Clearly defining pediatric massive transfusion: Cutting through the fog and friction with combat data

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BACKGROUND: Massive transfusion (MT) in pediatric patients remains poorly defined. Using the largest existing registry of transfused pediatric trauma patients, we sought a data-driven MT threshold.

METHODS: The Department of Defense Trauma Registry was queried from 2001 to 2013 for pediatric trauma patients (<18 years). Burns, drowning, isolated head injury, and missing Injury Severity Score (ISS) were excluded. MT was evaluated as a weight-based volume of *all* blood products transfused in the first 24 hours. Mortality at 24 hours and in the hospital was calculated for increasing transfusion volumes. Sensitivity and specificity curves for predicting mortality were used to identify an optimal MT threshold. Patients above and below this threshold (MT+ and MT−, respectively) were compared.

RESULTS: The Department of Defense Trauma Registry yielded 4,990 combat-injured pediatric trauma patients, of whom 1,113 were transfused and constituted the study cohort. Sensitivity and specificity for 24-hour and in-hospital mortality were optimal at 40.1-mL/kg and 38.6-mL/kg total blood products in the first 24 hours, respectively. With the use of a pragmatic threshold of 40 mL/kg, patients were divided into MT+ (n = 443) and MT− (n = 670). MT+ patients were more often in shock (68.1% vs. 47.0%, $p < 0.001$), hypothermic (13.0% vs. 3.4%, $p < 0.001$), coagulopathic (45.0% vs. 29.6%, $p < 0.001$), and thrombocytopenic (10.6% vs. 5.0%, $p = 0.002$) on presentation. MT+ patients had a higher ISS, more mechanical ventilator days, and longer intensive care unit and hospital stay. MT+ was independently associated with an increased 24-hour mortality (odds ratio, 2.50; 95% confidence interval, 1.28–4.88; $p = 0.007$) and in-hospital mortality (odds ratio, 2.58; 95% confidence interval, 1.70–3.92; $p < 0.001$).

CONCLUSION: Based on this large cohort of transfused combat-injured pediatric patients, a threshold of 40 mL/kg of *all* blood products given at any time in the first 24 hours reliably identifies critically injured children at high risk for early and in-hospital death. This evidence-based definition will provide a consistent framework for future research and protocol development in pediatric resuscitation. (*J Trauma Acute Care Surg*. 2015;78: 22–29.

LEVEL OF EVIDENCE: Diagnostic study, level II. Prognostic/epidemiologic study, level III.

KEY WORDS: Pediatric trauma; massive transfusion; damage control resuscitation; combat injury.

Preventing death from traumatic injury in both adult and pediatric patients requires the rapid, accurate identification of those who have bled significantly or who harbor injuries with significant bleeding potential. Identifying such patients early and responding with data-driven treatment strategies represent the singular focus of numerous ongoing investigative efforts in the trauma community.

Delivery of a massive transfusion (MT) has been used by some to identify patients at risk for death from hemorrhage.[1] MT has classically been defined as the administration of a large volume of whole blood (WB) or packed red blood cells (PRBCs) over a given time period (e.g., one blood volume over 24 hours).[1,2] However, most definitions are based on arbitrary volumes of products transfused over different time frames and have never been validated as predictive of mortality.[3–5] Ultimately, the principal obstacle to creating a valid definition of MT is the heterogeneity of populations studied.[1,6,7]

For pediatric patients, all current MT variations in the adult literature have little relevance because of differences in patient size, patient physiology, and injury demographics.[8,9] The most commonly held MT definition in the field of pediatric transfusion is the administration of 50% circulating blood volume over 24 hours. However, like the adult MT definitions, this definition is arbitrary and has never been validated, leading some to question the very utility of such a measure.[1,8–10]

Notwithstanding these limitations, some pediatric trauma centers have recently established MT protocols to facilitate the delivery of a "balanced resuscitation" to bleeding patients.[3,11–14]

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TABLE 1. Blood Product Volumes

Blood Product	Theater	Blood Product Volume (mL) per Unit*
WB	OIF, OEF	450
PRBC	OIF, OEF	250
FFP	OIF, OEF	250
Plt	OIF, OEF	250
Cryo	OIF	90
	OEF	150

*Values obtained by L.P.N. on-site in Bagram, Afghanistan, and verified by the Chief, Blood Research, US Army Institute of Surgical Research.
OIF, Operation Iraqi Freedom; OEF, Operation Enduring Freedom (Afghanistan).

As in the adult population, however, clinical triggers that guide MT protocol activation have proven unreliable because no validated MT prediction models exist for children, and such models cannot be developed without a consistent, evidence-based definition of MT.

All the inherent limitations of the MT concept aside, a validated pediatric-specific MT definition may permit the identification of children at risk for shock, coagulopathy, and death secondary to hemorrhage. Furthermore, a pediatric-specific definition may facilitate the further development and optimization of pediatric resuscitation strategies. The purpose of the present study is to define MT in a pediatric trauma population by evaluating the outcomes of transfused, injured children in Iraq and Afghanistan.

