Trauma Induced Coagulopathy

Hunter B. Moore
Ernest E. Moore
Matthew D. Neal
Editors

Second Edition

Springer

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HBM dedicates this book to his wife Brooke A Moore and Baby Estelle.

MDN: with love and gratitude to my "first family" Ellie, Cameron, and Donielle, and to my "second family" at UPMC Trauma built by the consummate surgeon, scholar, and family man, Andrew B. Peitzman, MD.

EEM dedicates this book to his wife Sarah Van Duzer-Moore, MD; son Peter K. Moore, MD, and his wife Tiffany Tello, MD; and of course other son Hunter B. Moore, MD, PhD, and his wife Brooke A Moore, MA.

HBM and EEM also dedicate this second edition to Eduardo Gonzalez for his editorial contribution to the first edition of this book. We wish him the best of luck in his academic plastic surgery career. We will be forever grateful for his monumental efforts in helping put the first edition together and never forget the countless hours spent in Steamboat cabin editing what seemed to be an endless list of chapters.

Preface – 2nd Edition

Like many good ideas in clinical medicine, *Trauma Induced Coagulopathy* was the product of a multidisciplinary research meeting. As the process unfolded, multiple classic papers were identified that addressed different concepts of coagulation changes following injury. It soon became apparent that consolidation of all of these concepts was too large for practical distribution or synthesis into a review article. We agreed the most useful reference would be a text of chapters written by those conducting research in various fields related to coagulation resulting in the first edition of *Trauma Induced Coagulopathy* in 2016. With the growing interest in understanding and managing coagulation in trauma, an updated second edition was due. During this interval, the Trans-Agency Consortium on Trauma Induced Coagulopathy (TACTIC), supported by the National Institutes of Health and coordinated with clinical trials funded by the Department of Defense, made significant efforts to enhance multidisciplinary research in trauma resulting in countless new discoveries. International collaboration and consensus resulted in a definition of TIC proposed by a working group of the International Society of Thrombosis and Hemostasis (ISTH). Several large clinical trials were also completed during this time, in addition to new clinical devices for measuring coagulation. The second edition has been expanded to 46 chapters from its original 35 to incorporate the massive global efforts in understanding, diagnosing, and treating trauma induced coagulopathy. At the time of publication, the world is focused on the vexing problem of COVID-19, and we have rapidly come to realize that a profound hypercoagulable state markedly contributes to morbidity and mortality. Knowledge gained from our collaborations and summarized in this text is now being deployed against the COVID-19 associated coagulopathy. At the same time, uncontrolled hemorrhage remains the leading cause of preventable death following trauma throughout the world, and the driving mechanisms remain to be established.

Aurora, CO, USA — Hunter B. Moore
Pittsburgh, PA, USA — Mathew D. Neal
Denver, CO, USA — Ernest E. Moore

Contents

Part I Introduction

1 Historical Perspective of Trauma-Induced Coagulopathy 3
Ernest E. Moore and Hunter B. Moore

2 Epidemiology of Hemorrhage-Related Mortality 13
Angela Sauaia, Ernest E. Moore, Charles E. Wade, and John B. Holcomb

Part II Physiology of Hemostasis

3 Cell-Mediated Hemostasis 31
Maureane Hoffman

4 Thrombin-Antithrombin System 43
Toshiaki Iba

5 Physiology of Haemostasis: Plasmin-Antiplasmin System 53
Nicola J. Mutch and Claire S. Whyte

Part III Pathophysiology of Trauma Induced Coagulopathy

6 Thrombin Formation 77
Beth A. Bouchard and Kalev Freeman

7 Platelets 85
Zachary A. Matthay and Lucy Zumwinkle Kornblith

8 Fibrinogen 101
Nathan J. White, Eduardo Gonzalez, Ernest E. Moore, and Hunter B. Moore

9 Defining and Assessing the Endotheliopathy of Trauma and Its Implications on Trauma-Induced Coagulopathy and Trauma-Related Outcomes 117
Alison Baker Nair, Martin A. Schreiber, and Shibani Pati

10 Protein C 135
Joshua J. Sumislawski, Benjamin M. Howard, and Mitchell Jay Cohen

11 Fibrinolysis Dysregulation Following Trauma 157
Hunter B. Moore and Ernest E. Moore

12 Complement System 175
Narcis I. Popescu and Florea Lupu

13 Neutrophils, Inflammation, and Innate Immunity in Trauma-Induced Coagulopathy 199
Christopher D. Barrett and Michael B. Yaffe

