5.34). The main conclusion of iTacTic was: “In adult trauma patients presenting with signs of haemorrhagic shock, [there was] no benefit of viscoelastic haemostatic assay augmented protocols when compared to conventional coagulation tests augmented protocols.”

What are the data specific to pediatric trauma patients? Leeper et al [46] concluded that plasma transfusion should not be targeted to INR thresholds but rather to TEG activated clotting time and clinical bleeding; however, this conclusion is not supported by data. Rowell et al [47] also concluded that routine plasma transfusion to correct a moderately elevated INR before neurological intervention should be re-examined. Bauer et al. [48] reported that the transfusion of plasma in children with acute TBI based on TEG rather than INR may lead to improved outcomes. Some pediatric intensivists state that coagulation tests including abnormal INR and VET could prompt them to prescribe plasma in patients assessed to be at high risk for bleeding when adequate surgical hemostasis is achieved, even in non-bleeding patient [49].

In summary, there are no convincing data on which coagulation system test should be utilized to monitor patients with severe trauma, moderate to severe TBI or non-traumatic ICH. Standard laboratory hemostatic testing might be considered in all pediatric patients with VETs used as adjuncts to inform decisions regarding the transfusion of plasma and/or platelets in these populations.

5. **In a neurologically stable critically ill pediatric patient with severe trauma, moderate or severe TBI and/or ICH, platelet transfusion if the platelet count is $> 100 \times 10^9/L$ ($100,000/mm^3$) may not be beneficial. 91% Agreement ($n=23$), Median 9 (IQR 8–9).**

Rationale —The consensus that platelet transfusion may not be beneficial in neurologically stable critically ill pediatric patient with severe trauma, moderate or severe TBI and/or ICH if the platelet count is $> 100 \times 10^9/L$ was strong (91% agreement).

The American Society of Anesthesiologists considers that a platelet transfusion might be indicated despite an adequate platelet count if a platelet dysfunction is known or suspected, including if the patient is receiving an antiplatelet agent [50].

In contrast to the above statement, in situations with neurologic instability, i.e. the GCS is deteriorating, increasing intracranial pressure (ICP), decreasing cerebral perfusion pressure or increasing seizure activity, it is unclear if the transfusion of platelets may be beneficial even when the platelet count is $> 100 \times 10^9/L$ if one suspects that the neurological deterioration could be attributable to expanding intracranial hematoma or intracerebral hemorrhage and other causes are ruled out.

Consensus was not reached on a threshold platelet count that could guide platelet transfusion if the platelet count is $> 100 \times 10^9/L$. The American Society of Anesthesiologists suggests a threshold of $50 \times 10^9/L$ in surgical patients in the presence of significant bleeding [50].

6. **If an ICP monitoring device must be inserted in a neurologically deteriorating critically ill pediatric patient with TBI and/or ICH, platelet transfusion might be considered if the platelet count is $< 100 \times 10^9/L$ ($100,000/mm^3$). 86% Agreement ($n=22$), Median 7.5 (IQR 7–9).**

Rationale —In the absence of published studies, we asked the following question to members of TAXI-CAB: “Do you think we should set platelet count thresholds for placement of intracranial pressure (ICP) monitors in critically ill children with TBI and/or ICH?”. Twenty-one responses were received, 12 positives (57%), 9 negatives (43%). We also asked: “If you think we should set thresholds, below what platelet count would you suggest that platelets be transfused prophylactically prior to ICP monitor insertion?” We received 13 responses: 6 respondents choose a threshold platelet count of $100 \times 10^9/L$ and 3 choose a threshold of $50 \times 10^9/L$. Thereafter, the statement above received strong agreement (86%). The American Society of Neurosurgery, the American Society of Anesthesiology and the C¹⁷ Council [50, 51] make no recommendations for a threshold platelet count levels for placement of ICP monitor.