PATIENTS AND METHODS

This study was initiated under a protocol reviewed and approved by the San Antonio Military Medical Center Institutional Review Board. We queried the Department of Defense Trauma Registry (DoDTR) for all injured patients younger than 18 years admitted to US combat support hospitals in Iraq and Afghanistan from 2001 to 2013. To clearly identify a cohort of patients at risk for death from hemorrhage rather than from head trauma, we then excluded all patients with a severe isolated head injury (head Abbreviated Injury Scale [AIS] score ≥ 3 with no other injuries) or a predominant head injury (head AIS score ≥ 2 over the next highest AIS score) from the analysis.[5] Patients with predominant thermal injury, those with nontraumatic mechanisms (e.g., drowning and asphyxiation) and those with missing Injury Severity Score (ISS) data were also excluded. The final cohort for this study included only those patients who received at least one blood product in the first 24 hours after injury including WB, PRBCs, fresh frozen plasma (FFP), platelets (Plt) or cryoprecipitate (Cryo).

The primary end points were 24-hour and in-hospital mortality as these children were generally managed within our deployed medical system until discharge. Data retrieved included the demographics of age, weight, sex, and injury mechanism. Measures of injury severity including Glasgow Coma Scale (GCS), AIS for each body region, and ISS were also retrieved. Physiologic and laboratory data included admission temperature, hematocrit, base excess (BE), Plt count, and international normalized ratio (INR). For the purposes of this study, hypothermia was defined as temperature of 35 °C or lower, coagulopathy was defined as an INR of 1.5 or greater, and shock was defined as a BE of −6 or less.[15,16] Length of stay (LOS), length of intensive care unit (ICU) stay, need for mechanical ventilation, and total ventilator days were also retrieved.

Resuscitation data included the 24-hour volumes for crystalloid and colloid and the number of units of WB, PRBC, FFP, Plt, and Cryo. Units were converted to a volume in milliliters using the average volume of component units administered in each theater of operation (Table 1). The volume of blood products administered was then converted to milliliters per kilogram body weight for each patient. Missing weights were imputed to avoid introducing bias into the results. To determine the optimal imputation strategy for missing weights, mean recorded weights for each age and sex grouping (in 1-year increments) were compared with the mean expected weights published by the World Health Organization (WHO, ages 1–10 years)[17] and the Centers for Disease Control (CDC, ages 1–17 years).[18]

Mortality was evaluated for increasing volumes of all blood products to determine if an inflection point existed for a particular transfusion volume. In addition, sensitivity and specificity for predicting 24-hour and in-hospital mortality were plotted against blood product transfusion volume to determine the intersection of these curves. Patients receiving blood product amounts below this point (MT−) were compared with patients above (MT+) with univariate analysis. X^2 and Mann-Whitney U-tests were used as appropriate. Values are presented as median (25–75% interquartile range [IQR]) and frequency (percentage). Multivariate logistic regression was performed to determine any independent association between the MT definition and death reported as odds ratio (OR) (95% confidence interval [CI]). $p < 0.05$ was considered statistically significant. Statistical analysis was performed with IBM SPSS (version 19, Armonk, NY).

RESULTS

During the 12-year study period, 4,990 patients younger than 18 years were recorded in the DoDTR. From this cohort, 1,341 were excluded for a thermal injury or nontraumatic mechanism, an isolated or predominant head injury, or incomplete ISS data. Of the remaining 3,649 patients, 1,113 (31%) received blood

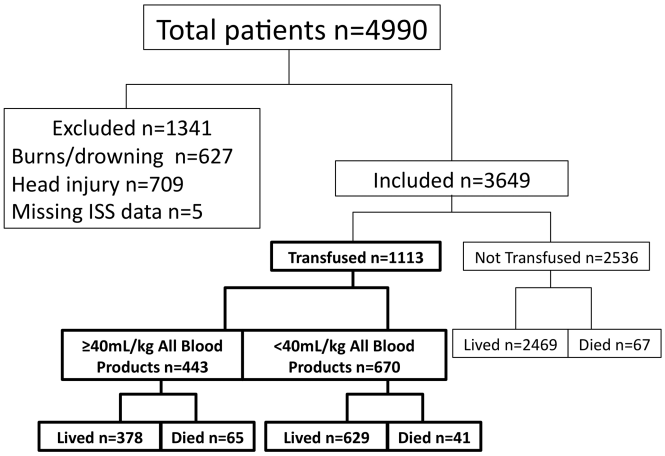

Figure 1. Flow diagram for determining the study cohort (bold).

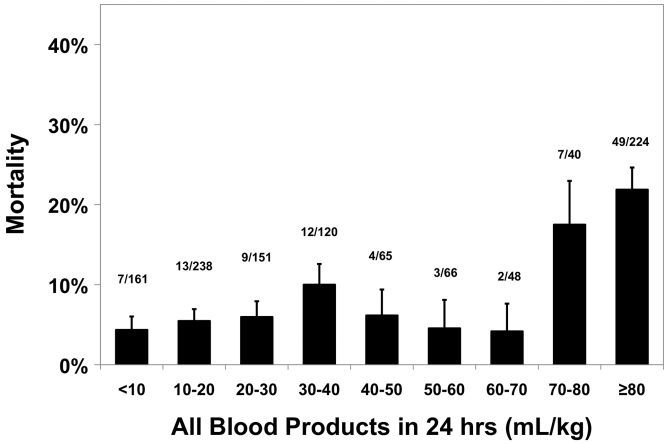

Figure 2. Mortality for incremental increases in volume of all blood products transfused. Error bars denote the SE for each proportion. Source data are presented as number died over total number of patients [(n died) / (total n)] for each incremental volume group.

products during the first 24 hours of their hospitalization and were included in the analysis (Fig. 1).