14 Disseminated Intravascular Coagulation 217
Satoshi Gando and Takeshi Wada

Part IV Coagulation Assessment

15 Grading Clinical Coagulopathy and Predicting Massive Transfusion 245
Sophie Thorn and Marc Maegele

16 Prothrombin and Partial Thromboplastin Time 265
Elizabeth P. Crowe, Ruchika Goel, and Paul M. Ness

17 Fibrinogen Assays 271
Christoph J. Schlimp and Herbert Schöchl

18 Rotational Thromboelastometry (ROTEM®) 279
Klaus Görlinger, Daniel Dirkmann, and Alexander A. Hanke

19 Thromboelastography (TEG® 5000 and TEG® 6s Hemostasis Analyzers with TEG Manager® Software) 313
Jan Hartmann and Robert A. Sikorski

Part V Management of Trauma Induced Coagulopathy

20 Red Blood Cell Transfusion 335
Anne M. Winkler

21 Plasma Transfusion 353
Jason B. Brill, Bryan A. Cotton, and Ryan A. Lawless

22 Cryoprecipitate/Fibrinogen Concentrate Transfusions 373
Ross A. Davenport, Laura Green, and Karim Brohi

23 Platelet Transfusion 391
Michael Adam Meledeo, Kimberly A. Thomas, James A. Bynum, Kristin M. Reddoch-Cardenas, Todd M. Getz, Heather F. Pidcoke, Philip C. Spinella, and Andrew P. Cap

24 Whole Blood for the Resuscitation of Massively Bleeding Civilian Patients 429
Mark H. Yazer, Jansen N. Seheult, Marshall P. Bahr, Andrew N. Beckett, Darrell J. Triulzi, and Philip C. Spinella

25 Adjunct Factor Replacement 443
Jared R. Gallaher, Christopher M. Freeman, and Martin A. Schreiber

26 Anti-fibrinolytics 455
Dominik F. Draxler, Robert L. Medcalf, and Russell L. Gruen

27 Ratio-Driven Massive Transfusion Protocols 473
Krista J. Stephenson, Kyle J. Kalkwarf, and John B. Holcomb

28 Goal-Directed Massive Transfusion Management 487
Geoffrey Rogan Nunns, Hunter B. Moore, and Ernest E. Moore

29 Prehospital Resuscitation 495
Andrew-Paul Deeb and Joshua B. Brown

Part VI Management of Post Injury Hypercoagulability

30 Venous Thromboembolism After Trauma 515
Jonathan P. Meizoso and Kenneth G. Proctor

31 Fibrinolysis Shutdown and Venous Thromboembolism 535
Gregory R. Stettler, Ernest E. Moore, and Hunter B. Moore

32 Congenital and Acquired Hypercoagulable States 547
Joseph Emmerich

Part VII Special Populations

33 Pediatrics 569
Amelia C. Lucisano, Christine M. Leeper, and Barbara A. Gaines

34 Traumatic Brain Injury-Induced Coagulopathy 583
Jing-fei Dong, Fangyi Zhang, and Jianning Zhang

35 Blunt Solid Organ Injury: A Call for Timely Chemoprophylaxis in the Setting of Early Hypercoagulability 607
Julia R. Coleman and Fredric M. Pieracci

36 Pregnancy 617
Daniel Katz

37 Liver Failure 635
Kenichi A. Tanaka, Jonathan Chow, and Ezeldeen Abuelkasem

38 Pulmonary Coagulation in the Pathogenesis of Trauma-Associated Acute Respiratory Distress Syndrome . . 649
Christophe J. Langouët-Astrié and Eric P. Schmidt

39 Management of Chronically Anticoagulated Patients 663
Jerrold H. Levy

Part VIII Future Directions

40 Randomized Controlled Trials: Informing Clinical Practice for Traumatically Injured Patients 679
Katherine M. Reitz, Andrew D. Althouse, and Jason L. Sperry

41 The Quantra® System and SEER Sonorheometry 693
Todd W. Allen, Deborah Winegar, and Francesco Viola

42 Dried Plasma for Trauma Resuscitation 705
Anthony E. Pusateri and Richard B. Weiskopf

43 Synthetic Blood Substitutes 719
Anirban Sen Gupta

44 Flow-Based Coagulation and Fibrinolysis Assays 745
Matthew Sorrells and Keith B. Neeves

45 Animal Models of Coagulopathy 763
Daniel Lammers and Matthew J. Martin

46 Applications of Viscoelastic Hemostatic Assays at the Site of Care: Considerations and Implications 781
Jan Hartmann, Julie A. Ryan, and Dan Mason

