Western Trauma Association critical decisions in trauma: Damage-control resuscitation

Chasen A. Croft, MD, FACS, Manuel Lorenzo, MD, MBA, FACS, FCCM, Raul Coimbra, MD, PhD, FACS, Juan C. Duchesne, MD, FACS, FCCP, FCCM, Charles Fox, MD, FACS, Jennifer Hartwell, MD, John B. Holcomb, MD, FACS, Natasha Keric, MD, Matthew J. Martin, MD, FACS, Gregory A. Magee, MD, MSc, Laura J. Moore, MD, FACS, Alicia R. Privette, MD, FACS, Morgan Schellenberg, MD, FACS, Kevin M. Schuster, MD, MPH, FACS, Ronald Tesoriero, MD, FACS, Jordan A. Weinberg, MD, *and* **Deborah M. Stein, MD, MPH, FACS, FCCM**, *Gainesville, Florida*

KEY WORDS: Damage-control resuscitation; massive transfusion; whole blood. (*J Trauma Acute Care Surg.* 2025;98: 271–276.

Hemorrhage is one of the leading causes of preventable trauma deaths worldwide. Since the recognition of the lethal triad of hypothermia, acidosis, and coagulopathy, damage-control surgery (DCS) has become a tenet of trauma care. A natural sequala of DCS has been the reconsideration of hemorrhagic shock resuscitation. Now known as damage-control resuscitation (DCR), a term coined by Holcomb et al. in 2007 following observations during Operations Iraqi Freedom and Enduring Freedom, DCR represents a paradigm shift in the management of hemorrhagic shock.[1,2] Prior to DCR, volume restoration was obtained using large volume crystalloid-based resuscitation. This proved deleterious, and in the last two decades, crystalloid resuscitation has been replaced by whole blood, balanced component resuscitation, or both. The article and its associated algorithm (Fig. 1) aim to provide a stepwise approach to the initial management of hemorrhagic shock resuscitation based on the most current evidence-based recommendations and expert opinion. The letter designations within the algorithm represent decision points and correspond to lettered headings in this article, which elaborate on the thought processes and evidence for the current recommendations, as well as notable caveats during DCR. This algorithm is intended to be used in conjunction with DCS during the initial phases of trauma care.

Submitted: June 4, 2024, Revised: July 22, 2024, Accepted: July 26, 2024, Published online: November 13, 2024.

From the Department of Surgery, Division of Acute Care Surgery, University of Florida College of Medicine (C.A.C.), Gainesville, Florida; Methodist Dallas Medical Center (M.L.), Dallas, Texas; Department of Surgery, Loma Linda University School of Medicine (R.C.), Loma Linda, California; Department of Surgery, Division of Trauma, Acute Care & Critical Care Surgery, Tulane University School of Medicine (J.C.D.), New Orleans, Louisiana; Department of Surgery, Division of Vascular Surgery, University of Maryland School of Medicine (C.F.), Baltimore, Maryland; University of Kansas Medical Center (J.H.), Kansas City, Kansas; Department of Surgery, Division of Emergency General Surgery and Acute Care Surgery, University of Alabama at Birmingham (J.B.H.), Birmingham, Alabama; Department of Surgery, Division of Trauma and Acute Care Surgery, University of Alabama (J.B.H.), Bethesda, Maryland; Department of Surgery, Division of Trauma, Surgical Critical Care and Acute Care Surgery, University of Arizona College of Medicine-Phoenix (N.K.), Phoenix, Arizona; Division of Acute Care Surgery, Department of Surgery (M.J.M., M.S.), Los Angeles General Medical Center, Los Angeles, California; Division of Vascular Surgery and Endovascular Therapy (G.A.M.), Keck Medical Center of USC, Los Angeles, California; Department of Surgery, Division of Acute Care Surgery (L.J.M.), The University of Texas McGovern Medical School-Houston Red Duke Trauma Institute, Memorial Hermann Hospital, Houston, Texas; Department of Surgery, Division of General and Acute Care Surgery, Medical University of South Carolina (A.R.P.), North Charleston, South Carolina; Department of Surgery, Section of General Surgery, Trauma and Surgical Critical Care, Yale School of Medicine (K.M.S.), New Haven, Connecticut; Department of Surgery, Division of Trauma and Acute Care Surgery, UCSF Department of Surgery at Zuckerberg San Francisco General Hospital (R.T.), University of California, San Francisco, San Francisco, California; Department of Surgery, Division of Trauma and Acute Care Surgery, St. Joseph's Hospital and Medical Center (J.A.W.), Phoenix, Arizona; and Program in Trauma (D.M.S), University of Maryland School of Medicine, Baltimore, Maryland.

