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Update on the Massive Transfusion Guidelines on Hemorrhagic Shock: After the Wars

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Abstract Over the past decade, crystalloid- and red blood cell-dominated massive resuscitation practices have largely been replaced with high-ratio transfusion of plasma, platelets, and red blood cells (RBCs) in massively bleeding trauma patients. Literature from military and civilian experiences with massive transfusion (MT) was reviewed, beginning with military transfusion practices at the onset of the wars in Afghanistan and Iraq and continuing through to present day. Early and balanced resuscitation (1:1:1 ratio of plasma, platelets, and RBCs) is superior to crystalloid- or red blood cell-driven resuscitation. Military research from Afghanistan and Iraq stimulated civilian investigations into ratio-based MT. 1:1:1 resuscitation carries the most benefit for massively bleeding trauma patients. Thrombelastography-guided MT can be used to supplement empiric 1:1:1 therapy in order to detect and address specific coagulopathies. Future directions in MT research presently include resuscitation with fresh whole blood and pre-hospital plasma-based resuscitation.

Keywords Massive transfusion · Hemorrhagic shock · Thrombelastography · Hemostatic resuscitation · Military trauma medicine

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Introduction

The need for massive transfusion (MT) is independently associated with increased mortality [1–3]. Patients requiring MT are often severely injured and in hemorrhagic shock. Although only 3 % of civilian trauma patients and 5–8 % of military trauma casualties require MT, these patients utilize 70 % of all transfusions given to trauma patients. Death from traumatic hemorrhage typically occurs within 24 h, resulting from exsanguination exacerbated by coagulopathy, acidosis, and hypothermia [1, 4–6]. Severely injured trauma patients are coagulopathic immediately following injury [7]. This coagulopathy, termed the acute coagulopathy of trauma (ACoT), is independently associated with increased mortality [7]. Resuscitation-induced coagulopathy (RIC), a separate entity, is iatrogenic in nature and exacerbated by hemodilution, crystalloid infusion, and surgical exposures [8]. Given the risk of early death and significant coagulopathy, patients requiring MT for hemorrhagic shock require a tailored and data-driven approach to hemorrhage control.

While the cornerstone of this approach remains surgical control of bleeding, a transition has occurred over the past five decades to emphasize a trimodal approach consisting of initial damage control and resuscitation, definitive management, and restoration of normal physiology in the critical care setting [9]. Even with a basic understanding of the fundamental principles of hemostasis and coagulopathy, traumatic hemorrhage remains the second most lethal cause of early traumatic death and the most common cause of preventable death after trauma [4, 9, 10]. Multiple concepts have been developed in an attempt to reverse the "bloody vicious cycle," including hemostatic resuscitation, which is resuscitation that is not only designed to replace blood loss but also to correct the coagulopathy associated with trauma and bleeding [11].

MT has classically been defined as 10 units of RBCs given over 24 h (unit-based definition) or the replacement of an entire blood volume within 24 h (volume-based definition) [12]. The principles of MT are the same regardless of definition or indication (Table 1). These principles highlight decades of military and civilian research. The detrimental consequences of large-volume crystalloid resuscitation have been increasingly described since the Vietnam War [13]. Termed Da Nang lung and later renamed acute respiratory distress syndrome in the civilian nomenclature, massive crystalloid resuscitation was first noted to be a potential factor in the development of pulmonary edema in battlefield casualties by Simmons et al. in 1969 [13]. Subsequent civilian research has repeatedly associated crystalloid resuscitation with dysfunctional inflammation, hyperchloremic acidosis, elevation in blood pressure resulting in displacement of established clots [14•], significantly increased cardiopulmonary complications, and an increase in mortality [15, 16].