Index 787

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Part I

Introduction

1 Historical Perspective of Trauma-Induced Coagulopathy

Ernest E. Moore and Hunter B. Moore

Injury is the leading cause of death worldwide [1], and the third leading cause of mortality in the United States [2]. Despite advances in emergency medical systems and trauma care, deaths from injury have increased in the United States over the last decade [3]. In both the civilian [4] and military [5] settings, uncontrolled hemorrhage is the leading cause of preventable death after injury. In civilian studies, 80% of deaths from hemorrhage occur within the first 6 h, at a median time of 2.5 h [4]. Consequently, there is intense interest worldwide in the pathogenesis of coagulopathic bleeding after injury and its early management. While there have been substantial insights, the words of Mario Stefanini in his address to the New York Academy of Medicine in 1954 [6] remain applicable today: "The ponderous literature on the subject of hemostasis could perhaps be considered a classical example of the infinite ability of the human mind for abstract speculation. For several years, the number of working theories of the hemostatic mechanisms greatly exceeded and not always respected the confirmed experimental facts. In recent years, however, the revived interest in this field has led to an accumulation of new findings, which has been almost too rapid for their orderly incorporation into a logical working pattern. As a result, we have rapidly gone from a state of orderly ignorance to one of confused enlightenment, from which we have not emerged as yet."

The evolution of our understanding of the complexities of coagulopathy associated with trauma has been, in large part, the result of collaboration between civilian and military investigators and clinicians. Observations during war, due to a concentrated experience, often stimulate research in civilian academic centers, which culminates in advances in our patient care and understanding the fundamental problem. The earliest reports of coagulopathy in injured patients were generated from military research teams, often including civilian consultants, during major wars. These novel observations would then intensify hemostasis research in civilian centers. Ultimately, the resulting findings improved coagulopathy management in subsequent conflicts, and primed the environment for making new observations. The specific contributions to our understanding of coagulopathy, however, are somewhat difficult to ascertain from World War I through Vietnam because the primary focus was on optimizing shock resuscitation at a time when plasma or whole blood was employed to replace acute blood loss [7]. Nonetheless, several landmark contributions are well recognized.

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In 1916 the US National Research Council formed a Subcommittee on Traumatic Shock that collaborated with the British Medical Research Committee to study wounded soldiers in the front lines of France. Among them was Walton B. Cannon from Harvard, who was perplexed by the inconsistencies of the prevailing toxin theory of shock. Based on observations made on the battlefield in France during 1918 [8], Cannon wrote "Whatever the nature of the bodily changes…the heart, nervous system and other organs are suffering from an insufficient blood supply" and later admonished "if the pressure is raised before the surgeon is ready…blood that is sorely needed may be lost." Cannon documented the dynamic nature of coagulation experimentally with epinephrine infusion into animals that provoked hypercoagulability followed by hypocoagulability [9]. Cannon also stated prophetically "…shock is a loss of homeostasis, and without homeostasis the patient does not survive." Interestingly, two pivotal discoveries made during the later years of WWI [10], Richard Lewisohn's demonstration that sodium citrate was a safe process to store blood in 1915 and Karl Landsteiner's discovery of major blood types in 1917, led to the transfusion of blood to soldiers at the end of the war [11]. In 1936, based largely on Cannon's war observations and his own research at Vanderbilt and Johns Hopkins, Alfred Blalock [12] concluded "the work of recent years has shown that shock is dependent on an inadequate supply of blood to the tissues, which may be brought about by the most diverse causes," that is, hematogenic, neurogenic, vasogenic, and cardiogenic.

In the spring of 1940, with major victories achieved by Germany and Japan, the US involvement in the war appeared inevitable. Military experts recognized that bottled whole blood would be logistically impractical and enlisted the expertise of Edwin Cohen, a Harvard biochemist, to deconstruct blood in order to deliver its components to the battlefield [13]. Cohen was successful in purifying albumin as well as preparing plasma. At the onset of World War II, the National Research Council's Committee on Transfusion recommended that dried plasma—not blood—would be used if combat occurred outside the continental United States because it was easy to prepare and transport, whereas whole blood had to be typed, cross-matched, and refrigerated. However, based on the work of consultant Edward D. Churchill [14] in North Africa, who concluded, "wound shock is blood volume loss," the policy was changed to whole blood administration and implemented in Italy in 1943. In the preface to Colonel Churchill's review, Brigidar General Fred Rankin stated, "The present-day health standards of our troops and survival rate among our wounded have been unequalled in the history of war-fare. Perhaps one of the most important factors contributing to this highly record has been the role played by professional consultants."

In 1952, the Board for the Study of the Severely Wounded systematically reviewed the cause of death in 186 war casualties. The report was dominated by the discovery of a new syndrome "post-traumatic renal failure" that was attributed to prolonged hypoperfusion. This observation ultimately led to a paradigm shift in resuscitation, incorporating crystalloid as a fundamental component of initial fluid administration [15]. Contemporary studies in civilian hospitals, based on observations in trauma and burn patients, reported a "severe bleeding tendency" implicating fibrinolysis [16, 17]. The plasmin–antiplasmin system had been characterized at this point [18]. Alternatively, others postulated the loss of a labile clotting factor in whole blood and recognized the key role of platelets in hemostasis [19, 20]. In 1954, Stefanini [6] noted that post-injury hemorrhage persisting despite surgical control of bleeding was variously referred to as medical bleeding, diffuse bleeding diathesis, post-transfusion bleeding disorder, and disseminated intravascular coagulation (DIC), reflecting a general lack of consensus in the pathophysiology.

