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# Massive Transfusion in Children

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ABSTRACT

Massive transfusions occur frequently in pediatric trauma patients, among some children undergoing surgery, or in children with critical illness. Over the last years, many authors have studied different aspects of massive transfusions, starting with an operative definition. Some information is available on transfusion strategies and adjunctive treatments. Areas that require additional investigation include: studies to assess which children benefit from transfusion protocols based on fixed ratios of blood components vs transfusion strategies based on biophysical parameters and laboratory tests; whether goal-directed therapies that are personalized to the recipient will improve outcomes; or which laboratory tests best define the risk of bleeding and what clinical indicators should prompt the start and stop of massive transfusion protocols. In addition, critical issues that require further study include transfusion support with whole blood vs reconstituted whole blood prepared from packed red blood cells, plasma, and platelets; and the generation of high quality evidence that would lead to treatments which decrease adverse consequences of transfusion and improve outcomes.



**Contents**



## Definition

The need for massive transfusion occurs in various clinical settings including trauma, surgical complications, cardiac surgery and extracorporeal membrane oxygenation. Trauma is the leading cause of death in children over 1 year of age, with hemorrhage as the most common cause of medically preventable death [1]. Approximately 5 to 15% of all children with traumatic injury require blood transfusion [2,3]. Of those receiving blood, up to 40% require a massive transfusion [3,4]. However, defining massive transfusion is no easy task. Originally, massive transfusion in adults was defined as the delivery of ≥10 U of a combination of stored red blood cells (RBCs) and fresh whole blood (FWB) in the first 24 hours after injury [5]. Some authors have sought to determine a data-driven massive transfusion definition in children. Using a large database of 1113 injured pediatric patients excluding isolated or predominant head injury, Neff et al showed that a threshold of 40 mL/kg of all blood products given at any time in the first 24 hours identifies critically injured children at high risk for early and in-hospital death [6]. However, although this threshold is mathematically optimal, the sensitivity and specificity for in-hospital mortality are only 60% and 60%, respectively. As there was no single, clear-cut inflection point for increased mortality with increasing transfusion volume, the validity of such an arbitrary limit is certainly useful for research but is less helpful for clinical use and for the development of protocols that help decide when to initiate a massive transfusion protocol. Furthermore, most of definitions of massive transfusion fail to exclude

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exsanguinating patients who die before reaching the massive transfusion threshold and include those who are not exsanguinating based on transfusion requirement within a 24-hour period [7].

Recently, some authors have tried validating a more prospective definition of critical bleeding, based on an hourly count of transfusion units instead of a 24-hour count. In adults, a secondary analysis of an observational study showed that patients who received more than 4 U of RBCs per hour have an increased risk of mortality [7]. Unfortunately, there are no similar pediatric studies. A recent survey in the US and Canada indicated that, in children, massive transfusion protocol activation criteria are most often based on 'physician discretion', a non-specific trigger [8]. Only 15% of the respondents based their decision to initiate a massive transfusion protocol using a threshold amount of transfused blood product, whereas 17% used vital signs or physical exam findings and 7% used a specific laboratory threshold. These observations emphasize the importance of developing a working definition of massive transfusion.

Despite the frequency of the need for massive transfusion, many questions are still unanswered. Currently used definitions of massive transfusion are based on increased risk of mortality associated with massive bleeding in military and civilian trauma patients but may not apply in other situations, such as bleeding after cardiac surgery or in association with extracorporeal life support (ECLS), which can involve massive blood loss with a different risk threshold.

## Transfusion Strategies

The historical concept behind treatment of hemorrhagic shock involved crystalloid infusion to compensate for volume depletion and transfusion of RBCs to compensate for decreased oxygen delivery. The Advanced Trauma Life Support (ATLS) guidelines still recommend resuscitation with 2 L of crystalloid solution before moving on to type-specific blood for hemorrhagic shock [9]. The Pediatric Advanced Life Support (PALS) currently recommends that RBC transfusion be considered "if the child remains hemodynamically unstable despite 2 to 3 boluses of 20 mL/kg of isotonic crystalloid" [10].