During hemorrhage, restoration of tissue oxygenation and perfusion are critical. Red blood cell (RBC) transfusion increases 2,3-DPG concentrations and functional capillary density which are critical for tissue survival [17]. Hemostatic resuscitation addresses the underlying cellular pathophysiology of ACoT and RIC [8, 18] and has become the standard of care in hemorrhagic shock management following the wars in Iraq and Afghanistan. Following MT initiation and emergent hemorrhage control, laboratory-guided resuscitation should take precedence over empiric transfusion of blood products to characterize and correct the resultant coagulopathy. Additionally, as reflected by the principles of damage control resuscitation (DCR), hemostatic resuscitation has shaped current practical surgical applications (Table 2) [8].

Table 1 Principles of massive transfusion

1.	Avoidance of crystalloids
2.	Maintenance of tissue oxygenation and perfusion
3.	Hemostatic resuscitation
4.	Laboratory follow-up

Table 2 Principles of damage control resuscitation

1.	Compressible hemorrhage control
2.	Hypotensive resuscitation
3.	Rapid surgical control of bleeding
4.	Avoidance of crystalloids and colloids
5.	Prevention or correction of acidosis, hypothermia, and hypocalcemia
6.	Hemostatic resuscitation

Underlying these principles, yet notably absent, is a data-driven ratio to guide the transfusion of blood product components. The initial investigations to define the optimal MT ratio stem from the recent conflicts in the Middle East. Although largely retrospective and single center in design, military research again provides the framework to answer pivotal questions. The purpose of this review is to update the current MT guidelines for hemorrhagic shock management following the recent conflicts in the Middle East.

The Recent Wars

Following the terrorist attacks on September 11, 2001, the United States began Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Since initiation, these two combat operations have led to more combat-related injuries since the Vietnam War and an unprecedented level of wound severity and subsequent disability [19]. Military transfusion practices evolved to address these new injury patterns and spurred a paradigm shift in the resuscitative approach to massively bleeding patients.

In 2007, Borgman et al. [20] published a retrospective review of 246 patients who received MT at a combat support hospital (CSH) in Iraq over 2 years. On logistic regression, a high plasma:RBC transfusion ratio (1:1.4) was independently associated with improved survival [odds ratio (OR) 8.6; 95 % confidence interval (CI) 2.1–35.2] when compared to patients receiving a low transfusion ratio (1:8) [20]. The analysis included fresh whole blood (FWB) transfusions, routinely used at CSHs. Given the undefined clinical outcomes associated with FWB transfusions, the authors repeated the analysis excluding patients receiving FWB. The reduction in mortality remained after exclusion of this variable. Furthermore, the reduction in overall mortality was complimented by a significantly longer median time to death in the high-ratio group when compared to patients in the low-ratio group (38 vs. 2 h, $p < 0.001$) [20]. Extending the time to death affords combat causalities the opportunity to receive critical interventions and reflects the initial advantages of hemostatic resuscitation.

In 2008, Spinella et al. [21] retrospectively reviewed 708 patients who received at least one blood product transfusion from 2003 to 2004 at a CSH in Iraq. The study evaluated the individual influence of RBC and FFP transfusions on survival. Using multivariable logistic regression, the authors demonstrated an independent association with increasing survival and number of units of FFP transfused (OR 1.16; 95 % CI 1.05–1.28; $p = 0.003$) [21]. Conversely, there was a significant decrease in survival with every unit of RBCs transfused (OR 0.84; 95 % CI 0.79–0.9; $p = 0.001$) [21]. At 24 h, the median number of

units of FFP transfused was 0, the mean was 3, and the overall percentage of patients receiving FFP during this time frame was 48 %. This study highlights the independent influence of FFP for achieving hemostasis. As 43 % of patients in this study died from hemorrhage, the implications of hemostatic resuscitation on early mortality from hemorrhage become even more critical.