During the Korean War, William Stone is credited with promoting surgical research teams in the combat zone in Korea [21]. Scott and Crosby [22], representing one such team, reported that the prothrombin time (PT) was doubled in combat casualties while platelet count and fibrin-

ogen were increased. They also speculated that the cause was due to a labile clotting factor during blood storage. Artz and Fitts [23] observed that severely injured soldiers in the Korean Conflict required both return of shed blood and crystalloid for optimal survival, inspiring the later seminal work of Tom Shires [24] defining the scientific basis for crystalloids.

After the Korean War, civilian studies implicated a number of causative factors responsible for bleeding associated with major surgery requiring transfusion, including DIC [25], fibrinolysis [26], compromised viability of platelets in stored blood [27], and the loss of the labile factors V and VIII during storage [28]. The initial response to experimental hemorrhagic shock was hypercoagulability, followed by a progressive state of hypocoagulability with decreases in factors V, VIII, IX, X, and XI along with reduced fibrinogen and platelets [29]. The early clinical studies in Baltimore further identified a third phase of hypercoagulability in those who survived the intermediate period of hypocoagulability [30]. The authors concluded that in surviving patients, the oscillatory pattern converges into a "dynamic homeostatic state," whereas, in nonsurvivors, "fluctuations exceeded safe limits and behaved like a runaway system."

Based on the compelling experimental work by Shires et al. [24], the major change in resuscitation strategy in Vietnam was the administration of large volumes of crystalloid. This policy virtually eliminated acute kidney dysfunction, but led to a new entity coined "Da Nang Lung" [31], later termed the acute respiratory distress syndrome (ARDS) as the civilian counterpart [32]. The first large study on coagulation disorders in combat casualties from Vietnam was reported by Simmons et al. [33]. In their comprehensive analysis of 244 injured soldiers, the authors concluded that there is "an initial phase of hypercoagulability followed by hypocoagulability and this seemed best explained by DIC. Massive transfusion is accompanied by a dilutional coagulopathy compatible with factor levels in stored blood. Platelet levels fell, but PT, partial thromboplastin time (PTT), and fibrinogen levels are less affected. Fresh whole blood partially counteracts this dilutional state, but is rarely necessary." Miller et al. [34] studied 21 patients requiring a massive transfusion in Vietnam. Significant coagulation defects were not evident until 20 units of stored blood was administered. A dilutional defect in platelets appeared to be the primary cause for bleeding, and this was reversed with fresh whole blood administration. Interestingly, they reported no evidence of DIC or fibrinolysis. In 1974, John A. Collins [35] systematically reviewed the problems associated with massive transfusion and offered these observations: [1] "Early complete replacement of blood volume in the massively bleeding patient lessens the impact of exchange transfusion with stored blood," [2] "an intact circulation is a very good defense against the metabolic problems of massive transfusion," and [3] "historically as new problems associated with massive transfusion have been defined, they have almost always been grossly overstated."

Coagulation research in civilian institutions in the early 1970s began to elucidate the molecular events resulting in thrombin generation as the common end product of the extrinsic and intrinsic clotting pathways [36, 37]. In the clinical arena, trauma surgeons recognized that controlling bleeding from the liver was a priority to improve survival following trauma, but much of the work concentrated on techniques to achieve mechanical hemostasis with some mention of packing when bleeding continued [38–40]. It was also noted that tissue disruption from blunt trauma was associated with more problematic bleeding than penetrating wounds, stimulating resurgent interest in DIC and subsequent pulmonary microemboli [40, 41]. In the later 1970s, trauma surgeons began to recognize that bleeding following massive transfusion with stored blood required supplemental clotting factors. This literature is confounded by the fact that blood banks began to implement blood component therapy [42], a policy change that unmasked the prevalence of a trauma-related coagulopathy. In 1979, our group [43] and others [44–46] observed that the majority of patients succumbing to liver injuries died of a coagulopathy, after surgical control of bleeding. We recommended pre-emp-