Weight data were missing in 380 (34%) transfused patients. Of the 4,990 injured pediatric patients in the DoDTR, 2,596 with recorded weights were used to determine the optimal imputation strategy for missing weights. Mean recorded weights for each age and sex group were compared with both the WHO and the CDC mean weights and were found to be significantly different in 13 (36%) of the 36 groups (Supplemental Digital Content 1, http://links.lww.com/TA/A490 and http://links.lww.com/TA/A491). Consequently, missing weights were imputed using the sex-specific mean value for a given age rather than the WHO or CDC mean weight to more closely approximate the study population.

Evaluation of crude mortality for increasing volume of all blood products transfused demonstrated a bimodal distribution with a possible inflection point at 70-mL/kg to 80-mL/kg transfused blood products (Fig. 2). However, a plot of sensitivity and specificity for 24-hour mortality indicated that a threshold of 40.1 mL/kg of all blood products was optimal (Fig. 3*A*). A similar plot for in-hospital mortality suggested a threshold of 38.6 mL/kg of all blood products transfused (Fig. 3*B*). Thus, a pragmatic value of 40 mL/kg was chosen to define an MT as a result of this analysis.

Complete demographics compared between the MT+ and MT− groups are shown in Table 2. A greater percentage of the MT+ cohort sustained injury from explosion (63.4% vs. 50.6%, $p < 0.001$), and MT+ patients were more severely injured, with a higher ISS (17 vs. 13, $p < 0.001$). Upon presentation, MT+ patients exhibited a lower GCS score (13 vs. 15, $p < 0.001$) and were more often hypothermic (13.0% vs. 3.4%, $p < 0.001$), in shock (68.1% vs. 47.0%, $p < 0.001$), coagulopathic (45.0% vs. 29.6%, $p < 0.001$), and thrombocytopenic (10.6% vs. 5.0%, $p = 0.002$). MT+ patients received more crystalloids during the first 24 hours (81.8 mL/kg vs. 61.2 mL/kg, $p < 0.001$) in addition to a greater total volume of blood products (80.4 mL/kg vs. 16.7 mL/kg, $p < 0.001$). Tranexamic acid use was more frequent in the MT+ group (12.4% vs. 1.3%, $p < 0.001$).

MT+ patients had more ventilator days (2 days vs. 1 day, $p < 0.001$), longer ICU stays (4 days vs. 2 days, $p < 0.001$), and longer hospital stays (8 days vs. 5 days, $p < 0.001$). Both 24-hour mortality (5.4% vs. 2.2%, $p = 0.005$) and in-hospital mortality (14.7% vs. 6.1%, $p < 0.001$) were higher in the MT+ group. Multivariate logistic regression was performed by including those fixed demographic factors with $p < 0.2$ between MT+ and MT− in the model, namely, age, sex, weight, and injury mechanism. Mortality was significantly greater in the MT+ group at both 24 hours (OR, 2.50; 95 CI, 1.28–4.88; $p = 0.007$) and in-hospital (OR, 2.58; 95% CI, 1.70–3.92; $p < 0.001$).

DISCUSSION

The purpose of the present study was to determine if MT could be clearly defined in a pediatric trauma population. There was no single, clear-cut inflection point for increased mortality with increasing transfusion volume; however, sensitivity and specificity analysis suggested a threshold of 40 mL/kg of all blood products given within the first 24 hours as a potential MT definition. Further comparison between MT+ and MT− groups confirmed that, indeed, this definition successfully differentiates pediatric trauma patients at increased risk for both early and late death. This is the first study to provide objective evidence that a mortality threshold for blood product

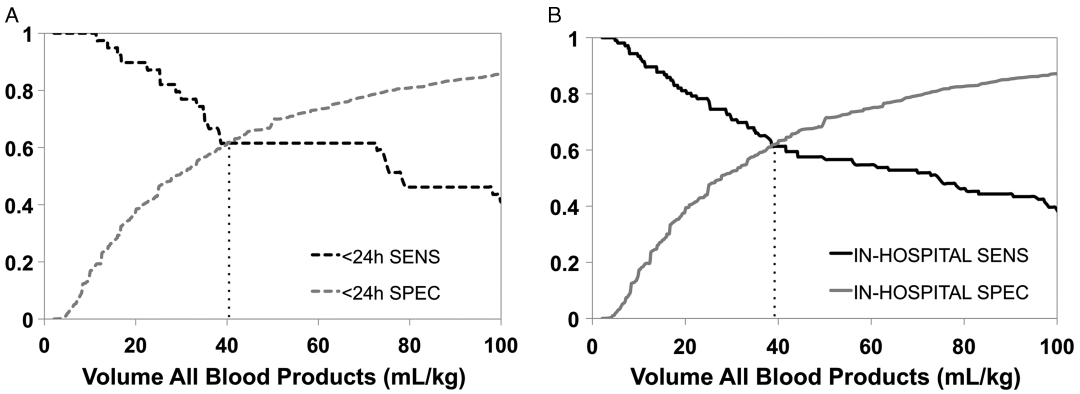

Figure 3. Sensitivity and specificity curves for 24-hour (*A*) and in-hospital (*B*) mortality for increasing transfusion volumes. The intersection of these curves was used to determine an optimal definition for MT.