In 2009, Perkins et al. [1] retrospectively reviewed 462 patients who received MT at a CSH in Iraq over 2.5 years. The authors recognized the growing body of knowledge advocating for a balanced transfusion ratio of RBC:FFP; therefore, the study evaluated the impact of the RBC:apheresis platelets (aPLT) ratio. Patients were grouped into low (<1:16), medium (1:16 to <1:8), and high (≥1:8) RBC:aPLT ratios. The authors demonstrate that patients receiving a high transfusion ratio, when compared to a low ratio, were more likely to survive to 24 h (95 vs. 64 %, $p < 0.001$) and 30 days (75 vs. 42 %, $p < 0.001$). Comparing a high transfusion ratio to a medium ratio, the authors demonstrated increased survival at 24 h (95 vs. 87 %, $p = 0.04$). Lack of follow-up at 30 days precluded a mortality analysis at this time point. Additionally, the authors demonstrated a significantly increased median time to death when low (2.3 h) and medium (7.6 h) ratios were compared to a high (80.2 h) transfusion ratio ($p < 0.001$). Although this study did not address the optimal timing to initial platelet transfusion, the authors acknowledge the potential for survival bias.

In light of the fact that increased ratios of plasma and platelets occur over time, the possibility exists that high ratios occur because patients survive long enough as opposed to patients surviving because they receive high-ratio resuscitation. As demonstrated in the latter study, the median time to platelet administration was 2.5 h, while the median time to death in the low platelet group was 2.3 h. In order to avoid survival bias, prospective and randomized trials were required.

Following the work previously described [20], a clinical practice guideline (CPG) was established by the Joint Theater System of the US military to emphasize the principles of DCR. Simmons et al. [22] retrospectively reviewed the impact of this CPG by comparing MT ratios pre- and post-CPG implementation. The authors demonstrated not only an increase in the transfusion ratio of RBC to plasma and platelets but also a reduction in crystalloid infusion following CPG initiation. This study highlights a critical and nearly unique attribute of combat medicine: the ability to rapidly adopt and implement data-driven principles in a dynamic environment and on an impressive scale.

In 2012, Pidcoke et al. [7] reviewed all combat transfusion data from 2003 to 2012. The authors aimed to study the effects of multiple CPGs produced over the study period. 3632 combat patients involved in OIF or OEF who received at least one transfusion were included. During OIF, the FFP:RBC ratio was significantly lower than during OEF (0.6 vs. 0.82, $p \leq 0.001$). During OIF, the PLT:RBC transfusion ratio was significantly lower than during OEF (0.26 vs. 0.60, $p \leq 0.001$). MT patients were often coagulopathic at presentation which was associated with increased mortality; however, when considering the PLT:RBC ratio, there was a strong association with survival in this population (OR 0.124, CI 0.067–0.23, $p \leq 0.001$). Additionally, the absolute number of patients receiving MT increased over time while the mortality in this population decreased, reflecting the survival impact of a 1:1:1 MT transfusion strategy.

Transition to Civilian Practice

Early Civilian Work

While the military quickly adopted the 1:1 MT ratio, a number of civilian research teams questioned the applicability of this strategy to the civilian population. Snyder et al. retrospectively reviewed 134 patients receiving MT and found no difference in survival at 24 h when comparing high-ratio (≥1:2) FFP:RBC transfusion to low-ratio (<1:2) transfusion after accounting for the timing of product administration (RR 0.84; 95 % CI 0.47–1.50) [23]. Magnotti et al. retrospectively reviewed 103 patients requiring MT in the first 24 h and found that achieving a high-ratio resuscitation (≥1:2) conveyed no survival advantage (HR 0.558; 95 % CI 0.279–1.114) [24]. Further, achieving high-ratio resuscitation at 6 h did not confer a survival advantage when compared to those achieving high-ratio resuscitation at 24 h ($p = 0.92$) [24]. These authors both comment that patients are likely to transition to a high transfusion ratio over time, emphasizing again the limitation of survival bias on resuscitation studies [23, 24].

