being superior to antibiotic administration after 60 minutes (but still within a time frame that we would categorize as "early") with regard to associated infection risk during index hospitalization. We understand the concerns about the methodology and conclusions of our study, but we believe that it provides valuable insights into the relationship between the timing of antibiotic prophylaxis and infection risk during the index hospitalization for open fractures, which is the quality metric that TQIP evaluates (e.g., only index hospitalization).[3] Despite the limitations of registry data, our study controlled for known risk factors of infection, such as age, comorbidities, injury severity, nerve/vascular trauma, washout of the femur/tibia, blood transfusion, and admission vitals. While our study did not show a significant association between early antibiotic administration and decreased risk of infection during the index hospitalization, we acknowledge that this conclusion applies only to this period. As such, we would not advocate for delaying antibiotics and agree with you that early antibiotic administration is an important component of the initial care in these patients. However, we would argue against the assertion that antibiotic administration within 60 minutes is a primary factor driving the incidence of delayed infections and chronic complications including nonunion. It is well studied in many areas of traumatic injury that initial prophylactic antibiotics are aimed at prevention of early infections, most commonly superficial site infections, and do not impact the incidence of delayed infections. We would also note that in the study cited to support "antibiotics within 66 minutes," the 66-minute cutpoint was selected retrospectively and the claimed benefit is from a sample size of 33 patients.[4] Other studies with much larger sample sizes have been unable to confirm or support this finding. What is consistent throughout the literature is that the primary drivers of chronic infection, osteomyelitis, and nonunion appear to be local wound factors, the surgical management and technique, and patient factors. This is highlighted in a 2015 multicenter study of 791 long bone fractures that found delayed healing and nonunion was associated with patient smoking history, fracture grade and contamination, and deep wound infection. Of note, time to antibiotic administration had no association with these chronic infectious and healing complications on multivariate analysis.[5]

To clarify the details of our analysis and the specific outcomes we studied, we would be happy to adjust our title to "Antibiotic administration within 1 hour for open lower extremity fractures is not associated with decreased risk of infection during index hospitalization" if the journal permits this, as we agree it is more accurate. That said, we have already explicitly put forth this limitation in the article in its current version.

Finally, we also agree that more research is needed to clarify the optimal timing of prophylactic antibiotics for open fractures and how best to define the acceptable temporal window for "early" antibiotic administration in patients with open fractures. We believe that our study contributes to the ongoing discussion and research in this area and helps to further tailor and optimize guidelines that will truly impact patient outcomes. We also hope that prospective multicenter studies may be able to shed even more light into this area and appreciate the opportunity to engage in this dialogue and encourage the collaborative efforts of both trauma and orthopedic surgeons to care for this population.

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OPEN

Serial "death diamond" TEGs are a bedside indicator of futile resuscitation during massive transfusion

To the Editor:

Loudon *et al.* demonstrated that among patients who received transfusion for trauma resuscitation defined as "massive transfusion" (10 to 19 U PRBCs/4 hours), the odds of mortality exceed survival beyond 16 U PRBCs/4 hours. For those defined as "ultramassive transfusion" (≥20 U PRBCs/4 hours) survival approaches zero beyond 36 U PRBCs/4 hours.[1] Loudon and colleagues suggested that trauma surgeons should view efforts as "heroic" beyond 16 U PRBCs/4 hours and "near futile" beyond 36 U PRBCs/4 hours.

They are to be congratulated for providing an objective and reproducible marker for futile resuscitation, particularly during a time of urgent blood bank shortage. As a limitation of their study, they mention that viscoelastic tests (VETs), such as thromboelastography (TEG), were not used. First described in 2015, a characteristic rapid TEG (rTEG) pattern called a "Death Diamond" (DD) correlates strongly with futile resuscitation. Specifically, a DD is defined as a rTEG tracing with a time to maximum amplitude of ≤14 minutes and time from maximum amplitude to total lysis of <30 minutes, which is highly predictive of death (Fig. 1).[2] Viscoelastic tests enable goal-directed blood product resuscitation and have improved mortality while simultaneously reducing blood component