Presented at the 53rd Western Trauma Association Annual Meeting, February 29, 2024, Snowmass, CO.

Address for correspondence: Chasen A. Croft, MD, FACS, University of Florida College of Medicine, 1600 SW Archer Road, M-602, Box 100108, Gainesville, FL 32610-0108; email: chasen.croft@surgery.ufl.edu.

DOI: 10.1097/TA.0000000000004466

ALGORITHM

Prehospital Care

The methods and means by which prehospital care is provided vary widely and depend on state and local protocols. The WTA has published a decision algorithm specifically targeting prehospital care.[3] A main component of prehospital care is the appropriate initial triage for risk of hemorrhage and initiating goal-directed resuscitation based on suspected injuries. Key concepts during prehospital care include obtaining IV access, implementing hemorrhage control techniques, and rapidly restoring circulating blood volume. In ideal settings, prehospital resuscitation should include transfusion of whole blood, if available, or packed red blood cells and plasma.[4] In the absence of blood products, judicious use of crystalloid fluids is reasonable. If active hemorrhage is suspected, tranexamic acid (TA) should be administered in the prehospital setting, if consistent with local protocols. In patients without suspected traumatic brain injury (TBI) permissive hypotension resuscitation to a systolic blood pressure (SBP) 90 mm Hg, should be implemented. However, in patients with

known or suspected TBI, SBP should be maintained at or above 110 mm Hg, if possible, as even short episodes of hypotension may result in increased TBI-associated morbidity and mortality, albeit at the possible expense of increased truncal hemorrhage.[5–7]

Recognition of Patients Requiring DCR and Initial Hemorrhage Control

The American College of Surgeons Advanced Trauma Life Support (ATLS) classifies hemorrhagic shock based on a combination of the amount of blood loss and associated clinical findings, including heart rate, blood pressure, and Glasgow Coma Scale.[8] While this is a practical and simplistic method for defining hemorrhagic shock, recent literature questions the accuracy of this classification and the associated clinical findings. While the most basic definition of a shock state is end-organ hypoperfusion, this may not always be accompanied by hypotension. Historically, SBP of less than 90 mm Hg has been the threshold of hemorrhagic shock. However, geriatric and pregnant patients may not exhibit the same physiologic response to shock and may, in fact, present with shock despite SBP being significantly higher than 100 mm Hg. In addition, medications, such as beta-blockers, may alter the physiologic response to significant blood loss. Therefore, SBP and heart rate alone should not be the only defining parameters when identifying candidates for DCR.[9] Evidence of active external hemorrhage or suspected noncompressible hemorrhage, based on the mechanism of injury, should raise suspicion for progression to life-threatening hemorrhagic shock requiring DCR. In addition, a base deficit (BD) of ≤5.0 mmol/L, shock index (SI) ≥ 1, or need for prehospital blood transfusion have all been validated as indicators for needing DCR.[10–14] Once active hemorrhage is identified, hemorrhage control techniques must be implemented expeditiously. Depending on the known or suspected source of hemorrhage, these techniques may include compression dressings, placement of a tourniquet, placement of a pelvic binder, or performing resuscitative endovascular balloon occlusion of the aorta (REBOA)/resuscitative thoracotomy (RT). In addition to these maneuvers, adequate IV access must be obtained, if not already performed. Options for vascular access include two large-bore IVs, intraosseous catheter placement, or large-bore central venous lines. Blood samples should be drawn for a type and crossmatch, to assess hemoglobin levels, BD, coagulation parameters (PT/PTT/INR, rapid thromboelastography [TEG]/rotational thromboelastometry [ROTEM if available), ionized calcium (iCa) and fibrinogen levels.