tive fresh frozen plasma (FFP): "If the patients remain hypotensive after the second unit of whole blood, FFP should be administered then and with every fourth unit thereafter." Furthermore, we advocated fresh whole blood "…if bleeding persists despite normal PT, PTT, and bleeding times" [43]. Stimulated by these findings, we analyzed a group of patients who developed life-threatening coagulopathy with major vascular injuries and noted the compelling association of metabolic acidosis and hypothermia. Confirming the independent effects of acidosis and hypothermia on coagulation experimentally [47], we proposed the "bloody vicious cycle" in 1981 [48], which subsequently became known as the "lethal triad." The concept of truncating definitive repair of all injuries in coagulopathic patients in the operating room, to allow for correction of hypothermia, acidosis, and coagulopathy in the intensive care unit, was the fundamental basis for "damage control surgery" introduced by Harlan Stone et al. in 1983 [49]. In studying our coagulopathic injured patients in 1981 [48], we noted that higher ratios of FFP to stored blood were associated with improved survival and advocated presumptive FFP:blood administration of 1:4 in the emergency department. Charles Lucas and Anna Ledgerwood also conducted animal work that supported the concept of pre-emptive FFP during massive transfusion [50]. In the later 1980s [51], the Detroit General Group systematically studied coagulation abnormalities in patients requiring a massive transfusion of stored red blood cells (RBC) and postulated consumption of factors, reflected in standard measures of coagulopathy, that is, PT, PTT, and thrombin time (TT). Collectively, the coagulopathy associated with severe trauma was believed to be secondary to both consumption and dilution of clotting factors. There was also considerable interest in the early administration of platelets due to the long-term observation of deteriorating platelet numbers in stored blood, although clinical trials failed to confirm a benefit of pre-emptive platelet administration [52].

In the ensuing decade much of the clinical investigation centered on optimizing the use of damage control surgery for refractory coagulopathy [53–55]. Coagulation research during this period was further complicated by the practice of aggressive crystalloid resuscitation targeting supra-physiologic oxygen delivery, promulgated by William Shoemaker et al. [56]. This resulted in an epidemic of compartment syndromes, with much attention diverted to the urgent need to decompress the abdomen following protracted shock managed with high-volume crystalloid resuscitation [57]. In retrospect, most of the compartment syndromes and, to a large extent, coagulopathies were generated by overzealous infusion of crystalloid driven by the subsequently disproven concept of supra-physiologic oxygen delivery [58]. There is no question that chasing oxygen delivery with Swan-Ganz catheters and attempting to correct metabolic acidosis with large-volume crystalloid loading added a substantial component of dilutional coagulopathy [59].

The first decade of the twenty-first century perhaps represents the most significant insights gained into trauma-associated coagulopathy in modern history, and many of the contributing investigators are authors in this monograph. Progress was unquestionably inspired by the revolutionary concept of the cell-based model of coagulation proposed by Hoffman and Monroe [60] who emphasized the fundamental role of platelets as a platform for clotting factor assembly and thrombin generation on damaged endothelium. Paradoxically, these new insights led to the unbridled use of activated factor VII, which was ultimately proven unjustified [61, 62]. In 2003, MacLeod et al. [63] from the University of Miami made the observation that 28% of severely injured patients had an elevated PT on arrival to the hospital, and this was associated with an increased risk of mortality. At the same time, Karim Brohi [64] from the Royal London Hospital reported that 24% of severely injured patients had prolonged clotting times, and extended their analysis to demonstrate this abnormality was independent of fluid administration and, consequently, termed the syndrome the "acute coagulopathy of trauma" (ACOT). Stimulated by his observations on the ACOT in London, Brohi pursued a trauma research fellow-

ship with another fellow, Mitch Cohen, and colleagues in San Francisco. Together, in 2007, this civilian research team provided enticing evidence that activation of protein C is a mechanistic component of ACOT [65]. Shortly thereafter, Par Johansson [66] from Copenhagen added evidence of endothelial glycocalyx degradation, stimulating interest in the endotheliopathy of ACOT. Additional evidence has implicated the innate immune response in general [67], and neutrophils specifically [68] in the pathogenesis of ACOT.

Simultaneous with these provocative studies in civilian trauma centers, the military recognized coagulopathy as the most common source of preventable death in soldiers in the war in Iraq [69]. When confronted with this challenge, the US Army suggested the best solution was to replace the acute blood loss with a blood component formula that would replicate the whole blood lost, thus the genesis of the 1:1:1 concept [70]. In 2007, Borgman et al. [71] reported the US military experience in Iraq suggesting a survival benefit for soldiers resuscitated with an FFP:RBC ratio approaching 1:1 when they required a massive transfusion (10 units of red blood cells (RBC) in 24 h). This report was extrapolated to support the proposed "damage control resuscitation" concept with 1:1:1 as the centerpiece. Although the relative simplicity of this recommendation is appealing, this concept is not intuitive biologically and has prompted vigorous debate that continues today [72–75]. Ultimately these debates stimulated the National Institutes of Health (NIH) to conduct a Trans-Agency Coagulopathy in Trauma Workshop, held in Bethesda in April 2010. Out of this meeting came the consensus that the term "trauma-induced coagulopathy" (TIC) should be employed to describe what was previously referred to as ACOT in order to ensure a common language for research.