In 2008, Scalea et al. [25] prospectively observed 806 critically injured trauma patients requiring ICU admission; 81 patients required MT. This group found that higher RBC:FFP ratios administered in the first 24 h did not correlate with decreased mortality, shorter hospital length of stay, or shorter ICU length of stay. However, there were a few limitations to this study that likely impacted the conclusions of the group. Mortality within the first 24 h following admission was 4 % among the entire study group, suggesting that the population being studied was not ideal for measuring the effects of MT in severely injured patients. Additionally, the group only studied patients who survived to the time of ICU admission. Finally, this group noted that the amount of RBCs transfused in the 1:1 group was significantly less than the amount transfused to the

non-1:1 group (6.5 vs. 9.3, $p = 0.02$); this suggests that patients in the 1:1 group achieved hemostasis at higher rates than the non-1:1 group and benefited from balanced resuscitation.

PROMMTT and PROPPR

Early prospective work addressing the limitations associated with retrospective studies began with the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study published in 2013 [26••]. Of 905 patients enrolled, overall mortality was 25 %; of note, 94 % of hemorrhagic deaths occurred within 24 h and 60 % of hemorrhagic deaths occurred within 3 h of admission. In the first 6 h, patients in the high-ratio plasma:RBC (≥1:1) group had lower mortality rates than patients in the low-ratio (<1:2) group (hazard ratio 0.23, $p < 0.001$); patients in the high-ratio platelet:RBC (≥1:1) group had lower mortality rates than patients in the low-ratio (<1:2) group (hazard ratio 0.37, $p = 0.04$). Similarly, patients in the moderate-ratio plasma:RBC (≥1:2 to <1:1) had lower mortality rates than patients in the low-ratio group (HR 0.42, $p < 0.01$).

Following the PROMMTT trial, Holcomb et al. began the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial to compare outcomes and safety of 1:1:1 versus 1:1:2 transfusion ratios in severely injured trauma patients admitted to 12 Level 1 trauma centers in the US [27••]. These ratios were achieved by delivering blood products in coolers with the assigned ratio. 680 patients were prospectively enrolled and randomized to either the 1:1:1 arm ($n = 338$) or the 1:1:2 arm ($n = 342$). Overall, there was no difference between the 1:1:1 and 1:1:2 groups in 24-h mortality (12.7 vs. 17 %, $p = 0.12$) or 30-day mortality (22.4 vs. 26.1 %, $p = 0.26$). However, rates of achieving hemostasis were higher in the 1:1:1 group (86.1 vs. 78.1 %, $p = 0.006$) and death by exsanguination in the first 24 h was lower in the 1:1:1 group (9.2 vs. 14.6 %; difference of −5.4 %, 95 % CI −10.4 to −0.5 %). There were no differences between the study groups in any of the 23 measured complications or in hospital-free days, ventilator-free days, ICU-free days, or disposition at 30 days. The group concluded that while there was no difference in either 24-h or 30-day mortality, 1:1:1 therapy is safe, reduces early hemorrhagic death, and promotes hemostasis.

Current Trends in Civilian MT

In 2015, a survey of 245 trauma center in the US found that 95.1 % of centers reported the implementation of MT protocols [28]. The majority of respondents noted the influence of military research on implementing a MT protocol (35.1 % replied "important," 28 % replied "very important") [28]. Compared to 2006, current MT protocols have largely replaced crystalloid-based resuscitation for early component-based therapy. Implementing a MT protocol is associated with a decreased median number of total blood products transfused in the first 24 h [29]. Plasma is immediately available at 69 % of trauma centers; [30] among the 12 PROPPR study sites, 11 were able to provide 6 units of plasma within 10 min and 12 units within 20 min of ED arrival [31]. Storing thawed plasma in the ED or maintaining thawed plasma in the blood bank has decreased the time to plasma administration [32–35]. Between 68 and 87 % of centers report targeting high (≥1:2) plasma:RBC ratios, and between 68 and 78.6 % of sites target high (≥1:2) platelet:RBC ratios at the start of MT [28, 30]. A major concern for maintaining thawed plasma is waste; while one study reported improved utilization following MT protocol implementation (reduction of waste from 14 to 2 %, $p < 0.05$) [36], other studies demonstrate increased plasma waste associated with maintaining thawed plasma for fixed-ratio MT protocols [37, 38].