Blood Product Administration

The next vital component of DCR is the restoration of circulating blood volume.[15] Similar to the prehospital phase of care, variability exists in blood resuscitation protocols based on resource availability. Historically, crystalloids were the resuscitation fluid of choice. High-volume crystalloid infusion has

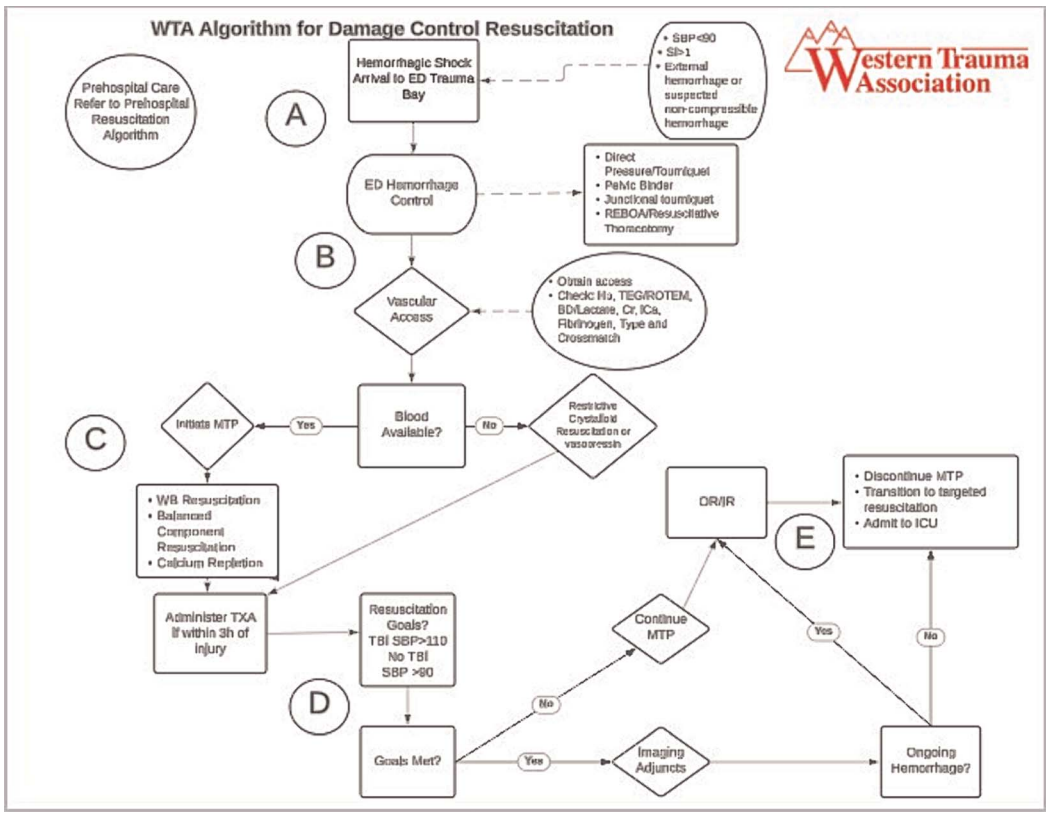

Figure 1. A Western Trauma Association critical decisions algorithm for DCR of patients presenting in hemorrhagic shock. ED, emergency department; SI, shock index; Hb, hemoglobin; Cr, creatinine; OR, operating room; IR, interventional radiology; ICU, intensive care unit.

been shown to worsen acid-base balance, increase the inflammatory response, induce hypothermia and endothelial membrane instability, and is associated with decreased tissue oxygenation and worsening of hemorrhagic coagulopathy, among other effects.[16–20] Therefore, we recommend limited or sparing use of crystalloid fluids during DCR. Current military and supporting civilian trauma literature recommend low-titer type O whole blood (LTOWB) as the initial resuscitative blood product of choice as warm fresh whole blood is not logistically available in civilian trauma centers and not yet approved by the Food and Drug Administration (FDA).[21–23] Low-titer type O whole blood improves the oxygen-carrying capacity and coagulation profile compared with blood component therapy.[24] Currently, the duration of cold storage of LTOWB ranges from 21 to 35 days, depending on the preservation process utilized, considerably increasing its availability and decreasing wasted resources.[25] The use of LTOWB decreases mortality risk and bleeding complications when compared with blood component therapy.[23,26] In one study, patients receiving whole blood had a significant reduction in the incidence of ARDS, duration of mechanical ventilation, need for massive transfusion protocol (MTP) activation, and transfusion volumes.[27] However, no difference in survival rates was found when comparing blood component therapy with whole blood.[28] Conversely, a recent meta-analysis of 24 studies, including 58,717 subjects, suggests hemostatic resuscitation with LTOWB may confer improved early and late survival compared with component therapy alone.[29] Nonetheless, LTOWB, if available at all, is often accessible in limited quantities, necessitating the utilization of a balanced component transfusion strategy. Aware of the limitation of resources and variability between trauma centers, an MTP should be promptly initiated. Civilian studies have shown that balanced component resuscitation for massive replacement of blood loss with thawed plasma, packed red blood cells and platelets is a successful strategy to minimize mortality from traumatic coagulopathy. Current literature recommends a ratio of 1:1:1 (plasma/platelets/pRBC) between components as the optimal resuscitative strategy; however, this ideal situation may not be feasible.[30] As such, a ratio of 1:1:2 is an acceptable; although not ideal, alternative.[21,28,30–34]