7. **If an ICP monitoring device must be inserted in a neurologically deteriorating critically ill pediatric patient with TBI and/or ICH, plasma transfusion if the INR is > 1.5 may not be beneficial. 87% Agreement ($n=23$), Median 8 (IQR 8–9).**

Rationale —For neurosurgery and spine guidelines, professional organizations have no recommendations on INR for placement of ICP monitor. However, in practice, INR is frequently used to support a decision to give a plasma transfusion before the placement of an ICP monitor. When also we asked 21 members of TAXI-CAB if they think we should set INR thresholds for placement of ICP monitors in critically ill children with TBI and/or ICH, eleven respondents believe that we should not. Bauer et al. [48] reported no hemorrhage after the placement of ventriculostomy in 31 TBI patients with INR 1.6. Davis et al. [52] stated that plasma transfusion to prevent bleeding after placement of ICP monitors results in no change when INR < 1.7 and may delay monitor placement. In a point-prevalence study on 443 patients who received at least one plasma transfusion in 101 PICU in 21 countries, Karam et al [53] reported plasma transfusion significantly improved INR only if the baseline INR was > 2.5. Given these data, we propose that giving a plasma transfusion if the INR is 1.5 may not be beneficial.

We did not reach consensus regarding management when the INR is > 1.5. However, there is some evidence that plasma transfusion significantly improved INR only in patients with a baseline INR greater than 2.5 (66). In addition, we do not know if there should be different thresholds between extra-axial versus intra-ventricular drain.

DISCUSSION

In practice, there is a consensus that monitoring of the coagulation system is suggested in children with severe trauma and TBI, given the high frequency of coagulopathy in these populations. The correct practice is less obvious in patients with ICH. Which test(s) should be obtained and at what frequency is unclear.

Plasma is transfused to correct multiple coagulation factor deficiencies. It should be transfused in critically ill children with severe trauma, TBI and/or ICH to treat active hemorrhage attributable to a coagulation abnormality or to prevent bleeding prior to an invasive procedure in a patient with abnormal hemostasis. The lack of evidence precludes any recommendation about plasma transfusion, other than that plasma transfusion may not be beneficial if the INR is 1.5, even when an ICP monitoring device must be inserted. In practice, clinical judgment is the best key to guide plasma transfusion in these populations.

Platelets are transfused to increase the platelet count in patients with thrombocytopenia and/or clinically significant platelet dysfunction. They are transfused in critically ill children with severe trauma, TBI and/or ICH to treat active hemorrhage attributable to thrombocytopenia or platelet dysfunction or to prevent bleeding prior to an invasive procedure with increased risk of bleeding. The lack of evidence precludes any recommendation about platelet transfusion.

It is possible that the risk of bleeding with thrombocytopenia is higher in children than in adults. In a pre-specified post-hoc analysis of the Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) trial, the risk of bleeding was higher with similar platelet count in children than in adults given prophylactic platelet transfusions for treatment-induced hypoproliferative thrombocytopenia (post-hoc analysis) (67). This does not establish specific

platelet count thresholds to guide the transfusion practice, but it suggests that we must be more cautious with children.

CONCLUSIONS

There is insufficient pediatric evidence to support specific thresholds for coagulation tests, including INR, VET and platelet count, and the transfusion of plasma and platelets in critically ill pediatric patients with severe trauma, moderate to severe TBI or non-traumatic ICH. The TAXI-CAB good practice and expert consensus statements put forward in this paper are derived from data collected in adults and/or from guidelines for adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX 1.: Transfusion and Anemia EXpertise Initiative – Control/ Avoidance of Bleeding (TAXI-CAB) Members