TABLE 2. Demographics for Transfused Patients Receiving 40 mL/kg or Greater (MT+) and Less Than 40 mL/kg (MT−) of all Blood Products

Variable	n = 1,113*	MT+, n = 443	MT−, n = 670	*p*
Age, y		10 [6 to 13]	10 [7 to 14]	0.036
Weight, kg	733	30.0 [20.0 to 40.0]	31.3 [22.0 to 45.5]	0.005
Sex, male, n (%)		334 (75.4)	536 (80.0)	0.069
Mechanism, n (%)				
Blunt		37 (8.4)	95 (14.2)	0.003
Explosion		281 (63.4)	339 (50.6)	<0.001
Penetrating		125 (28.2)	236 (35.2)	0.016
ISS		17 [11 to 24]	13 [9 to 18]	<0.001
Admission GCS score	1,011	13 [3 to 15]	15 [5 to 15]	<0.001
Admission temperature, °C	878	36.7 [36.0 to 37.3]	36.9 [36.4 to 37.6]	<0.001
Admission Hct	965	30.4 [26.0 to 35.6]	31.3 [26.9 to 35.8]	0.221
Admission BE	883	−8 [−13 to −5]	−5 [−8 to −3]	<0.001
Admission Plt, cell/μL	913	263 [160 to 383]	307 [210 to 402]	<0.001
Admission INR	701	1.4 [1.2 to 1.9]	1.2 [1.1 to 1.5]	<0.001
Temperature ≤ 35 °C, n (%)		46 (13.0)	18 (3.4)	<0.001
BE ≤ −6, n (%)		252 (68.1)	241 (47.0)	<0.001
INR ≥ 1.5, n (%)		116 (45.0)	131 (29.6)	<0.001
Hct ≤ 30, n (%)		188 (48.8)	255 (44.0)	0.137
Plt ≤ 100, n (%)		38 (10.6)	28 (5.0)	0.002
Crystalloids, mL/kg		81.8 [44.4 to 131.1]	61.2 [32.5 to 100.5]	<0.001
Colloids, mL/kg		0 [0 to 0] (4.8 ± 14.6)	0 [0 to 0] (1.9 ± 6.0)	<0.001
PRBC, mL/kg		43.8 [28.6 to 62.5]	12.5 [8.0 to 16.7]	<0.001
WB, mL/kg		0 [0 to 0] (3.0 ± 21.3)	0 [0 to 0] (0.1 ± 1.2)	<0.001
FFP, mL/kg		33.3 [20.9 to 50.0] (42.7 ± 50.4)	0 [0 to 10.0] (5.3 ± 7.1)	0.019
Plt, mL/kg		0 [0 to 10.0] (7.1 ± 14.1)	0 [0 to 0] (0.3 ± 2.0)	<0.001
Cryo, mL/kg		0 [0 to 1.5] (5.5 ± 16.9)	0 [0 to 0] (0.0 ± 0.5)	<0.001
All blood, mL/kg		80.4 [55.2 to 128.8]	16.7 [10.0 to 25.0]	<0.001
Total fluids, mL/kg		179.3 [132.1 to 255.9]	82.4 [48.8 to 120.5]	<0.001
Tranexamic acid, n (%)		55 (12.4)	9 (1.3)	<0.001
Mechanical ventilation, n (%)		376 (84.9)	376 (56.1)	<0.001
Ventilator days		2 [1 to 5]	1 [0 to 2]	<0.001
ICU LOS, d		4 [2 to 7]	2 [1 to 4]	<0.001
Hospital LOS, d		8 [3 to 14]	5 [3 to 9]	<0.001
Died, n (%)		65 (14.7)	41 (6.1)	<0.001
Died in <24 h, n (%)		24 (5.4)	15 (2.2)	0.005

*Number of patients with recorded data is 1,113 unless noted. All statistics reported as n (%) or median [IQR]. Mean ± SD is also reported for median values of 0.
Hct, hematocrit.

administration exists in the pediatric trauma population. Our results indicate that 40 mL/kg or greater of all products provides a benchmark for MT, which is approximately half the circulating blood volume of most children.[8,10]

During the last decade, numerous studies have stressed the importance of damage-control resuscitation and the use of balanced ratios of blood products in the adult trauma population.[4,19–22] The benefit of "balanced resuscitation" has led to the adoption of MT protocols in pediatric trauma centers as well.[3,11,12,14] However, there remains no consensus on the optimal strategy for blood product delivery and no clear trigger(s) for MT protocol activation.[22] Moreover, MT protocol use and early plasma administration have not demonstrated a clear survival benefit in pediatric trauma.[4,11,13] There is additional concern that overly aggressive transfusion strategies in minor trauma may lead to increased harm.[8,23–25] Clearly, there is a need to validate MT protocols and establish criteria for MT protocol activation to rapidly mobilize blood products while also minimizing the waste of limited resources.[3] As an initial step in addressing these pressing issues, an optimal definition for MT must be developed.

The original concept of an MT stemmed from the idea of an exchange transfusion given to bleeding patients and was thought to portend a poor outcome.[2] With the division of WB into components, most modern definitions of MT emphasize the volume of PRBC transfused and have not accounted for the other blood products administered (i.e., FFP, Plt, and Cryo).[4,5,26–28] Regarding the volume of PRBCs that constitute an MT and the time interval of administration, there remains significant variation in the recent literature for both adult and pediatric patient

TABLE 3. Current Literature on MT in Both Adult and Pediatric Patients Demonstrating the Range of Different Definitions Used