Fibrinogen deficiency has been identified in patients requiring massive transfusion due to hemorrhage. Early treatment and replacement as part of MTP has been recommended to decrease transfusion rates and mortality in trauma patients in hemorrhagic shock. In the United States, cryoprecipitate infusion is the standard replacement therapy which, along with FFP, corrects hypofibrinogenemia more efficiently.[35,36] In Europe, fibrinogen concentrates are readily available and have been shown to improve low fibrinogen levels due to the coagulopathy of trauma.[37] While acute fibrinogen deficiency can be treated with cryoprecitate, the CRYOSTAT-2 randomized trial suggests that early, empiric high-dose (≥5 pooled units) cryoprecipitate does not improve clinical outcomes nor improve mortality.[38] One pooled unit of cryoprecipitate (100 mL, 2 g fibrinogen equivalent) per 7 to 8 units of pRBC transfused is the appropriate dose that provides a significant survival benefit while limiting the total amount of blood components transfused.[39] As such, it is recommended that every round of MTP (6 units of PRBCs) should include one unit of pooled cryoprecipitate. The geriatric population is a group that requires special consideration, as many of these patients may be prescribed direct oral anticoagulants (DOACs). The management hemorrhagic shock in these patients is controversial as no current guidelines are established, and their reversal are determined by the treating physician based on the clinical picture at the time of the resuscitation and the indication for the use of DOACs. Regardless of the indication for DOAC, in general, reversal should be done expeditiously in patients presenting with hemorrhagic shock.

A high-normal iCa level should be maintained to counteract the citrate content of stored blood products, correct patient calcium deficiency prior to the trauma, and remedy homeostasis alterations during the shock state.[40,41] Hypocalcemia should be prevented in patients with hemorrhagic shock as it exacerbates the acidosis and coagulopathy associated with the coexisting hypoperfusion, as calcium is critical in several essential physiologic roles.[42] Ionized calcium levels should be monitored closely during resuscitation and calcium replacement therapy of 1–2 g calcium chloride or 3–6 g calcium gluconate per each MTP round should be administered promptly, without delay while obtaining laboratory values. Abnormal calcium levels during trauma resuscitation could be associated with increased mortality and use of blood products.[43,44]

Tranexamic acid should be given to patients at risk of hemorrhagic shock who have not already received a dose during the prehospital phase. Studies have shown reduced mortality in trauma patients receiving TXA despite their increased injury severity and transfusion requirements. The patient should only receive the initial TXA dose if administered within 3 hours of injury. When given >3 hours postinjury, TXA increases the risk of mortality.[45–47] This mortality data was not analyzed in patients with hyperfibrinolysis, as documented by viscoelastic testing (ROTEM or TEG). However, documented hyperfibrinolysis in the setting of ongoing hemorrhage should be treated according to clinical judgment.[48] Historically, for eligible patients (see section above titled Recognition of Patients Requiring DCR), TXA was given as a 1-g bolus over 10 minutes followed by 1-g intravenous infusion over 8 hours. This often resulted in the infusion being delayed or, in some cases, inadvertently omitted altogether. As such, it is now recommended that TXA be administered IV or IO as a 2-g bolus, negating the need for the infusion dose.[49] It should be noted that rapid infusion of TXA has been infrequently associated with transient hypotension.

