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Facing futility in hemorrhagic shock: when to say ‘when’ in children and adults

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INTRODUCTION

The last two decades have seen increased efforts at early identification of those likely to require life-saving interventions such as rapid response teams, massive transfusion delivery, extracorporeal membrane oxygenation, and emergent surgical procedures.[1–3] However, it was not until recently that this same level of interest was directed at limiting early interventions in severely injured patients where such efforts might be futile. Not surprisingly, it was the COVID-19 pandemic and its disruption of vital supply chains that brought this to the forefront. During the early months of the COVID-19 pandemic, a 50% reduction in blood donations was offset by a significant drop in demand for products due to restrictions on elective surgery.[4] However, as society and its institutions began reopening, with surgical schedules returning to ‘normal’ and trauma volumes rebounding, the supply of blood required was unable to keep up. Adding to this was an increase in trauma, particularly penetrating trauma, resulting in an estimated 12% surplus usage, combined with a loss of plasma products to convalescent programs.[5] Finally, with increased attention to mass shootings and hospital disaster preparedness, surgeons and physicians have found the need to urgently address unforeseen critical shortages and vulnerability in the delivery of care.[6]

Although it took the extremes of the COVID-19 pandemic to expose the fragility of the healthcare system, the state of the industry had been problematic for decades, with many providers in the USA practicing for years with little regard for resource utilization. Although blood is but one of many precious resources we have shown disregard for, it is one in particular for which there is often no adequate substitute. Doughty *et al* responded by evaluating a triage tool for rationing of blood in massively bleeding patient in anticipation of the COVID-19 shortage.[7] This tool and its processes were aimed at providing a transparent, ‘fair’ distribution of available blood resources. Their guideline would be triggered when a less than 2-day national supply was noted, with each hospital triaging bleeding patients to transfusion or assess for futility at predefined increments. The predominate factors guiding these triage lists were Sequential Organ Failure Assessment scores, need for ongoing transfusions, and likelihood of arrest from hemorrhage.

Identifying futility in severely injured adult patients

With continued improvements in prehospital care and advancing technology for life support in the intensive care unit, however, patients with poor to grave prognoses can be sustained for prolonged periods.[7] As such, an increasing number of investigators have looked at futility in the trauma population, particularly among those receiving massive transfusion (MT) (>10 units of red blood cells (RBCs)) or even ultra-massive transfusion (UMT) (>20 units of RBCs in 24 hours). Morris *et al* evaluated MT patients and noted that although mortality increased with transfusion volume and age, a significant percent of older adults successfully resuscitated.[8] The authors argued that age alone should not be considered a contraindication to high-volume transfusion. Investigators from Johns Hopkins agreed that although age and transfusion volume alone could not be used as markers of futility, a nadir pH of <7.00 was associated with nearly 100% mortality in those MT patients 65 years of age and older.[9] When investigators mined the American College of Surgeons-Trauma Quality Improvement Program database for over 5000 UMT patients admitted between 2013 and 2018, they were unable to identify a futility threshold for mean RBC transfusion rate calculated within 4 or 24 hours.[10] However, the database query noted that all patients with a mean RBC transfusion rate of ≥7 units/hour calculated within 24 hours of arrival experienced in-hospital death.

But what about 2024? Since that study whose patients only included those admitted between 2013 and 2018, significant improvements in prehospital care have occurred, including the rapid expansion of blood product availability in the field. Perhaps early blood transfusion in the field, particularly with whole blood, could help patients avoid physiologic exhaustion, bettering tolerating their initial blood loss, which might lead to improved outcomes. Investigators evaluated this with the specific hypothesis that blood transfusion volumes would be a poor marker for futility after the availability of prehospital blood transfusions. Clements *et al* evaluated 2299 patients who received emergency-release blood products in the prehospital or emergency department setting.[11] They evaluated those who received an MT up to 50 units in 4 hours and those who received a super-UMT (>50 units in the first 4 hours). The investigators found that those in the super-UMT group were more likely to sustain penetrating injury, have lower field and arrival blood pressure, and received larger

Table 1 Predictors of 100% futility using the Suspension of Transfusions and Other Procedures (STOP) criteria

STOP criteria for 100% futility	PPV	NPV
Arrival SBP ≤50 mm Hg and LY-30 ≥30%	100%	78%
Arrival SBP ≤50 mm Hg and lactate ≥15	100%	77%
Arrival SBP ≤70 mm Hg, lactate ≥15, and LY-30 ≥30%	100%	77%
ROSC and lactate ≥12	100%	78%
ROSC and LY-30 ≥30%	100%	76%
ROSC and field GCS of 3	100%	77%

