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REVIEW

Damage control resuscitation

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ABSTRACT

The early recognition and management of hemorrhage shock are among the most difficult tasks challenging the clinician during primary assessment of the acutely bleeding patient. Often with little time, within a chaotic setting, and without sufficient clinical data, a decision must be reached to begin transfusion of blood components in massive amounts. The practice of massive transfusion has advanced considerably and is now a more complete and, arguably, more effective process. This new therapeutic paradigm, referred to as damage control resuscitation (DCR), differs considerably in many important respects from previous management strategies for catastrophic blood loss. We review several important elements of DCR including immediate correction of specific coagulopathies induced by hemorrhage and management of several extreme homeostatic imbalances that may appear in the aftermath of resuscitation. We also emphasize that the foremost objective in managing exsanguinating hemorrhage is always expedient and definitive control of the source of bleeding.

1. Introduction

During the past decade, the practice of massive transfusion (MT) has expanded appreciably from simply a definition to now a more comprehensive management strategy for hemorrhagic shock referred to as damage control resuscitation (DCR). This new therapeutic paradigm is based on a broader understanding of the pathophysiology of hemorrhagic shock and now integrates advances from multiple disciplines [1–6]. Recently, comprehensive transfusion guidelines for management of hemorrhage after injury have been developed in part by the Resuscitation Outcomes Consortium [7], Trauma Outcomes Group, and the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) studies [8,9], and these guidelines continue to be refined. Substantial reductions in mortality and blood product waste can be demonstrated after introduction of a resuscitation strategy for the exsanguinating patient that includes the diagnosis of specific hemorrhage-associated coagulopathies and identification of several extreme metabolic imbalances that may develop as a result of severe shock or in the aftermath of massive resuscitation [4,10,11]. Moreover, many resuscitation principles developed in the context of care of the seriously injured patient are applicable to the management of severe hemorrhage occurring as a complication in other specialties such as peripheral vascular and cardiovascular surgery, transplant surgery, critical care, cardiology, general surgery, obstetrics, and neurosurgery.

However, clinicians who are required to treat life-threatening blood loss may be unfamiliar with the rapid and substantial progress that has been made and is still ongoing concerning this aspect of resuscitation [12,13]. There are several potential explanations for this uncertainty regarding the management of severe hemorrhage. The definition of MT and the manner by which MT is integrated into DCR strategies can be arbitrary and inexact. By one typically used definition (≥10 units of packed red blood cells within a 24-hour period), a patient may be considered massively transfused after receiving blood at a deliberate rate of one unit every 2 h over the course of 20 h. This is, of course, a distinctly different clinical scenario than a patient receiving the same amount of blood within 2 h or even less [14]. Moreover, resuscitations for massive blood loss are rare events. For example, in our hospital DCR is initiated most frequently by the trauma service although no more than 5% of seriously injured patients require resuscitation of this magnitude[1]; and, DCR may be required even less frequently to manage, bleeding complications on other services [15] (Table 1). Furthermore, a major tenet of current DCR strategies involves administration of blood components (plasma and platelets) in a predefined ratio relative to the number of

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[1] Similar to other centers [15] MT accounts for 75% of the total amount of blood used for trauma patients.

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Table 1
Massive transfusion events Methodist Hospital in 2013 by service line.

	MBTB activations % (N)	Component usage for MT (% of total usage)			
		RBCs	Plasma	Cryo	Platelets
Trauma	62.2% (79)	75.5%	72.0%	59.3%	65.6%
CV/PV surgery	17.3% (22)	11.8%	15.2%	25.4%	17.6%
Critical care	11.8% (15)	7.1%	7.8%	6.8%	11.3%
Cardiology	3.1% (4)	2.1%	1.2%	0.0%	0.9%
General surgery	2.4% (3)	2.3%	2.7%	8.5%	3.6%
Obstetrics	2.4% (3)	0.6%	0.2%	0.0%	0.5%
Neurosurgery	0.8% (1)	0.8%	0.8%	0.0%	0.5%
Total	(127)				

MBTB, Massive Blood Transfusion Protocol.