Women of childbearing age require special consideration. Historically, Rhesus factor (Rh)-negative blood has been recommended for women of childbearing age as the administration of Rh-positive blood products to a Rh-negative woman of childbearing age may induce alloimmunization that may cause hemolytic reactions to subsequent transfusions or, more concerning, risks inducing hemolytic disease of the fetus and newborn in subsequent pregnancies. However, most MTPs utilize Rh-positive blood products as most blood donor centers use male donors to reduce the risk of transfusion-related acute lung injury. Current studies have shown that the risk of a woman developing alloimmunization, surviving hemorrhagic shock, producing anti-Rh antibodies, and subsequently getting pregnant with an Rh-positive fetus is exceedingly low and the benefits of Rh-positive transfusion far outweigh the risks. A recent survey among female respondents suggests that most would accept

lifesaving transfusion of Rh-positive blood products even with the potential low risk of future fetal harm.[50] The overall risk of alloimmunization for Rh-negative female patients in hemorrhagic shock exposed to Rh-positive blood is low varying from 3% to 20%.[51] As such, women of childbearing age in shock can receive Rh-positive blood, but conversion to Rh-negative blood should be undertaken once available. Current practices in obstetrics have introduced LTOWB as part of their transfusion strategies. Furthermore, Rh-immunoglobulin (Rhogam) should be administered to Rh-negative women, when feasible, if Rh-positive blood is utilized.

Although the classic principle in the management of bleeding is prompt resuscitation with blood products and definitive hemorrhage control, patients may present to facilities without blood component availability or surgical expertise. In this setting, recent literature recommends the use of low-dose vasopressin to counteract the refractory vasodilatation during transfer to definitive care.[52] It has been proposed that the use of vasopressin during acute resuscitation decreases blood product requirements and the risk of developing deep venous thrombosis.[53] It has been shown that supplementing exogenous vasopressin during resuscitation improves blood pressure, preserves renal mitochondrial function, and mitigates acute kidney injury.[54] Norepinephrine and phenylephrine use at this early stage of resuscitation has not been proven to be of benefit and is related to detrimental outcomes.[55] For institutions with no blood products available, we currently recommend the use of vasopressin and the judicious limited use of crystalloid fluid for resuscitation in patients in hemorrhagic shock awaiting transfer to an established trauma center.

Resuscitation Goals

As previously mentioned, blood pressure goals differ based on the presence or absence of a TBI. In patients with known or suspected TBI, maintaining SBP ≥ 100 mm Hg for patients 50 to 69 years old or at ≥110 mm Hg or above for patients 15 to 49 years or older than 70 years should be the goal for decreasing mortality and improving outcomes.[56] The goal is to prevent a secondary brain injury by maintaining an adequate cerebral perfusion pressure, which has been shown to have beneficial effects on the penumbra.[56,57] Several recent studies have demonstrated that whole blood transfusion was associated with decreased overall mortality, as well as TBI-related mortality among patients with concomitant hemorrhagic shock and TBI.[58–60] While vasopressors, specifically norepinephrine, have historically been used to maintain CPP, their use should be limited in the initial resuscitation phase and not be used until adequate volume repletion has been achieved. If TBI is not suspected, permissive hypotension (SBP ~ 90 mm Hg) should be attempted. A useful adjunct to assessing resuscitation goals is the serial measurement of either lactate or BD. Although both measurements are a gauge of end-organ perfusion, they can be affected by other metabolic and physiologic factors, such as acute drug/alcohol intoxication, underlying hepatic disease, and chronic renal failure. As such, lactate or BD trends should be followed as an indicator of adequate resuscitation, rather than relying on a single measurement.

Hypothermia should be monitored and treated throughout the resuscitative efforts as profound hypothermia has been shown to affect hemodynamics, as well as the clotting cascade. Active warming may be achieved via warm IV fluids, warm humidified ventilator circuitry, and passive warming of the environment.