This recommendation fails to take into account the coagulopathy found in many patients requiring massive transfusion. Indeed, the incidence of post traumatic coagulopathy varies according to the clinical context (blunt vs penetrating trauma, presence of brain injury, elective surgery) and the definition of coagulopathy (clinical findings vs laboratory test results) [11]. Damaged blood vessels; release of tissue factor; activation of the fibrinolytic and protein C pathways; reduced activity of coagulation factors due to hypothermia, hypoxia, and acidosis; and the dilutional effect due to colloids or crystalloids all contribute to the coagulopathy. In a recent retrospective analysis of 907 pediatric trauma patients requiring transfusion in Afghanistan and Iraq, Edwards et al showed that increased crystalloid administration was significantly associated with increased morbidity for patients requiring massive transfusions [12]. While there were clear trends toward increased mortality in high-volume and massive transfusion patients when crystalloid administration exceeded 100 mL/kg, it is important to note that this study was subject to survival bias as well as selection bias. Indeed, because availability of humanitarian care for children at combat hospitals is dependent on the discretion of the military facility, only the most severely injured children are admitted and were therefore included in this analysis. In addition, the use of crystalloid may have been a co-variant with time-delay between injury and definitive treatment. There has been an increasing focus on transfusing not only RBCs, but also plasma and platelets in massively bleeding patients. Observational studies in wounded adult trauma patients (both military and civilian) have shown increased survival in patients who have received plasma and platelets [13]. This has led to the 1:1:1 concept, whereby patients receive "equal doses" of RBCs, plasma, and platelets. The physiologic rationale for this is that a transfused product that resembles whole blood provides an effective "concentration" of each component. However, each additional product has a dilutional effect and it therefore becomes impossible to attain "normal" levels of all blood components because one product necessarily dilutes the others.

Currently, only one randomized controlled trial has evaluated the impact of plasma and platelet ratios in the setting of severe trauma. Holcomb et al randomized 680 severely injured adult patients to receive a blood product ratio of 1:1:1 (plasma, platelets, and packed RBCs) vs a blood product ratio of 1:1:2. The authors found no significant differences in mortality at 24 hours or at 30 days [14]. However, this trial did not enroll patients under the age of 15, so we do not know if these findings would apply to pediatric injury. We therefore have to rely on observational data from pediatric trauma patients in war situations. A recent study seems to indicate that resuscitation with product ratio of 1:1:1 was associated with higher mortality [12]. In 907 pediatric trauma patients requiring transfusion in Afghanistan and Iraq, those who received a greater than 0.8 FFP per RBC unit had a significantly higher mortality (18% vs 8%, $P < .0001$). This persisted after adjusting for age, injury severity, mechanism of injury, and volume of crystalloid administered. Platelets were not included in this analysis, as only 11% of the patients received platelets in the first 24 hours of admission, given the limited availability of this blood component at remote locations. Therefore, these results might not be generalizable to civilian patients treated with a 1:1:1 protocol.

These trials have put back in the spotlight some older studies on whole blood. In 1991, Manno et al randomized 161 children undergoing cardiopulmonary bypass to either fresh whole blood (FWB) stored for less than 6 hours vs older whole blood stored for 24 to 48 hours vs reconstituted whole blood (packed RBCs, plasma, and platelets) stored for 5 days maximum to meet immediate post-operative transfusion requirements [15]. They showed that transfusion of FWB was associated with significantly less post-op blood loss than transfusion of reconstituted blood ($51 \pm 9$ mL/kg vs $74 \pm 9$ mL/kg, $P = .03$). There were no differences between FWB and older whole blood ($51 \pm 9$ mL/kg vs $45 \pm 9$, $P =$ NS). Reconstituted blood was also associated with abnormal platelet aggregation at 30 minutes and 3 hours. One of the limitations of this study is the definition of transfusion requirements, which was not protocol-based. Another limitation might be the fact that whole blood was generally provided from directed blood donors.

In another randomized controlled trial in children with congenital heart disease, Mou et al randomized patients undergoing cardiopulmonary bypass priming to FWB vs reconstituted blood [16]. The group that received reconstituted blood had a shorter length of stay in intensive care as well as a smaller cumulative fluid balance at 48 hours. However, early postoperative chest-tube output was similar in both groups. It is difficult to generalize the results of these studies to other bleeding patients, as the intervention was only the bypass priming and not perioperative or postoperative transfusions.

Furthermore, the authors indicate that strict guidelines for postoperative transfusion were instituted, but these are not described in the manuscript.

Jobes et al published a retrospective analysis of 3836 children undergoing cardiopulmonary bypass who received whole blood to prime the bypass circuit. Volume replacement after surgery was either FWB or any other blood product and was left to the physician's discretion. The authors concluded that, compared with published reports of component use, the use of FWB reduced donor exposure [17].

Neither transfusion thresholds, nor the proportion of physicians who chose to use FWB after surgery were reported. Furthermore, the authors did not report the volume of transfused blood products. These results are therefore difficult to generalize to other centers and cannot be transposed to other populations of bleeding patients. Prospective controlled trials, comparing whole blood vs a 1:1:1 ratio of blood products, are needed in massively bleeding patients. There is also an interest in concentrated plasma or in the use of factor concentrates, as these could decrease the dilutional effect of regular plasma transfusion and enhance the speed of administration [18].