Conspicuous among the many questions is whether platelets should be given empirically with the initial administration of FFP and RBC units in patients at risk for TIC. In contrast to platelets for first-line therapy in the United States, the European approach has been to load fibrinogen [76]. Theoretically platelets contribute more to clot strength than fibrinogen, but each component can compensate for deficiencies in the other. A recent randomized study with empiric platelet transfusion for intracranial hemorrhage indicated adverse outcome [77]. The current limitation in assessing platelet function for hemostasis has hampered resolution of this topic [78, 79]. Furthermore is the ongoing debate of the optimal ratio of FFP:RBC units in the patient at risk for TIC. The only randomized trial to date failed to demonstrate a prolonged survival advantage of a 1:1 versus 1:2 FFP:RBC ratio when delivered with platelets [80]. Of note, this randomized trial showed improved survival at 3 h, but statistical difference was lost at 24 h as well as the FDA standard of mortality at 30 days due to attrition in both study groups. The controversy has prompted another NIH workshop to define optimal endpoints for clinical hemostasis research, and it appears a 3–6 h endpoint may be acceptable in certain studies [81]. Independent of the optimal ratio debate, the concept of plasma first resuscitation was extended to prehospital studies, suggesting patients with extended transport times may benefit from plasma in the field [82, 83].

The role of systemic fibrinolysis in TIC has added another layer of controversy. The role of dysregulated fibrinolysis was largely overlooked until the widespread implementation of global viscoelastic hemostatic assays in trauma care, such as thrombelastography (TEG) and thromboelastometry (ROTEM) [84–87]. The CRASH-2 trial reported in 2010 [88] prompted unbridled use of tranexamic acid (TXA) until the limitations of this study were acknowledged [89, 90]. Consequently, it was generally accepted in the United States that TXA should be reserved for selected populations until randomized trials clarify the indications. The most recent randomized trial of prehospital TXA for TBI reported a survival benefit of 2 gm, but without viscoelastic evidence of inhibited fibrinolysis suggesting the benefit may be derived from anti-inflammatory effects (personal communication Martin Schreiber MD). The elucidation of fibrinolysis shutdown [91–93] and subtypes [94] with an associated risk of thromboembolism has added to

the concern of routine TXA administration. Furthermore, the issue of whether goal-directed therapy via viscoelastic assays such as TEG or ROTEM is the optimal management for TIC remains debated. A large retrospective study indicated that TEG-driven resuscitation was more effective than 1:1:1 approach [95], and our recent single-institution randomized study [96] indicated that TEG was more effective in guiding a massive transfusion protocol than conventional laboratory tests (PT/INR, aPTT, platelet count, and d -dimers). In 2013, driven by these ongoing controversies, the NIH funded a Trans-Agency Research Consortium for Trauma-Induced Coagulopathy (TACTIC) in collaboration with the Department of Defense (DOD) with the aim of elucidating the underlying mechanisms of TIC from "road to rehabilitation" [97].

Interestingly, the most recent chapter in hemostasis management of the severely injured is the return to stored low titer O negative whole blood (LTOWB) as the initial resuscitation fluid. Stimulated by military success of the walking donor policy with fresh whole blood [98], the current trend is to administer LTOWB in the field [99] as well as the emergency department [100] back to the future.

In sum, the need to define the scientific basis for blood component administration and regulation of fibrinolysis in the critically injured patient is as clear today as it was 60 years ago and, as optimistically articulated by Mario Stefanini [6], we are making substantive progress. "While the multiplicity of hypotheses and the conflict of experimental findings still deny us a firm theoretical basis for the interpretation of the mechanisms of hemostasis, the impact of the advances of the last 10 years on the diagnosis and management of the bleeding patient has been staggering. New diagnostic tests have greatly increased the accuracy of the diagnosis; broader interest in the isolation of coagulation factors and of platelets points to more specific methods of treatment in the near future. One feels that, with the unending ferment of ideas and fervor of investigation in this field, great progress lies ahead."