Transition to Targeted Therapy

If the patient is a responder to resuscitative measures, consider performing adjunct imaging studies to further identify the injuries and the source of hemorrhage, if still unknown. If there are radiographic signs of ongoing hemorrhage or injuries requiring surgical intervention, the patient should be promptly transported to the operating room. For nonresponders or transient-responders, those that demonstrate continued physiologic deterioration despite volume repletion, DCR utilizing the massive transfusion protocol should continue in conjunction with immediate transfer to the operating room or interventional radiology suite for definitive hemorrhage control. Once active bleeding control is achieved, the patient should be considered for transitioning from a massive transfusion protocol to a targeted resuscitation strategy based on hemodynamics and viscoelastic testing.[61]

CONCLUSION

Prompt and definitive hemorrhage control is the main goal in the management of the actively bleeding patient. Damage-control resuscitation is the current mainstay in improving survival in this group of patients. Whole blood and/or balanced component therapy resuscitation and TXA should be initiated in the prehospital setting and adjuncts, such as early administration of fibrinogen (cryoprecipitate) and calcium repletion, should be started immediately upon arrival to the trauma bay as part of the DCR. Strategies, such as hypotensive resuscitation, limited use of crystalloids, and DCS, should be utilized, if necessary, as part of the definitive management of the bleeding patient. Even as significant advances in resuscitative strategies have been developed over the last five decades, further investigations into the optimal management of hemorrhagic shock continues.

AUTHORSHIP

C.A.C., M.L., C.F., J.Ha., N.K., M.J.M., G.A.M., L.J.M., A.R.P., M.S., K.M.S., R.T., R.C., D.M.S. participated in the concept and design. C.A.C., M.L. participated in the literature review. C.A.C., M.L. participated in the drafting of the article. C.A.C., M.L., CF, J.Ha., J.Ho., NK, M.J.M., G.A.M., L.J.M., A.R.P., M.S., K.M.S., R.T., D.M.S., R.C., J.C.D. participated in the critical revision.

DISCLOSURE

Conflict of interest disclosure: All JTACS Disclosure forms have been supplied and are provided as supplemental digital content (http://links.lww.com/TA/E36). Funding: This is an unfunded algorithm created through the Western Trauma Association.

REFERENCES

1. Holcomb JB. Damage control resuscitation. *J Trauma* 2007;62(6 Suppl): S36–7.
2. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 2007;62(2):307–10.
3. Sperry JL, Martin MJ, Moore EE, et al. Prehospital resuscitation in adult patients following injury: a Western Trauma Association critical decisions algorithm. *J Trauma Acute Care Surg* 2019;87(5):1228–31.
4. Schaefer RM, Bank EA, Krohmer JR, et al. Removing the barriers to prehospital blood: a roadmap to success. *J Trauma Acute Care Surg* 2024; 97(2S Suppl 1):S138-S144.
5. Rice AD, Hu C, Spaite DW, et al. Correlation between prehospital and in-hospital hypotension and outcomes after traumatic brain injury. *Am J Emerg Med* 2023;65:95–103.