(* for executive committee) Co-chairs: Marianne E. Nellis, MD, MS*, Weill Cornell Medicine, New York, NY, and Robert I. Parker, MD*, Renaissance School of Medicine, State University of New York at Stony Brook, Stony Brook, NY; Content Experts: Section 1. Laboratory assays used to assess need for plasma and/or platelet transfusions: Scot T. Bateman, MD*, University of Massachusetts Medical School, Worcester, MA, Meghan Delaney, DO, MPH, The George Washington University Health Sciences, Washington, DC, Kenneth E. Remy, MD, MHSc, MSCI, Washington University of St. Louis, St. Louis, MO, Katherine Steffen, MD, Stanford University, Palo Alto, CA; Section 2. Traumatic brain injury and intracranial hemorrhage: David F. Bauer, MD, MPH, Baylor College of Medicine, Houston, TX, Jacques Lacroix, MD, Université de Montréal, Montreal, QC, Canada, Daniel Nishijima, MD, Davis School of Medicine, Davis, CA; Section 3. Following cardiopulmonary bypass: Jill M. Cholette, MD, University of Rochester Golisano Children's Hospital, Rochester, NY, Sitaram Emani, MD, Harvard Medical School, Boston, MA, Juan Ibla, MD, Harvard Medical School, Boston, MA, Marie E. Steiner, MD, MS, University of Minnesota, Minneapolis, MN; Section 4. Supported by extracorporeal membrane oxygenation: Melania M. Bembea, MD, PhD, Johns Hopkins University School

of Medicine, Baltimore, MD, Jill M. Cholette, MD, University of Rochester Golisano Children's Hospital, Rochester, NY, Jennifer A. Muszynski, MD, MPH, Nationwide Children's Hospital, Columbus, OH, Adam M. Vogel, MD, Baylor College of Medicine, Houston, TX; Section 5. Following severe trauma: Susan M. Goobie, MD, Harvard Medical School, Boston, MA, Thorsten Haas, MD, University Children's Hospital Zurich, Switzerland, Daniel Nishijima, MD, Davis School of Medicine, Davis, CA, Robert T. Russell, MD, MPH, University of Alabama Birmingham, Birmingham, AL, Adam M. Vogel, MD, Baylor College of Medicine, Houston, TX; Section 6. With oncologic diagnosis or following hematopoietic stem cell transplantation: Gemma Crighton, MD, Royal Children's Hospital, Melbourne, Australia, Ruchika Goel, MD, MPH, Johns Hopkins University, Baltimore, MD, Jacques Lacroix, MD, Université de Montréal, Montreal, QC, Canada, Lani Lieberman, MD, University of Toronto, Canada, Simon J. Stanworth, MD, University of Oxford, UK, Marie E. Steiner, MD, MS, University of Minnesota, Minneapolis, MN; Section 7. With acute liver failure or following liver transplantation: Susan M. Goobie, MD, Harvard Medical School, Boston, MA, Oliver Karam, MD, PhD*, Children's Hospital of Richmond at VCU, Richmond, VA, Paul A. Stricker, MD, Perelman School of Medicine at the University of Pennsylvania, PA; Section 8. Following non-cardiac surgery: Susan M. Goobie, MD, Harvard Medical School, Boston, MA, Thorsten Haas, MD, University Children's Hospital Zurich, Switzerland, Marisa Tucci, MD, Université de Montréal, Montreal, QC, Canada, Adam M. Vogel, MD, Baylor College of Medicine, Houston, TX; Section 9. Invasive procedures outside of the operating room: Gemma Crighton, MD, Royal Children's Hospital, Melbourne, Australia, Jacques Lacroix, MD, Université de Montréal, Montreal, QC, Canada, Robert T. Russell, MD, MPH, University of Alabama Birmingham, Birmingham, AL, Paul A. Stricker, MD, Perelman School of Medicine at the University of Pennsylvania, PA; Section 10. Sepsis and/or disseminated intravascular coagulation: Oliver Karam, MD, PhD*, Children's Hospital of Richmond at VCU, Richmond, VA, Simon J. Stanworth, MD, University of Oxford, UK, Katherine Steffen, MD, Stanford University, Palo Alto, CA, Stacey L. Valentine, MD, MPH*, University of Massachusetts Medical School, Worcester, MA; Section 11. Product processing and selection: Meghan Delaney, DO, MPH, The George Washington University Health Sciences, Washington, DC, Ruchika Goel, MD, MPH, Johns Hopkins University, Baltimore, MD, Oliver Karam, MD, PhD*, Children's Hospital of Richmond at VCU, Richmond, VA, Jennifer A. Muszynski, MD, MPH, Nationwide Children's Hospital, Columbus, OH; Evidence-based medicine: Melania M. Bembea, MD, PhD, Johns Hopkins University School of Medicine, Baltimore, MD, Diana Delgado and Michelle Demetres, Weill Cornell Medicine, New York, NY; Implementation science: Katherine Steffen, MD, Stanford University, Palo Alto, CA.