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2 Epidemiology of Hemorrhage-Related Mortality

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Frequency

Uncontrolled bleeding has been reported to cause at least one quarter of all injury-related deaths [1–9], and over 40% of potentially preventable postinjury deaths, both in military [10, 11] and civilian settings [3, 12–14]. A review of preventable and potentially preventable deaths in an urban trauma center from 1998 to 2005 in Los Angeles, California, documented that 40% were due to hemorrhage [15]. A 2019 systematic literature review of pre-hospital deaths due to trauma indicated that exsanguination was responsible for 54–81% of trauma deaths deemed potentially or definitely preventable in studies conducted throughout the world from 2000 to 2013 [16]. The reports on the causes of postinjury death differ widely depending on the data source and definitions. Studies using civilian hospital, state, or national trauma registries (e.g., the American College of Surgeons sponsored National Trauma Data Bank, NTDB[1]) do not include deaths prior to admission, which still represent for over half of the trauma fatalities [17]. Similarly, military patients killed in action (i.e., before arriving at a medical treatment facility) are sometimes not included [11, 18]. It is important that the readers verify these different ways to represent the data (e.g., in-hospital, population-based) when appraising articles.

In a 2011 study by investigators at the United States Army Institute of Surgical Research (USAISR) of combat fatalities occurring in the deployed environment from October 2001 to June 2011, 87% occurred before arrival at a medical treatment facility [10]. Of these, 24% were considered potentially survivable, and were predominantly (91%) due to hemorrhage. During the same period, the USAISR group reported that only 4.6% of all combat deaths occurred after reaching a military treatment facility (a.k.a, died-of-wounds), of whom close to half were deemed potentially survivable, again largely due to acute hemorrhage (80%) [19].

In contrast to military literature, few studies have assessed the role of hemorrhage in civilian trauma deaths occurring in the pre-hospital setting, due to difficulties in obtaining granular

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[1]Available at https://www.facs.org/quality-programs/trauma/tqp/center-programs/ntdb, accessed 11/30/2019.

data [20–22]. The table shows the impact of hemorrhage in pre-hospital (when available) and in-hospital deaths in several epidemiological investigations listed in chronological order of the period covered by the study. A civilian 1992 epidemiologic study in Denver City and County, Colorado, found that 34% of the deaths occurred in the pre-hospital setting, and of these, over one third were due to exsanguination [3]. Overall, the study determined that 31% of all deaths attributed exclusively to bleeding (i.e., excluding those in combination with traumatic brain injury (TBI)) occurred in the pre-hospital phase. A similar study in San Diego, California, also in 1992, in which autopsy data were available for all fatalities, also found that 40% of the fatalities happened before arrival of pre-hospital providers, and that close to a third of all deaths were due to uncontrolled hemorrhage in the chest, abdomen, or both cavities [5]. Unfortunately, this study did not specify the impact of hemorrhage specifically in the pre-hospital setting.

Stewart et al. [23] studied in-hospital trauma fatalities from 1995 to 2001 occurring at one of three level 1 trauma centers in San Antonio, Texas, and attributed shock as the cause of death in 21% of the cases. Almost two decades later, a study of autopsies of individuals who died of trauma pre-hospital in the field in Miami-Dade county in 2011 [12] reported that hemorrhage caused a similar percentage of the deaths (34%), second only to neurotrauma (36%); combined hemorrhage and neurotrauma caused 15% of the deaths. Close to a third (29%) of all deaths were judged to be potentially survivable, due primarily (54%) or partially (10%) to hemorrhage. In a study in Harris County, Texas, Drake et al. [14] combined 2014 data from autopsy, medico-legal death investigation reports, emergency medical service, hospital records, hospital trauma morbidity and mortality reports, in a comprehensive epidemiological investigation of trauma deaths. They determined that close to half (46%) of the fatalities still happened in the pre-hospital phase, 36% in the index-hospitalization, and 18% after the index-hospitalization. Hemorrhage was implicated in 20% of the deaths in the pre-hospital phase and 20% of the in-hospital deaths. These investigators also demonstrated that hemorrhage was most impactful in deaths that were deemed preventable/potentially preventable (P/PP): hemorrhage caused 55% of the P/PP deaths in the pre-hospital phase, and 28% of the in-hospital P/PP deaths. A prospective, multicenter Western Trauma Association study of trauma deaths between December 2015 and August 2017 in 18 trauma centers across the United States, published in 2019, reported exsanguination caused 23% of all deaths among patients who were transported to trauma centers, second to TBI (45%) and followed by physiologic collapse (25%) [6]. Notably, over half (58%) of all bleeding-related deaths occurred during transport or in the emergency department. Collectively, these studies demonstrate the substantial impact of hemorrhage in trauma deaths in general, and among deaths at the scene and P/PP deaths specifically. They highlight the need for improved resuscitation strategies in the pre-hospital arena as well as better data monitoring of this phase in trauma care.