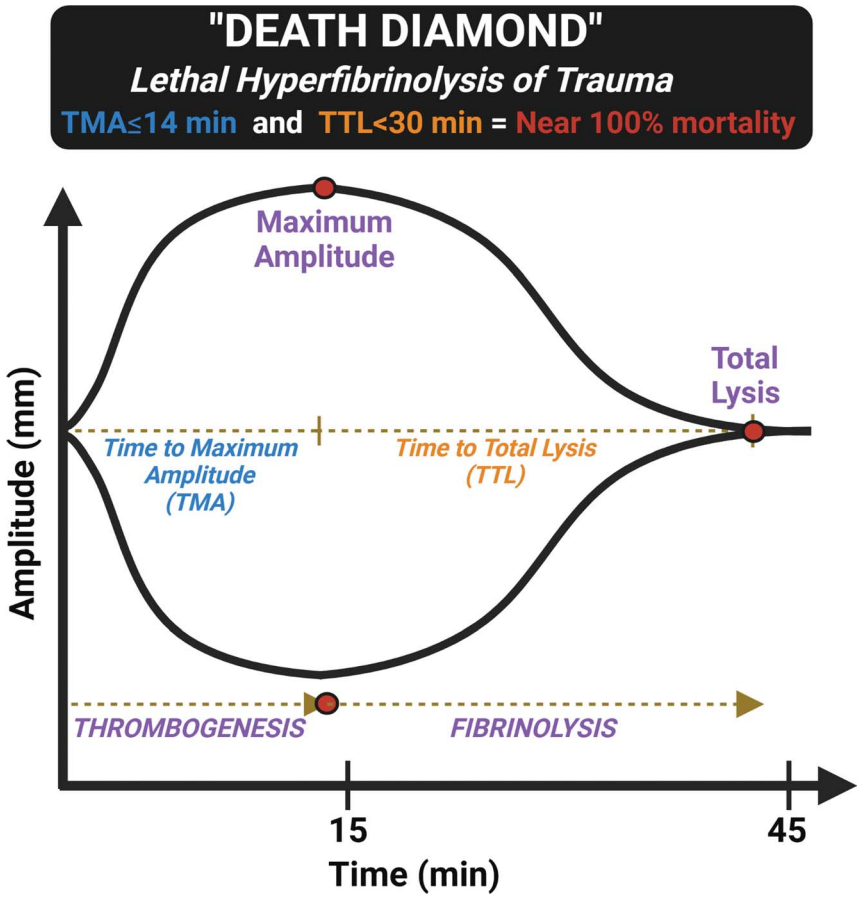

Figure 1. Schematic of an rTEG DD tracing. It has previously been demonstrated an index DD tracing portends near 100% mortality with TMA ≤14 minutes from the start of the test and TTL <30 minutes from the maximum amplitude. TMA, time to maximum amplitude; TTL, time to total lysis.

waste, yet there are few VET-based criteria that define futile resuscitation.[2,3]

Patients with a DD pattern comprised only 2.4% of the original 2015 DD study, yet these patients received nearly four times as many units of blood products (approximately 36 U per patient in <4 hours to death) compared with survivors. Interestingly, the 36 units per patient within 4 hours is the same number of units in 4 hours, which Loudon *et al.* described as a cutoff defining futile resuscitation. Furthermore, the initial 2015 DD study was refined by a 2022 follow-up study which demonstrated that serial DDs (i.e., the "double death diamond" [DDD]) within 3 hours of arrival predicted 100% mortality in trauma patients receiving massive transfusion.[2,3]

Clinical findings, biomarkers, and guidelines to assist the trauma surgeon prognosticate futility of massive transfusion are not well defined. The use of blood pressure, pulse rate, pH, base deficit, lactic acid, fibrinogen, and international normalized ratio are not able to predict futile resuscitation.[4] This was reinforced by the 2015 DD article, whereby survivors and nonsurvivors demonstrated no statistically significant difference in the index base deficit, pH, or number of units of blood transfused.[2]

We do not recommend that resuscitation should cease because of a single DD rTEG. However, if serial DD traces are observed following the initial resuscitation, the trauma surgeon's consideration to cease resuscitative efforts seems prudent. Because of the importance of accurately defining these limits such as time scales between serial DD TEGs, further research is clearly needed. In light of recent national blood product shortages, this situation is analogous to the now-accepted restrictions on emergency department resuscitative thoracotomy, which began with the study of parameters that predicted certain death and now are widely accepted guidelines.[5]

Therefore, should the surgeon be confronted with failure to achieve hemostasis as documented by the presence of serial DD rTEG patterns after large volumes of blood products, it would be reasonable to assume that the patient is deteriorating into a state of irreversible hemostatic exhaustion characteristic of early trauma-induced coagulopathy.