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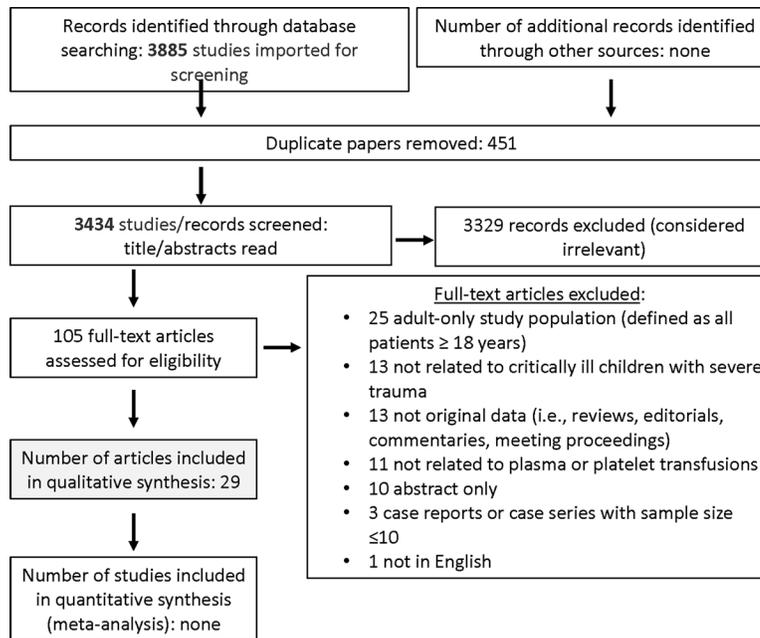


Figure 1: Papers flow chart for critically ill children with severe trauma
 PRISMA diagram for studies on plasma and/or platelets in critically ill children with severe pediatric trauma.

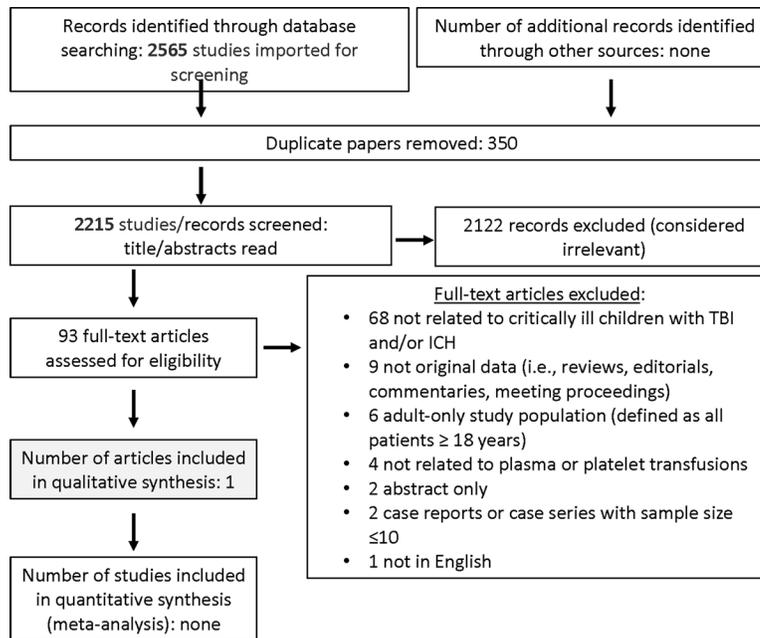


Figure 2: Papers flow chart for critically ill children with TBI and ICH
 PRISMA diagram for studies on plasma and/or platelets in critically ill children with traumatic brain injury and/or intracranial hemorrhage.