High-ratio MT aims to reduce early trauma hemorrhagic death [26••, 27••, 39]; therefore, rapid identification of patients requiring MT is critical. The assessment of blood consumption (ABC) score assesses four variables: penetrating mechanism of injury, systolic blood pressure (BP) ≤90 mmHg, heart rate (HR) ≥120 bpm, or a positive focused assessment with sonography in trauma (FAST) exam to predict the need for MT [40]. In 2009, Nunez et al. demonstrated that the ABC score correctly identified 85 % of patients requiring MT (sensitivity = 75 %, specificity = 86 %) [40]. Noting the operator-dependent nature of the FAST exam and variability in the accuracy of the HR parameter, Calcutt et al. developed the revised Massive Transfusion Score MTS (SBP <90, base deficit ≥6, temperature <35.5 °C, INR >1.5, and hemoglobin <11 g/dL) and showed it to be superior to the ABC score for predicting patients requiring MT within 24 h [41]. In 2013, Savage et al. developed the critical administration threshold (CAT) to analyze both volume of transfusion and rate of transfusion in an attempt to more rapidly identify MT patients [42•]. The authors defined CAT-positive patients as those requiring 3 units of RBCs within an hour and showed that CAT-positive patients had a higher unadjusted risk of death compared to patients meeting traditional MT criteria of 10 units of RBCs in 24 h (RR 3.58 vs. RR 1.82) [42•]. The CAT score is particularly effective for attempting to eliminate survival bias, and it includes patients who are massively exsanguinating but do so prior to receiving 10 units while excluding less critically injured patients who slowly receive 10 units over 24 h.

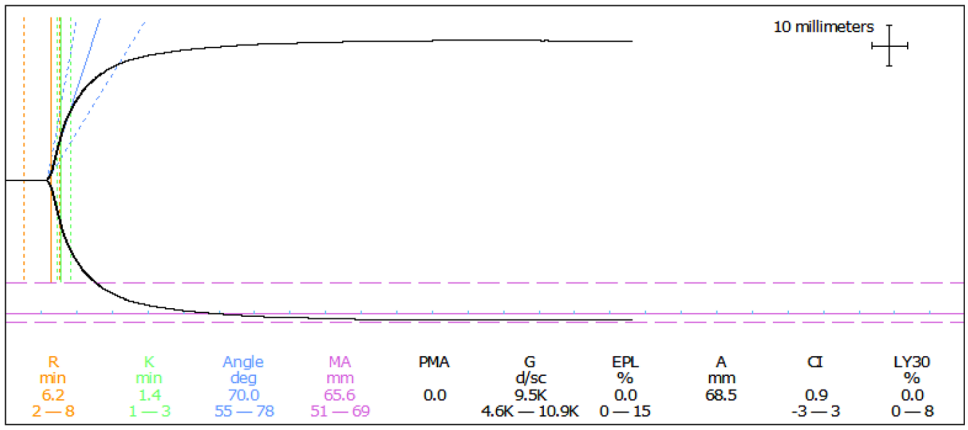

Fig. 1 Sample TEG tracing. Table 3 describes the calculation for each specific measure

Table 3 Common TEG measurements

Variable	Description of measurement	Element of coagulation investigated
Activated clotting time (ACT)—*rapid-TEG only*	Calculated value of the time from start of test to trace amplitude of 2 mm	Rate of clot formation, reflects clotting factor levels/functionality
Reaction rate (*r*)	Time from start of test to trace amplitude of 2 mm	Rate of clot formation, reflects clotting factor levels/functionality
Kinetic time (k-time)	Time (min) for trace amplitude of 2 mm to trace amplitude of 20 mm	Rate of clot formation, reflects fibrinogen and platelet function
α-angle	Angle between the baseline to a line running tangent to the slope of the trace	Rate of clot strengthening, reflects fibrinogen and platelet function
Clot amplitude at 5 min (CA5)	Amplitude measured at 5 min	Clot strength 5 min after start of test
Maximum amplitude (MA)	Greatest amplitude achieved in the trace	Platelet and fibrin contributions to maximum clot strength
G-value (shear modulus strength)	Calculated from amplitude, measures clot strength at any given amplitude	Absolute clot strength
Lysis at 30 min (LY30)	Percentage of clot lysed 30 min after reaching MA	Rate of fibrinolysis