GCS, Glasgow Coma Scale; LY-30, percent amplitude reduction of the clot at 30 min after maximal amplitude achieved, reflecting the degree of fibrinolysis; NPV, negative predictive value; PPV, positive predictive value; ROSC, return of spontaneous circulation; SBP, systolic blood pressure.

prehospital and emergency department resuscitation volumes. Predictably, patients in the super-UMT group had lower survival than those in the ≤50 cohort (31% vs. 79%; $p<0.05$). However, there was no futility threshold for these patients, with a 22% survival rate at 150 units in the first 4 hours. Moreover, patients whose resuscitation began with whole blood had 43% increased odds of survival compared with those who received only component therapy and higher 30-day survival at transfusion volumes >50 units. Similarly, Gurney *et al* hypothesized that in combat settings, there would be no general threshold where blood product transfusion became futile to the bleeding soldier.[12] The investigators evaluated survival in 11 476 combat casualties who received at least one unit of blood product at US military medical treatment facilities during combat settings, between 2002 and 2020. They found that nearly 80% of combat casualties receiving greater than 100 units of blood survived to 24 hours. As with the Clements *et al*'s study in civilian patients, these authors also concluded that, although responsible blood stewardship is critical, futility should not be declared based on high transfusion volumes alone.

So, if the number of units or the rate at which they are transfused is *not* a cut-off, what is? In 2011, a group of investigators evaluated 704 massive transfusion patients from 23 trauma centers in the hopes of identifying cut-off points of futility.[13] The authors aimed to identify combinations of two or more variables that might predict greater than 90% mortality. Despite an exhaustive examination of extreme biochemical and physiologic variables, the authors were unable to identify variables that determined 100% mortality and struggled to find those with even 90% prediction. The only combination that exceeded 90% was severe brain injury (with head Abbreviated Injury Scale score of 5) and age of 65 years or greater. More recently, Van Gent *et al* evaluated these same variables with extreme cut-offs in three separate study populations of severely injured patients receiving transfusions.[14] The authors set out specifically to identify arrival laboratory values and hemodynamics, available early in the patient's resuscitation, that would predict 100% mortality (futility). They began by querying a previously collected single-center database of all trauma patients 15 years and older who met highest level trauma team activation and were admitted between 2010 and 2016. This generated several values with 100% positive predictive value (PPV) for death. This included cardiac arrest at any point with return of spontaneous circulation (ROSC) plus any of the following: initial rapid thrombelastography (LY-30) value of 30% or more, base deficit of 10 or greater, or natural field Glasgow Coma Scale score of 3. These values, as well as other combinations with PPV of 90% or greater, were then validated with two other datasets: a prospective, single-center dataset from 2017 through 2021 of severely injured patients receiving any emergency release blood (including prehospital products) and a multicenter, randomized trial of hemorrhagic shock patients (PROPPR). The developmental dataset was comprised of 9509 patients with a median age 36 years, median Injury Severity Score (ISS) of 17, and in-hospital mortality of 17%. The first validation dataset was comprised of 2137 patients with a median age of 38 years, median ISS of 28, and in-hospital mortality of 30%, whereas the multicenter validation dataset was comprised of 680 patients with a median age 34 years, median ISS of 26, and in-hospital mortality of 24%.

The validation sets identified patients whose PPV reached or approached 100%, including the following combinations: arrival systolic 50 mm Hg or less plus lactate of 15 or more or LY-30 of 30% or greater; arrival systolic of 70 mm Hg or less plus LY-30 of 90% or greater; and ROSC plus LY-30 of 30% or greater, lactate 12 or greater, or base deficit of 12 or more. Using three variables to achieve 100% PPV for death, the authors were also able to identify an additional combination of arrival systolic of 70 mm Hg or less, lactate of 15 or greater, and LY-30 of 30% or more. Although several combinations of arrival vital and laboratory values had 100% PPV, multiple combinations of less extreme values were noted to exceed 97% mortality; however, these were not universally fatal. The authors then generated a table of cut-off points that they defined as the STOP criteria or Suspension of Transfusions and Other Procedures (table 1). Of note, among datasets, up to 10% of patients with 100% predicted mortality consumed >100 units of blood products during their early resuscitation. Extreme admission physiology and laboratory values, with and without traumatic arrest and ROSC, are capable of predicting 100% mortality in severely injured adults. However, additional validation likely required prior to widespread adoption.