Loudon and colleagues' study will prompt other traumatologists to further elucidate the predictive value of the serial DDs as a biomarker for futile resuscitation. Describing a threshold number of PRBC units transfused within 4 hours combined with serial bedside viscoelastic parameters, as well as clinical and laboratory markers of shock (e.g., lactate, base deficit, hyperfibrinolysis), may reduce wastage of blood products through evidence-based stewardship. Most recently, the Suspension of Transfusions and Other Procedures (STOP) criteria have incorporated predictable "cut points" combining markers for shock such as serum lactate and degree of fibrinolysis, which together predict futility of resuscitation with a positive predictive value of 100%. Based on the STOP criteria, the concept of a "futility time out" at selected periods of massive transfusion has been proposed.[4] Serial DDs may serve as rapid check points to gauge the likelihood of successful continued resuscitation while other STOP data points are collected and analyzed during the hectic moments of providing massive transfusion. Loudon *et al.*'s work, combined with the use of serial DDs incorporated within the STOP criteria, may serve as building blocks toward a larger randomized trial using adjunctive VETs to define reproducible cut points that predict futile resuscitation. In the future with more studies similar to Loudon and colleagues' analysis, resuscitation practices may be significantly changed while leading to more rational use of scarce blood products.

AUTHORSHIP

E.E.M., H.B.M., andM.M.W. conceptualized the letter. E.E.M., S.G.T., D.W., and M.M.W. contributed to the literature review. E.E.M., H.B.M., S.G.T., M.S.F., S.S., J.R.C., J.B.M., C.M.B., D.W., M.M.W. contributed to the critical writing and revising of the letter.

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Response to Moore and Colleagues

To the Editors:

We appreciate the comments from Moore and colleagues regarding additional indicators of transfusion futility. As they point out, markers that tell us when enough is enough are not well defined.[1] Facing a critical blood shortage, we conducted a pragmatic review of our resuscitation practice to ensure the efficacy of every unit of blood transfused. While the acute blood product shortages of 2022 have abated somewhat, we have not seen supplies return to pre-COVID era normal. If faced with further critical scarcity, we plan to utilize the objective methodology offered in our article.[2]

Farrell et al.[1] offer an important tool to assess futility—viscoelastic tests (VET), "Death Diamond" (DD), "Double Death Diamond" (DDD). Identifying a patient with irreversible trauma-induced coagulopathy (TIC) is a clear marker of futility. Several other indicators have been studied with varying success. These include simple pH nadir, lactic acidosis, electrolyte ratios, pre-hospital shock index, and multiple inflammatory biomarkers. It is likely that a combination of some of these will provide the necessary understanding of the metabolic state of a patient during a shock resuscitation attempt and allow for a more objective "futility time-out."[3–5]

Defining unsalvageable physiology is only one part of a futility guideline in massive transfusion. Determination of futility can also be made for the patient requiring a resource that is unavailable. If demand for blood exceeds supply—as in mass casualty or combat scenarios—usual care will be abandoned for sufficient care. In such a situation, we offer units transfused in 4 hours as an easy clinical assessment for odds of survival. Our article defines resuscitations >16 U PRBC in 4 hours as heroic, as patients are more likely to die.[2]

Similar analysis is being performed on a larger dataset, which may help define the role balanced transfusion volume has on odds of survival. Further work is needed to define the characteristics of survivor outliers—those who defy >16 U in 4 hours cutoff. Large prospective studies are needed to create an objective framework for reassessment of futility in massive transfusion. Criteria should be standardized with universal triggers to stop a resuscitation effort.

The era of blood product shortages is likely not over. Trauma center supply chains continue to be challenged. Future combat scenarios are obviously unpredictable, but blood constraints are certainly not out of the question. Trauma surgeons must remain continually aware of their center's blood bank inventory. This inventory versus the projected blood volume requirements of a resuscitation—or several—must be kept in mind when employing local futility check points. If the blood supply is unavailable, the projected volume needed exceeds supply, and the physiology indicates futility, the effort should probably be stopped. Lastly, optimum efforts to stop hemorrhage must not be overlooked. Without those, none of this matters.

AUTHORSHIP

A.M.L. participated in the literature search, writing. A.P.R. participated in the literature search, writing. J.J.H. participated in the literature search, writing. M.L.M. participated in the writing, critical revision.

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