Thrombelastography-Guided MT

Hemorrhagic shock management demands constant clinical reassessment and laboratory guidance. Managing coagulopathy in the setting of traumatic injury and hemorrhagic shock is extremely complex, mandating the use of rapid and accurate hemostatic assessment. Viscoelastic testing has been shown to be a feasible alternative to conventional coagulation testing in the trauma bay [43••]. Thrombelastography (TEG) and rotational thromboelastometry (ROTEM) are viscoelastic tests that dynamically assess clotting mechanics using a whole blood sample [44•]. A TEG tracing from a healthy patient can be seen in Fig. 1; parameters frequently measured in TEG tracings and corresponding definitions are shown in Table 3. While conventional coagulation assays (CCAs) such as prothrombin time (PT), International Normalized Ratio (INR), partial thromboplastin time (PTT), fibrinogen level, and platelet count each assess a single arm or element of the classic coagulation cascade, these tests require the presence of a nearby laboratory. TEG and ROTEM can rapidly and accurately assess the entire hemostatic system at the bedside.

TEG and ROTEM guide resuscitation efforts through early detection of coagulopathy and accurate prediction of future transfusion needs. Plotkin et al. showed that trauma patients with an MA <54 mm on admission required more blood products when compared to patients with an MA ≥54 mm (16 ± 11.4 vs. 6 ± 6.5, $p < 0.05$) [45]. Separately, Holcomb et al. showed that a TEG alpha-angle of <56° was predictive of MT of plasma (≥6 units in 6 h), platelets (≥2 units in 6 h), and cryoprecipitate (≥20 units in 6 h) among trauma patients requiring the highest level of activation ($p < 0.001$ for all variables) [43••]. Kornblith et al. found that patients with lower fibrinogen levels on the TEG-Functional Fibrinogen (TEG-FF) assay required more RBC and FFP transfusions in the first 24 h when compared to patients with high levels of functional fibrinogen (40.9

vs. 4.8 %, $p = 0.009$) [46]. Finally, Hagemo et al. demonstrated that ROTEM was a valid predictor of both ACoT and MT, with the CA5 of various ROTEM assays successfully detecting ACoT in 67.5 % of cases and need for MT in 77.5 % of cases [47].

Recent evidence suggests that TEG can be used to guide MT therapy. Gonzalez et al. conducted a prospective randomized trial of patients requiring MT to have management guided by either conventional coagulation assays (CCAs) or guided by TEG [48••]. The group found that 28-day survival was higher in the TEG-guided cohort compared to the CCA-guided cohort ($p = 0.032$) [48••]. A hazard model demonstrated a higher risk of mortality in the CCA-guided cohort when compared to the TEG-guided cohort (HR 2.17; 95 % CI 1.034–4.576) [48••]. Interestingly, the group noted that a higher plasma:RBC ratio was associated with lower predicted survival in the TEG-guided cohort but higher predicted survival in the CCA-guided cohort ($p = 0.027$); the authors inferred that the use of TEG may permit a more precise transfusion approach [48••]. Tapia et al. compared TEG-guided MT to 1:1:1 ratio-based MT and noted no difference in amount of blood product transfused or in 30-day mortality following blunt trauma between groups; however, following penetrating trauma, there was a higher mortality in the MT protocol group compared to the TEG-guided group [49••]. The authors concluded that TEG-guided MT was equivalent to a 1:1:1 MT strategy for patients with blunt injury and that 1:1:1 resuscitation may not be optimal therapy in all patients [49••]. Together, these findings suggest that early use of TEG may help distinguish patients truly requiring MT and create a patient-specific approach to resuscitation.