Most studies outside the United States reveal a similar high impact of hemorrhage in trauma deaths. A 2005 population-based investigation in Newcastle, Australia, attributed bleeding as the cause of 33% of all deaths (both pre- and in-hospital) [7]. In Canada, where blunt mechanism predominates, a study of deaths occurring in a level 1 trauma center from 1999 to 2003 implicated hemorrhage in 15% of all in-hospital deaths, of which 16% (mostly due to blunt pelvic injury) were judged to be preventable [24]. In Stavenger, Norway, where the autopsy rate exceeds 95%, 25% of the trauma deaths from 1996 to 2004 were due to exsanguination, half of which occurred within 1 hour postinjury [8]. In a population-based study in Berlin [25], of 440 trauma deaths during 2010, 10% were attributed to exsanguination, which was defined very narrowly as: "*coincident/singular blunt and/or penetrating severe injury/ies to various organ/s or organ systems, which were primarily lethal due to hemorrhagic shock without destruction/dysfunctions of vital structures as the leading cause of death.*" Of the remainder, close to half were ascribed to "polytrauma" and 38% to TBI. It would be plausible to assume that a substantial proportion of the so-called "polytrauma" deaths were associated with hemorrhage. Sixty percent of the deaths in the Berlin study occurred at the scene,

of which 14% were attributed to exsanguination, and 24% of all exsanguination-related deaths occurred at the scene. Another Canadian study in the Foothills Medical Centre in Calgary analyzed 1000 consecutive in-hospital trauma deaths among 9941 patients admitted from 2005 to 2013, of which 27% were attributed to exsanguination [26]. In a hospital-based study in Turkey, from 2010 to 2013, 22% were attributed to circulatory collapse and another 11% to circulatory collapse plus TBI [27]. In Brazil, hemorrhage claimed 18% of the trauma deaths in an urban hospital. In an assessment of in-hospital deaths in a Netherlands urban trauma center reported that exsanguination caused 9% of the 2007–2012 fatalities and only 3% in 2013–2016 [28]. These were the periods before and after the implementation of hemostatic resuscitation and damage control procedures in their hospital. TBI was the main cause of death in both periods (58% in 2007–2012 and 76% in 2013–2016). The definition of exsanguination was not specified in the article, but a number of death causes potentially related to hemorrhage were listed (e.g., chest injury, cardiac arrest). A number of reasons may explain the different proportion of hemorrhage in non-US versus US studies including (but not limited to) higher frequency of penetrating trauma in the United States versus other countries; different definitions of hemorrhagic and TBI deaths and disparities in injury prevention (e.g., alcohol-related injuries, road conditions, trauma systems, emergency medical services, availability of resuscitation-related resources).

Temporal Trends

Temporal trends in cause-specific mortality proportions were evaluated at the Scripps Mercy Hospital, in San Diego, California, US from 2000 to 2011, finding no significant change in the proportion attributed to acute hemorrhagic shock, which remained slightly over one quarter of all deaths [4]. In an urban trauma center in Texas, a comparison of the proportion of deaths due to hemorrhage before (2005–2006) and after (2012–2013) the implementation of a bleeding-control bundle of care showed an unadjusted decrease from 36% to 25% [9]. Specifically among early in-hospital deaths (<1 hour postinjury), there was a reduction in the proportion of hemorrhage as the primary cause from 60% in 2005–2006 to 38% in 2012–2013. The authors credited the improvement to the implementation of a multi-modal bleeding control bundle encompassing: (1) accurate identification of the bleeding patient; (2) pre-hospital and hospital damage control resuscitation: (3) pre-hospital and hospital use of hemostatic techniques such as extremity and junctional tourniquets, pelvic binders, and hemostatic dressings; (4) resuscitative endovascular balloon occlusion of the aorta; (5) coagulation monitoring with thrombelastography; (6) tranexamic acid for significant fibrinolysis; (7) decreased time to operating room and interventional radiology; and (8) goal-directed resuscitation with blood products as bleeding slows. A subsequent study using the same dataset showed that among potentially preventable in-hospital deaths, hemorrhage remained frequent (2005–2006: 48% vs. 2012–2013: 43%, $p = 0.55$) [29].

The study of the epidemiology of hemorrhagic deaths requires focused attention to the denominator used in the report or study. As the above-cited investigations demonstrate, a substantial proportion of the deaths occurring pre-hospital, both in civilian and military settings, are unequivocally non-preventable, for which primary prevention may be the only solution. Of course, the judgment of whether a death is preventable or non-preventable may involve some degree of subjectivity. In non-obvious cases, it is advisable to apply more objective criteria to estimate the probability of survival, such as the TRISS [30, 31] (Trauma and Injury Severity Score) probability of death (e.g., classify as non-preventable deaths of injured patients with <10% TRISS probability of survival), or similar model. Removing the non-preventable deaths from the denominator, and concentrating only on the subset of PP/P deaths, highlights the group who may benefit the most from focused interventions.

Mechanisms

In the recent Western Trauma Association study, attending providers of 18 US trauma centers adjudicated the cause of death (COD) immedi-