	MT Definition	Population
Nosanov et al., 2013[4]	≥50% TBV PRBC in 24 h	Civilian pediatric
Diab et al., 2013[10]	>50% TBV PRBC in 3 h *or* >100% TBV PRBC in 24 h	Civilian pediatric (review)
Borgman et al., 2007[20]	≥10 U PRBC in 24 h	Military adult
Spinella et al., 2011[5]	≥5 U PRBC in 6 h *and* ≥10 U PRBC in 24 h	Military adult
Cap et al., 2012[27]	≥10 U PRBC in 24 h	Military adult
Holcomb et al., 2008[30]	≥10 U PRBC in 24 h	Civilian adult
Nunez et al., 2009[26]	≥10 U PRBC in 24 h	Civilian adult
Kashuk et al., 2009[28]	≥10 U PRBC in 6 h	Civilian adult
Savage et al., 2013[6]	≥3 U PRBC/h	Civilian adult
Rahbar et al., 2013[7]	≥4 U any resuscitative fluid in the first 30 min	Civilian adult
Levi et al., 2011[37]	>50% TBV PRBC in 3 h >100% TBV PRBC in 6 h >100% TBV PRBC in 24 h >50% TBV PRBC/h ≥4 U PRBC/h	Civilian adult (Survey of MT practice)

TBV, total blood volume.

populations (Table 3), and as Stanworth et al.[1] have illustrated, there is no identifiable mortality threshold at traditionally accepted MT definitions. Furthermore, MT is a retrospectively applied label subject to survival bias,[1,29] and reaching an MT threshold requires timely action by the managing physician and may be further confounded by logistical issues in the blood bank that cannot be accounted for in studies (e.g., the thawing of FFP, overall blood product availability, and blood typing). These inherent problems have led several groups to offer end points other than MT as surrogates for hemorrhage volume, severity of illness, or risk for mortality in bleeding trauma patients by narrowing the time frame from initial presentation or by evaluating the rate of blood product administration.[6,7] To date, however, no such approach has been explored in pediatric trauma.

One unique feature of the present study is the inclusion of all blood products administered instead of PRBC units alone. This approach to defining MT reflects the current trend to deliver blood products in a balanced method to avoid or treat acute traumatic coagulopathy and to prevent deaths from hemorrhage.[20,22,30,31] This approach is also consistent with historic MT definitions, which were based on a volume of WB transfused.[2] Additional prospective studies such as the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) are needed to conclusively determine if defining MT in such a way reliably identifies critically injured patients.[7]

Another unique feature of this study is that the majority of MT+ patients sustained their injuries from explosions. This mechanism of injury combines the blunt force of the blast with penetrating fragmentation injuries. Thus, injuries from explosions can be particularly devastating.[32,33] Given the predominance of blunt trauma found in the civilian pediatric population,[15] the results of the present study may not apply to the general pediatric trauma population. However, explosions as a mechanism of injury are becoming more commonplace because of terrorist attacks targeting civilian populations and the global burden of unmarked landmines.[34,35] Nevertheless, the findings of this study should not be translated to the civilian pediatric trauma population without specific validation.

To our knowledge, this represents one of the largest studies of transfusion practices in pediatric trauma. The present study differs significantly from other descriptions of pediatric MT in that we excluded patients with isolated or predominant head injury.[4] While head injury represents an important cause of mortality in the pediatric population, many of these deaths are considered nonpreventable, and these patients do not often require or receive a large-volume resuscitation.[5,8,36]

Limitations in this study include those inherent in retrospective analyses including missing or incorrect data. However, those who review charts and input DoDTR data undergo extensive training, and multiple quality assurance measures have been enacted. On careful inspection for data veracity, the only variations we identified were the potential misestimation of some patient ages and the recording of Cryo units in multiples of 10 rather than multiples of 1 in a small number of patients. Regarding patient ages, as we evaluated the data set for an optimal imputation strategy, we found that the mean recorded weights were statistically higher or lower than the expected mean weight published by the WHO and CDC for several of the age and sex groups. This suggested either that the study population was overweight in some cases and thinner in others relative to the global population or that some recorded ages were estimations.[18] Based on this finding, to best represent the study population, we imputed missing weights with the mean of recorded weights for each age and sex group assuming a similar inaccuracy in the estimation of ages for all patients. The sensitivity/specificity analysis was repeated with CDC imputed weights and revealed the same intersection at 40 mL/kg. We also performed the analysis without the Cryo data and found that the MT threshold remained the same.

This study is also limited by the absence of data on specific cause of death. Consequently, we were unable to definitively identify those children who died of hemorrhagic shock. However, we feel that our evaluation of those who died in less than 24 hours without isolated or predominant head injury represented an appropriate surrogate.

The final limitation of this study stems from the lack of data on transfusion rate or timing within the first 24 hours in the DoDTR. Furthermore, our calculations for blood product volumes administered included those patients who did not survive the first 24 hours, which falsely lowers the mean volume of product received. To evaluate for any such lead-time bias, we created separate sensitivity/specificity curves for 24-hour and in-hospital mortality and saw no clinically significant difference in the value at which these curves intersected. Future iterations of the DoDTR should include more granular data on blood product administration and on the timing of death within the first 24 hours based on growing evidence that early and

aggressive damage-control resuscitation within the first 6 hours has a persistent benefit at the 24-hour mark.[25,30,31]

CONCLUSION

Current evidence guiding the conduct of pediatric MT or predicting its use is lacking. Using a cohort of transfused combat-injured pediatric patients, we found that an MT threshold of 40 mL/kg of *all* blood products given in the first 24 hours is optimal. This definition of MT is independent of injury mechanism, accounts for modern transfusion practices, and effectively identifies transfused pediatric trauma patients at risk for both early and late death. Investigators should consider using this definition of MT in future studies on pediatric resuscitation.