Update on the Current Guidelines

Successful MT depends on appropriate identification of patients requiring MT, initial resuscitation and cardiovascular stabilization, and further individualized therapy guided by laboratory analysis (Fig. 2). A ratio-based strategy using a balanced 1:1:1 ratio should be immediately

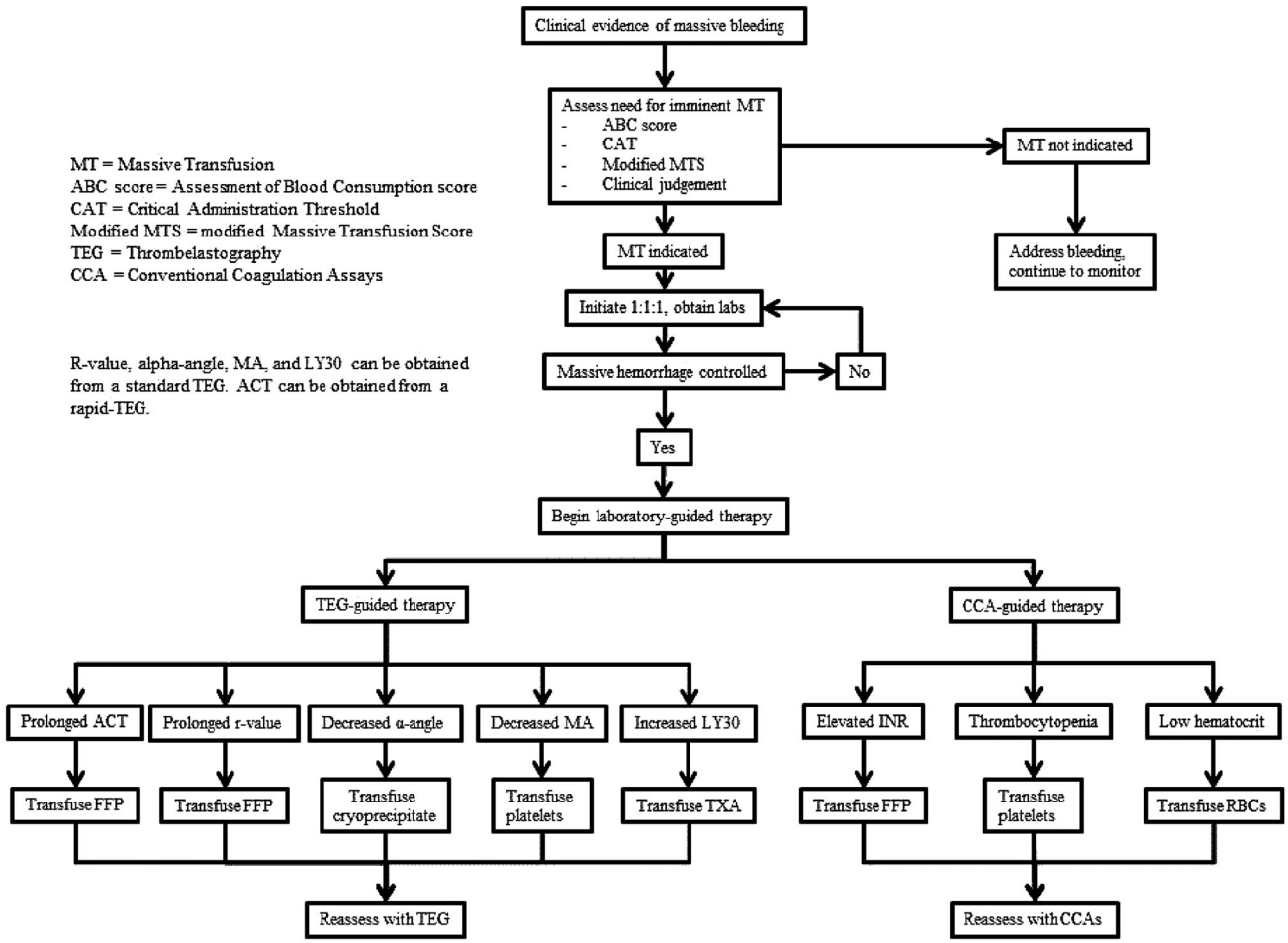

Fig. 2 Sample MT algorithm

initiated once a patient is identified by one of the standardized scoring systems (ABC, modified MTS, or CAT) to likely require a MT. As resuscitation continues, the patient is assessed for the presence of existing or developing coagulopathy through TEG or CCAs. No guidelines exist to suggest when a patient should transition from 1:1:1 to TEG-guided resuscitation; however, the transition should occur once massive hemorrhage is controlled. This transition might occur in the resuscitation bay, operating room, or interventional suite. Individual provider bias and clinical circumstance will influence where this transition point occurs. Utilizing an initial ratio-based strategy reinforced by laboratory and clinical indicators recognizes the dynamic nature of hemorrhagic shock and elicits the most appropriate clinical response.

Future Directions

Whole Blood Resuscitation

CSHs in OEF and OIF routinely use FWB for resuscitation [50, 51]. Nessen et al. compared the use of component therapy including FWB supplementation to the use of component therapy alone and found that after correcting for injury severity, combat casualties who received combined component and FWB therapy had significantly improved survival (OR 0.096; 95 % CI 0.02–0.53) [52]. Additional studies have compared military casualties who received FWB to those who did not receive FWB and found that there was no statistically significant difference between the two groups regarding the incidence of transfusion reactions ($p = 0.82$) and patients who received whole blood were more likely to survive [53, 54]. One group noted that proper selection of donors and rapid screening tests for infectious agents could detect HIV, HCV, and HBsAg with between 98 and 99 % sensitivity