6. Spaite DW, Bobrow BJ, Keim SM, et al. Association of statewide implementation of the prehospital traumatic brain injury treatment guidelines with patient survival following traumatic brain injury: the Excellence in Prehospital INJURY CARE (EPIC) study. *JAMA Surg* 2019;154(7):e191152.
7. Hawryluk GWJ, Lulla A, Bell R, et al. Guidelines for prehospital management of traumatic brain injury 3rd edition: executive summary. *Neurosurgery* 2023;93(6):e159-e69.
8. Galvagno SM, Jr., Nahmias JT, Young DA. Advanced trauma life support ((R)) update 2019: management and applications for adults and special populations. *Anesthesiol Clin* 2019;37(1):13–32.
9. Bonanno FG. The need for a physiological classification of hemorrhagic shock. *J Emerg Trauma Shock* 2020;13(3):177–82.
10. Callcut RA, Cotton BA, Muskat P, et al. Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. *J Trauma Acute Care Surg* 2013;74(1):59–65, 7-8; discussion 6-7.
11. Callcut RA, Johannigman JA, Kadon KS, Hanseman DJ, Robinson BR. All massive transfusion criteria are not created equal: defining the predictive value of individual transfusion triggers to better determine who benefits from blood. *J Trauma* 2011;70(4):794–801.
12. Cannon CM, Braxton CC, Kling-Smith M, Mahnken JD, Carlton E, Moncure M. Utility of the shock index in predicting mortality in traumatically injured patients. *J Trauma* 2009;67(6):1426–30.
13. Vandromme MJ, Griffin RL, Kerby JD, McGwin G, Jr., Rue LW, 3rd, Weinberg JA. Identifying risk for massive transfusion in the relatively normotensive patient: utility of the prehospital shock index. *J Trauma* 2011;70(2):384–8; discussion 8-90.
14. Eastridge BJ, Malone D, Holcomb JB. Early predictors of transfusion and mortality after injury: a review of the data-based literature. *J Trauma* 2006; 60(6 Suppl):S20–5.
15. Cannon JW, Khan MA, Raja AS, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg* 2017;82(3):605–17.
16. Cotton BA, Guy JS, Morris JA, Jr., Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock* 2006;26(2):115–21.
17. Wu F, Chipman A, Pati S, Miyasawa B, Corash L, Kozar RA. Resuscitative strategies to modulate the endotheliopathy of trauma: from cell to patient. *Shock* 2020;53(5):575–84.
18. Eddy VA, Morris JA, Jr., Cullinane DC. Hypothermia, coagulopathy, and acidosis. *Surg Clin North Am* 2000;80(3):845–54.
19. Miller RD, Robbins TO, Tong MJ, Barton SL. Coagulation defects associated with massive blood transfusions. *Ann Surg* 1971;174(5):794–801.
20. Weykamp MB, Stern KE, Brakenridge SC, et al. Prehospital crystalloid resuscitation: practice variation and associations with clinical outcomes. *Shock* 2023;59(1):28–33.
21. Lammers DT, Holcomb JB. Damage control resuscitation in adult trauma patients: what you need to know. *J Trauma Acute Care Surg* 2023;95(4): 464–71.
22. Sperry JL, Cotton BA, Luther JF, et al. Whole blood resuscitation and association with survival in injured patients with an elevated probability of mortality. *J Am Coll Surg* 2023;237(2):206–19.
23. Hazelton JP, Ssentongo AE, Oh JS, et al. Use of cold-stored whole blood is associated with improved mortality in hemostatic resuscitation of major bleeding: a multicenter study. *Ann Surg* 2022;276(4):579–88.
24. Naumann DN, Boulton AJ, Sandhu A, et al. Fresh whole blood from walking blood banks for patients with traumatic hemorrhagic shock: a systematic review and meta-analysis. *J Trauma Acute Care Surg* 2020;89(4):792–800.
25. Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. *J Trauma Acute Care Surg* 2016;81(1):21–6.
26. Brill JB, Tang B, Hatton G, et al. Impact of incorporating whole blood into hemorrhagic shock resuscitation: analysis of 1,377 consecutive trauma patients receiving emergency-release uncrossmatched blood products. *J Am Coll Surg* 2022;234(4):408–18.
27. Duchesne J, Smith A, Lawicki S, et al. Single institution trial comparing whole blood vs balanced component therapy: 50 years later. *J Am Coll Surg* 2021;232(4):433–42.
28. Meneses E, Boneva D, McKenney M, Elkbuli A. Massive transfusion protocol in adult trauma population. *Am J Emerg Med* 2020;38(12):2661–6.
29. Morgan KM, Abou Khalil E, Feeney EV, et al. The efficacy of low-titer group O whole blood compared with component therapy in civilian trauma patients: a meta-analysis. *Crit Care Med* 2024;52(7):e390-e404.
30. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313(5): 471–82.
31. Chang R, Kerby JD, Kalkwarf KJ, et al. Earlier time to hemostasis is associated with decreased mortality and rate of complications: results from the pragmatic randomized optimal platelet and plasma ratio trial. *J Trauma Acute Care Surg* 2019;87(2):342–9.
32. Van Gent JM, Clements TW, Cotton BA. Resuscitation and care in the trauma bay. *Surg Clin North Am* 2024;104(2):279–92.
33. Black JA, Pierce VS, Juneja K, Holcomb JB. Complications of hemorrhagic shock and massive transfusion-a comparison before and after the damage control resuscitation era. *Shock* 2021;56(1):42–51.
34. Torres CM, Kent A, Scantling D, Joseph B, Haut ER, Sakran JV. Association of whole blood with survival among patients presenting with severe hemorrhage in US and Canadian adult civilian trauma centers. *JAMA Surg* 2023; 158(5):532–40.
35. Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012;10(7):1342–51.
36. Endo A, Senda A, Otomo Y, Firek M, Kojima M, Coimbra R. Clinical benefits of early concurrent use of cryoprecipitate and plasma compared with plasma only in bleeding trauma patients. *Crit Care Med* 2022;50(10): 1477–85.
37. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019;23(1):98.
38. Davenport R, Curry N, Fox EE, et al. Early and empirical high-dose cryoprecipitate for hemorrhage after traumatic injury: the CRYOSTAT-2 randomized clinical trial. *JAMA* 2023;330(19):1882–91.
39. Dorken-Gallastegi A, Bokenkamp M, Argandykov D, et al. Optimal dose of cryoprecipitate in massive transfusion following trauma. *J Trauma Acute Care Surg* 2024;96(1):137–44.
40. Vasudeva M, Mathew JK, Groombridge C, et al. Hypocalcemia in trauma patients: a systematic review. *J Trauma Acute Care Surg* 2021;90(2):396–402.
41. Moore HB, Tessmer MT, Moore EE, et al. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. *J Trauma Acute Care Surg* 2020; 88(5):588–96.
42. Chanthima P, Yuwapattanawong K, Thamjamrassri T, et al. Association between ionized calcium concentrations during hemostatic transfusion and calcium treatment with mortality in major trauma. *Anesth Analg* 2021;132(6): 1684–91.
43. Wray JP, Bridwell RE, Schauer SG, et al. The diamond of death: hypocalcemia in trauma and resuscitation. *Am J Emerg Med* 2021;41:104–9.
44. MacKay EJ, Stubna MD, Holena DN, et al. Abnormal calcium levels during trauma resuscitation are associated with increased mortality, increased blood product use, and greater hospital resource consumption: a pilot investigation. *Anesth Analg* 2017;125(3):895–901.
45. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376(9734):23–32.
46. Rowell SE, Meier EN, McKnight B, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA* 2020; 324(10):961–74.
47. Cornelius B, Moody K, Hopper K, et al. A retrospective study of transfusion requirements in trauma patients receiving tranexamic acid. *J Trauma Nurs* 2019;26(3):128–33.
48. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg* 2014; 77(6):811–7; discussion 7.
49. Drew B, Auten JD, Cap AP, et al. The use of tranexamic acid in tactical combat casualty care: TCCC proposed change 20-02. *J Spec Oper Med* 2020; 20(3):36–43.
50. Uhlich R, Hu P, Yazer M, et al. The females have spoken: a patient-centered national survey on the administration of emergent transfusions