AUTHORSHIP

L.P.N., J.W.C., and M.A.B. designed the study. M.A.B. performed the data acquisition. L.P.N., J.W.C., and M.A.B. performed the data analysis. All authors interpreted the data. L.P.N. and J.W.C. prepared the manuscript, which all authors critically revised.

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DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Stanworth SJ, Morris TP, Gaarder C, Goslings JC, Maegele M, Cohen MJ, König TC, Davenport RA, Pittet JF, Johansson PI, et al. Reappraising the concept of massive transfusion in trauma. *Crit Care*. 2010;14(6):R239.
2. Wilson RF, Mammen E, Walt AJ. Eight years of experience with massive blood transfusions. *J Trauma*. 1971;11(4):275–285.
3. Dehmer JJ, Adamson WT. Massive transfusion and blood product use in the pediatric trauma patient. *Semin Pediatr Surg*. 2010;19(4):286–291.
4. Nosanov L, Inaba K, Okoye O, Resnick S, Upperman J, Shulman I, Rhee P, Demetriades D. The impact of blood product ratios in massively transfused pediatric trauma patients. *Am J Surg*. 2013;206(5):655–660.
5. Brasel KJ, Vercruysse G, Spinella PC, Wade CE, Blackbourne LH, Borgman MA, Zarzabal LA, Du F, Perkins JG, Maegele M, et al. The association of blood component use ratios with the survival of massively transfused trauma patients with and without severe brain injury. *J Trauma*. 2011;71(2 Suppl 3): S343–S352.
6. Savage SA, Zarzaur BL, Croce MA, Fabian TC. Redefining massive transfusion when every second counts. *J Trauma Acute Care Surg*. 2013; 74(2):396–400; discussion 400–402.
7. Rahbar E, Fox EE, del Junco DJ, Harvin JA, Holcomb JB, Wade CE, Schreiber MA, Rahbar MH, Bulger EM, Phelan HA, et al.; PROMMT Study Group. Early resuscitation intensity as a surrogate for bleeding severity and early mortality in the PROMMTT study. *J Trauma Acute Care Surg*. 2013;75(1 Suppl 1):S16–S23.
8. Barcelona SL, Thompson AA, Coté CJ. Intraoperative pediatric blood transfusion therapy: a review of common issues. Part I: hematologic and physiologic differences from adults; metabolic and infectious risks. *Paediatr Anaesth*. 2005;15(9):716–726.
9. Paterson NA. Validation of a theoretically derived model for the management of massive blood loss in pediatric patients—a case report. *Paediatr Anaesth*. 2009;19(5):535–540.
10. Diab YA, Wong ECC, Luban NLC. Massive transfusion in children and neonates. *Br J Haematol*. 2013;161(1):15–26.
11. Chidester SJ, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. *J Trauma Acute Care Surg*. 2012;73(5):1273–1277.
12. Hendrickson JE, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F, Polstra B, Atkins E, Johnson KK, Bao G, et al. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. *Transfusion*. 2012;52(6):1228–1236.
13. Pickett PM, Tripi PA. Massive transfusion protocol in pediatric trauma. *Int Anesthesiol Clin*. 2011;49(2):62–67.
14. Dressler AM, Finck CM, Carroll CL, Bonanni CC, Spinella PC. Use of a massive transfusion protocol with hemostatic resuscitation for severe intraoperative bleeding in a child. *J Pediatr Surg*. 2010;45(7):1530–1533.
15. Borgman MA, Maegele M, Wade CE, Blackbourne LH, Spinella PC. Pediatric trauma BIG score: predicting mortality in children after military and civilian trauma. *Pediatrics*. 2011;127(4):e892–e897.
16. Patregnani JT, Borgman MA, Maegele M, Wade CE, Blackbourne LH, Spinella PC. Coagulopathy and shock on admission is associated with mortality for children with traumatic injuries at combat support hospitals. *Pediatr Crit Care Med*. 2012;13(3):273–277.
17. WHO. Weight-for-age. *WHO*. Available at: http://www.who.int/childgrowth/standards/weight_for_age/en/. Accessed July 31, 2014.
18. Growth Charts—Data Table of Weight-for-Age Charts. Available at: http://www.cdc.gov/growthcharts/html_charts/wtage.htm. Accessed July 8, 2014.
19. Sihler KC, Napolitano LM. Massive transfusion: new insights. *Chest*. 2009;136(6):1654–1667.
20. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63(4): 805–813.
21. Hendrickson JE, Shaz BH, Pereira G, Atkins E, Johnson KK, Bao G, Easley KA, Josephson CD. Coagulopathy is prevalent and associated with adverse outcomes in transfused pediatric trauma patients. *J Pediatr*. 2012; 160(2):204–209.
22. Schuster KM, Davis KA, Lui FY, Maerz LL, Kaplan LJ. The status of massive transfusion protocols in United States trauma centers: massive transfusion or massive confusion? *Transfusion*. 2010;50(7):1545–1551.
23. Sihler KC, Napolitano LM. Complications of massive transfusion. *Chest*. 2010;137(1):209–220.
24. Lee AC, Reduque LL, Luban NLC, Ness PM, Anton B, Heitmiller ES. Transfusion-associated hyperkalemic cardiac arrest in pediatric patients receiving massive transfusion. *Transfusion*. 2014;54(1):244–254.
25. Borgman MA, Spinella PC, Holcomb JB, Blackbourne LH, Wade CE, Lefering R, Bouillon B, Maegele M. The effect of FFP:RBC ratio on morbidity and mortality in trauma patients based on transfusion prediction score. *Vox Sang*. 2011;101(1):44–54.
26. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma*. 2009;66(2):346–352.
27. Cap AP, Spinella PC, Borgman MA, Blackbourne LH, Perkins JG. Timing and location of blood product transfusion and outcomes in massively transfused combat casualties. *J Trauma Acute Care Surg*. 2012;73(2 Suppl 1): S89–S94.
28. Kashuk JL, Moore EE, Johnson JL, Haenel J, Wilson M, Moore JB, Cothren CC, Biffl WL, Banerjee A, Sauaia A. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? *J Trauma*. 2008;65(2):261–270; discussion 270–271.
29. Del Junco DJ, Fox EE, Camp EA, Rahbar MH, Holcomb JB; PROMMTT Study Group. Seven deadly sins in trauma outcomes research: an epidemiologic post mortem for major causes of bias. *J Trauma Acute Care Surg*. 2013;75(1 Suppl 1):S97–S103.
30. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*. 2008;248(3): 447–458.
31. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. *Am J Surg*. 2009;197(5):565–570; discussion 570.