and specificity [54]. Cotton et al. found that the use of modified whole blood in civilian patients (defined as leukoreduced and, consequently, platelet-free whole blood units) reduced total transfusion volume among patients without brain injuries when compared to 1:1 RBC:plasma therapy [55•]. Given the paucity of data, further investigation into the use of FWB in MT protocols is necessary.

Balanced MT in the Pre-Hospital Setting

As the median time to hemorrhagic death was found to be 2.6 h in PROMMTT and 2.3 h in PROPPR [26••, 27••], pushing MT into the pre-hospital arena may prove critical for patients facing evacuation times ranging from 1 to 6 h [56]. Holcomb et al. studied the clinical impact of having thawed plasma and RBCs on rotor-winged ambulances [57]. The authors demonstrate that patients most in need of early transfusion (defined as those admitted directly to the OR, interventional radiology suite, ICU, or morgue) had lower 6-h mortality when transported on helicopters with access to plasma and RBCs (OR 0.23, $p < 0.03$) [57]. Brown et al. demonstrated that pre-hospital administration of RBCs in patients with severe blunt trauma was independently associated with a significant reduction in 24-h mortality (OR 0.05; 95 % CI 0.01–0.48), 30-day mortality (OR 0.36; 95 % CI 0.15–0.83), and trauma-induced coagulopathy (defined as admission INR >1.5) after adjustment (OR 0.12, 95 % CI 0.02–0.79) [58•]. In a separate study, Brown et al. also noted that pre-hospital RBC administration was associated with a decreased 24-h RBC requirement when compared to matched controls (coefficient −4.5 RBC units; 95 % CI −8.3 to −0.7) [59].

Conclusion

Management of hemorrhagic shock should emphasize hemostatic resuscitation highlighted by a balanced 1:1:1 resuscitation strategy. Transition from a ratio-based approach to a laboratory-guided approach should occur following surgical control of hemorrhage.

Compliance with Ethics Guidelines

Conflict of Interest Mr. Kemp Bohan, Dr. Yonge, and Dr. Schreiber declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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