Table 2 Futility cut-off points for children and adolescents

Suspension of Transfusions and Other Procedures criteria for 100% futility	PPV	NPV
Arrival pH ≤7.00 and INR ≥2.0	100%	58%
Arrival base deficit ≥20 and INR ≥2.0	100%	55%
Arrival pH ≤7.05 and LY-30 ≥20%	100%	56%
Arrival base deficit ≥12 and LY-30 ≥20%	100%	70%
TBI and INR ≥2.0	100%	63%
TBI and LY-30 ≥20%	100%	89%

INR, international normalized ratio; LY-30, percent amplitude reduction of the clot at 30 min after maximal amplitude achieved, reflecting the degree of fibrinolysis; NPV, negative predictive value; pH, potential of hydrogen; PPV, positive predictive value; TBI, traumatic brain injury.

Identifying futility in children and adolescents

Although numerous investigators have attempted to identify such futility cut-off points as those described above, children are almost universally excluded from these evaluations. From a resuscitation and transfusion futility perspective, Reppucci *et al* evaluated injured children and adolescents between 2 and 18 years old from the Trauma Quality Improvement Program database.[15] Examining those patients with complete age and blood transfusion data who met the MT definition of 40 mL/kg/24 hours, 633 patients were included who met the MT definition of 40 mL/kg/24 hours. Similar to the above adult studies, the authors were unable to identify an upper transfusion volume threshold to predict mortality in pediatric trauma patients, regardless of mechanism. In a study of 118 pediatric trauma patients younger than 13 years and were found pulseless and apneic after having had an injury, Brindis *et al* noted that only 5% survived.[16] Moreover, all of these 'survivors' were neurologically impaired with devastating anoxic brain injury. Capizzani *et al* did achieve 100% mortality prediction in a small study of 30 patients with prehospital traumatic cardiopulmonary arrest.[17] The authors identified 100% mortality in those with >15 min of cardiopulmonary resuscitation, with neurologically devastated 'survival' with either non-reactive pupils, no pulse, or disorganized ECG on arrival. These authors and others have noted the importance of objective measures to better forecast futile care and inform both physicians and parents, as well as set reasonable expectations and steward resource utilization.

Building on these previous few studies in children and adolescents, and aiming for similar absolute cut-off points produced in adults, Kalkwarf *et al* set out to identify extreme laboratory values, both isolated and in combination, that could be used to predict 100% mortality in severely injured children.[18] The investigators evaluated all pediatric trauma patients (less than 16 years of age) who met highest level trauma team activation and were admitted to a single center between 2010 and 2016. Among their 1292 pediatric patients, there was a 10% mortality rate. Although there were significant differences in gender, race, and mechanism among survivors or non-survivors, those who died were significantly younger (median age 11 vs. 14; $p=0.007$) and had higher ISS (median 30 vs. 12; $p<0.001$). Similar to adults, there were multiple extreme values that were greater than 90% predictive of mortality, but achieving 100% was more elusive. Single arrival laboratory values that achieved 100% PPV were base deficit of 22 or greater, lactate 15 or higher, pH of 6.95 or less, international normalized ratio of 3.0 or greater, or platelets 30 x 10^9/L or less. As with adults, fibrinolysis by rapid thrombelastography was a predictor and achieved 100% futility as a single value at 50% or higher. Consistent with the low platelets, rapid thrombelastography maximal amplitude of 30 mm or less was 100% fatal. Although the authors were unable to identify physiologic criteria for cut-offs, they were able to identify several combinations of extreme laboratory values that achieved 100% mortality (table 2). In the presence of traumatic brain injury, these patients tolerated even less extreme values before 100% fatality was noted. The authors concluded that extreme admission laboratory values, with and without brain injury, are capable of predicting 100% mortality in severely injured children. Although they did note that validation of their single-center findings was warranted, they argued that, if supported, these cut-off points provide objective data which should initiate discussion within pediatric trauma community regarding cessation of resuscitation in such patients.

CONCLUSIONS

Major improvements in trauma care during the last decade have improved survival rates in the severely injured. The unintended consequence is the presentation of patients with non-survivable injuries in a time frame in which intervention is considered and often employed due to prognostic uncertainty. In light of this, discerning survivability in these patients remains increasingly problematic. Evidence-based cut-off points of futility can guide early decisions for discontinuing aggressive treatment and use of precious resources in severely injured patients arriving in extremis. The STOP criteria provide futility cut-off points to help guide early decisions for discontinuing aggressive treatment of patients in extremis. Even in children, using these extreme admission laboratory values is capable of predicting 100% mortality and futility of additional care in severely injured children with a high level of accuracy.

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