32. Edwards MJ, Lustik M, Eichelberger MR, Elster E, Azarow K, Coppola C. Blast injury in children: an analysis from Afghanistan and Iraq, 2002–2010. *J Trauma Acute Care Surg*. 2012;73(5):1278–1283.
33. Eastridge BJ, Hardin M, Cantrell J, Oetjen-Gerdes L, Zubko T, Mallak C, Wade CE, Simmons J, Mace J, Mabry R, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. *J Trauma*. 2011;71(1 Suppl):S4–S8.
34. Surrency AB, Graitcer PL, Henderson AK. Key factors for civilian injuries and deaths from exploding landmines and ordnance. *Inj Prev*. 2007; 13(3):197–201.
35. Schneidman D. Surgeons put planning, preparation, past experience to work in efforts to save Boston Marathon bombing victims. *Bull Am Coll Surg*. 2013;98(9):9–17.
36. Talving P, Lustenberger T, Lam L, Inaba K, Mohseni S, Plurad D, Green DJ, Demetriades D. Coagulopathy after isolated severe traumatic brain injury in children. *J Trauma*. 2011;71(5):1205–1210.
37. Levi M, Fries D, Gombotz H, van der Linden P, Nascimento B, Callum JL, Bélisle S, Rizoli S, Hardy JF, Johansson PI, et al. Prevention and treatment of coagulopathy in patients receiving massive transfusions. *Vox Sang*. 2011;101(2):154–174.

DISCUSSION

Dr. Michael L. Nance (Philadelphia, Pennsylvania): The authors performed a retrospective analysis of pediatric patients in the Defense Department Trauma Registry for a 12-year period, encompassing the conflicts in Iraq and Afghanistan.

Subjects studied were non-head injured with a blunt or penetrating mechanism who required blood product transfusion within the first 24 hours of hospitalization. The authors set out to identify the volume of transfusion that best defined massive transfusion.

Based on sensitivity and specificity modeling and looking at 24-hour mortality and in-hospital mortality the authors concluded a value of 40ccs per kilogram of product as the optimal working definition for massive transfusion.

The study group included more than 1,100 children that received blood products during the first 24-hours of their hospitalization or roughly one-third of all eligible subjects received blood.

Of the children receiving any transfusion an astounding 40 percent were characterized as having required a massive transfusion.

This study suffers from the typical foibles of a retrospective, multi-era study with a large number of care providers. However, this is one of the largest supported series of pediatric patients requiring transfusion and was assembled in a registry with a fairly rigorous data collection. As such, I believe it is an important contribution.

I have a couple of comments and several questions for the authors.

The authors noted an association, not surprisingly, between the need for massive transfusion and factors such as a higher ISS, greater risk of shock, more hypothermia, higher mortality, essentially all of those factors that go hand-in-hand with more severe injury.

How, then, does one use this number, 40ccs per kilo of product, to understand what to do with their patient? What is of greater clinical significance is not identifying who had massive transfusion but, rather, predicting who will need a massive transfusion and who is at greatest risk on the front-end of the care. Most realize that by the time you get to a massive transfusion your patient is at high risk for adverse outcome.

There has been great interest in defining optimal transfusion ratios for the pediatric population but evidence is lacking. Can the authors comment whether based on analytic or anecdotal evidence whether there is a benefit of a 1:1:1 transfusion ratio in the pediatric population as has been advocated for in the adult population?

I would also be interested to know if the time to massive transfusion was of any consequence, that is, those that require transfusion usually do so very early on until definitive hemorrhage control is achieved.

If they haven't already, the authors might consider looking at the cohort that receives or reaches the massive transfusion threshold within a shorter time frame, such as 6 to 12 hours, as we try to understand the population better and the risk factors for meeting massive transfusion.

The authors appropriately note in the manuscript that the results of their study might not apply to the civilian pediatric trauma population.

And while I think this data is provocative and potentially very insightful I do, also, think that there is something very different about this population as compared to children we see in the stateside trauma centers where transfusion rates are far lower and massive transfusion is actually quite rare.

Transfusion is uncommon in the pediatric population so to understand what drives the need for transfusion one needs a large dataset such as has been collected here by the Defense Department.

I am grateful to the authors for utilizing their robust dataset to take on this important topic and would encourage their analyzing the data further to help understand how we can identify these patients early-on and how best to treat these more severely injured patients.