with the potential for future fetal harm. *J Trauma Acute Care Surg* 2023; 94(6):791–7.
51. Clements TW, Van Gent JM, Menon N, et al. Use of low-titer O-positive whole blood in female trauma patients: a literature review, qualitative multidisciplinary analysis of risk/benefit, and guidelines for its use as a universal product in hemorrhagic shock. *J Am Coll Surg* 2024;238(3):347–57.
52. Voelckel WG, Convertino VA, Lurie KG, et al. Vasopressin for hemorrhagic shock management: revisiting the potential value in civilian and combat casualty care. *J Trauma* 2010;69 Suppl 1:S69–74.
53. Sims CA, Holena D, Kim P, et al. Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial. *JAMA Surg* 2019;154(11): 994–1003.
54. Sims CA, Yuxia G, Singh K, Werlin EC, Reilly PM, Baur JA. Supplemental arginine vasopressin during the resuscitation of severe hemorrhagic shock preserves renal mitochondrial function. *PLoS One* 2017;12(10):e0186339.
55. Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. *J Trauma* 2008;64(1):9–14.
56. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017;80(1):6–15.
57. da Silva Meirelles L, Simon D, Regner A. Neurotrauma: the crosstalk between neurotrophins and inflammation in the acutely injured Brain. *Int J Mol Sci*. 2017;18(5):1082.
58. Hatton GE, Brill JB, Tang B, et al. Patients with both traumatic brain injury and hemorrhagic shock benefit from resuscitation with whole blood. *J Trauma Acute Care Surg* 2023;95(6):918–24.
59. Leibowitz A, Brotfain E, Koyfman L, et al. Treatment of combined traumatic brain injury and hemorrhagic shock with fractionated blood products versus fresh whole blood in a rat model. *Eur J Trauma Emerg Surg* 2019;45(2): 263–71.
60. Wu J, Moheimani H, Li S, et al. High dimensional multiomics reveals unique characteristics of early plasma administration in polytrauma patients with TBI. *Ann Surg* 2022;276(4):673–83.
61. Johansson PI, Stensballe J, Oliveri R, Wade CE, Ostrowski SR, Holcomb JB. How I treat patients with massive hemorrhage. *Blood* 2014;124(20): 3052–8.