I appreciate the opportunity to have reviewed this study and look forward to future studies by this group.

Dr. Martin Schreiber (Portland, Oregon): Nice study. I have to admit I have serious reservations about this study for a number of reasons.

Those of us who have worked with the DoD Trauma Registry realize that there are serious data limitations. In this particular study weight is a serious limitation yet we're getting a weight-based definition for massive transfusion. I think that's a major problem.

The issue, also raised by the author, was the one of survival bias. We are not going to get any information on people who died less than 24 hours after injury so, you know, we can't really tell what the real mortality of these patients was.

Now, the last thing I want to raise is an issue that hasn't been raised which is this study extended from 2001 to 2013. During that period of time the methods for caring for patients has changed dramatically.

In fact, the first time the damage control resuscitation clinical practice guideline appeared was in 2004. So for the period from 2001 to 2004 we didn't have a damage control clinical practice guideline.

There have been many iterations since that time and many changes. I think that you should go back and look at the

more recent period which is more reflective of our current management.

I don't think what was being done in 2001 was anything like what is being done in 2014. Thank you.

Dr. Bruce A. Bennett (Saint Paul, Minnesota): Colonel Neff, that was a nice look at the data. I appreciate that, having been downrange. My question: if you come up with this 40 per kilo as we do with constrained resources downrange, how would you conceive of utilizing this data?

If you felt that this was supported in another prospective study would you consider, once we reach the 40 per kilo threshold, is that a point where we terminate because of our resource limitations? Thanks.

Dr. Lucas P. Neff (San Antonio, Texas): Thank you for those excellent questions. Dr. Nance, thank you for reviewing our manuscript.

Your question about creation of a definition of massive transfusion relates also to Dr. Bennett's question—what do we do with this 40 milliliters per kilogram value that we think defines a pediatric massive transfusion? Our original objective with this DoD Trauma Registry data was to study transfusion ratios and replicate some of the damage control resuscitation studies from the adult literature that impacted resuscitation practices- using the same DoD trauma registry that these adult studies used.

Yet, when we started thinking about how we were going to construct these types of pediatric studies, we realized that there was no real consensus on what constituted a massive transfusion -so that we could group patients and begin to look at their ratios and the timing of products and outcomes.

And so we decided to step back, knowing that we have a fairly unique dataset, and try to build a foundation. And the creation of a definition that was predictive of increased mortality was the first step.

In terms of the data we used, you are exactly right. It is a retrospective look. The inherent limitation of the DoD Trauma Registry data is that you only have a snapshot in time and it cannot reflect what is happening "in the moment" during a resuscitation.

With respect to the timing of blood product administration, the DoD Trauma Registry doesn't have the ability to capture all of the data on the timing of blood products and definitive hemorrhage control in the operating room. It would just be nearly insurmountable data management issue, especially with all of the data that is contained within that registry.

So, we struggle with not being able to calculate the resuscitation intensity or the critical activation threshold, some of these other studies and other definitions that have been created that seem to be more on the mark. We just don't have the ability to capture that data and we are left to make reasonable inferences with that 24-hour retrospective snapshot.

Regarding the general applicability of the patients in this dataset to the larger civilian pediatric population- of course that is a concern and one that we have as well.

There have been other attempts to use this pediatric data to create predictive models for mortality that have then been compared to pediatric patients in civilian registries- a completely different population predominated by blunt injury. And those predictive mortality models performed the same in the civilian or war-injured children.

Granted, we are dealing with transfusion, and not just crude mortality. But we think that it may be erroneous to assume that some of our conclusions cannot translate to the general civilian population - we just have to do a deeper dive into the dataset. That is an area of further study.

I will mention that there is a prospective, observational study that is looking at massive transfusion in children for all types of reasons, headed up by one of our coauthors out of Washington University, Dr. Spinella. And so hopefully that will provide some more foundational information to guide future studies and potentially even validate some of our findings.

With respect to Dr. Schreiber's comments, certainly the weight was a significant issue and that is why we spent so much time looking at CDC and WHO data and really trying to understand how to best impute missing values and treat the data honestly.

And so when we did it in several different ways and found that we kept hitting that 40 milliliters per kilogram threshold where the sensitivity and specificity curves intersected, we felt that we could move forward with at least some degree of confidence, keeping in mind that the data is not perfect.

The long period of time in the study is certainly an issue because practices change over time. One of my co-authors, Dr. Jeremy Cannon, presented a poster already this week that tracks the transfusion practice over time.

And the bulk of the children that were transfused happened after 2006. You raise a valid point about looking at a time period that was more representative of current practices, but we wanted to get as much data as we could. We also don't know if the current adult resuscitation practices are the best for children. Maybe hemostatic damage control resuscitation is harmful for children. A more longitudinal study incorporating more types of transfusion practices over the last decade of war may help us get closer to the best method of caring for these children.

Dr. Bennett, to your question about whether this definition is a way of potentially limiting care in austere conditions, I don't think that anyone would advocate that resuscitative efforts should cease once a child reaches a 40-milliliter per kilogram threshold. In small children, 40-milliliters per kilogram may not amount to much blood and wouldn't be much of a burden on the blood bank at all. So, I don't think that the definition we proposed here has any clinical bearing whatsoever.

This definition is simply a research construct that will allow us to go back and look at those patients at increased risk for death and then look at their resuscitations in a retrospective fashion and understand the benefit of blood product ratios and volumes. But certainly it's difficult to be in downrange when the needs are great and the resources are limited. That's a very valid point.

Thank you very much.