units of RBC's transfused. However, the optimal ratios of these components (and others such as cryoprecipitate) that maximize survival and minimize blood component waste have been difficult to determine and are incompletely defined. Complicating matters still further, newer DCR strategies are based on goal-directed hemostatic resuscitation with rapid point-of-care (POC) viscoelastic assessment of coagulation [16]. Though promising with respect to outcomes, goal-directed DCR presents additional layers of complexity in that a viscoelastic coagulation test requires trained personnel to perform the assay and experienced clinicians to accurately interpret the results [17]. Lastly, whereas the fundamental precepts of hemorrhagic shock should vary little from one location to another, conclusions regarding many pathophysiologic mechanisms of the host response to massive blood loss and opinions on resuscitation strategies for catastrophic bleeding have differed substantially in different parts of the world. For clinicians attempting to discern the concepts and best practices of DCR, these disparities likely intensified uncertainties regarding the process more than any other factor. However, consensus is now emerging on several aspects of DCR as a result of recent international collaborations among experts in shock and resuscitation [18].

Here we examine DCR from a multidisciplinary perspective [19] by integrating descriptions of the pathophysiology, of hemorrhage-associated coagulopathies and the extreme homeostatic imbalances that may appear during severe hemorrhage, or in the aftermath of resuscitation. A comprehensive understanding of cardiovascular physiological principles, hematological advances in hemostasis at a molecular and cellular level, the capabilities of the hematological laboratory, and developments in transfusion medicine is essential for successful treatment of severe bleeding. However, we emphasize that resuscitation of the patient in hemorrhagic shock is, in effect, a means to an end. Definitive control of bleeding is the principal objective in any comprehensive resuscitation scheme for hemorrhagic shock, and therefore DCR must not eclipse emergent endoscopic [20], surgical [21] or angiographic [22] intervention [23,24].

2. Damage control resuscitation

2.1. *Hemorrhage-associated coagulopathy*

Predictably, disorders of hemostasis exacerbate hemorrhage and significantly complicate resuscitation. Dilution of platelets and coagulation factors during resuscitation was previously considered to be the major cause of hemorrhage-associated coagulopathy (technically, resuscitation-associated coagulopathy). With the exception of transfusions exceeding one blood volume (approximately 10–12 units), however, and in the absence of hypothermia and acidosis, the effect of resuscitation-induced hemodilution on coagulation is inconsequential [25]. Clotting factors do decline in the bleeding patient, but this decline is often out of proportion to the reduction that can be attributed to dilution alone [26,27]. In trauma patients, several specific hemostatic defects have been identified that are detectable in approximately 25%–56% of patients prior to resuscitation [28,29]. These bleeding diatheses are collectively referred to as trauma-induced coagulopathy, acute coagulopathy of trauma, acute traumatic coagulopathy, or trauma-associated coagulopathy [30,31]. Trauma-associated coagulopathy (TAC) is an independent predictor of adverse outcomes such as prolongation of I.C.U. and hospital lengths of stay, as well as a four-fold increase in mortality [31]. The recognition of coagulopathy at admission is crucial in that this abnormality predicts a subsequent transfusion requirement and informs the decision to proceed with DCR [32].

TAC is attributed to one of four basic mechanisms including, 1) a qualitative platelet defect (particularly after traumatic brain injury [TBI]) [33–36], 2) diffuse endothelial cell injury, 3) depletion of coagulation factors and platelets through hemorrhage and deposition into injuries, or 4) consumption of platelets and coagulation factors secondary to disseminated intravascular coagulation (DIC) or hyperfibrinolysis [37–49]. Trauma patients may have multiple or overlapping causes of coagulopathy, and these will shift frequently, unpredictably, and without warning through the course of resuscitation. Therefore, frequent reassessment of the coagulation system by any means is an essential component of DCR. Furthermore, TAC is unequivocally worsened by acidosis and hypothermia. Acidemia diminishes coagulation factor enzymatic activity, depletes fibrinogen and reduces the number of circulating platelets [50,51]. Hypothermia is an independent risk factor for death during hemorrhagic shock [52], impairing coagulation at core temperatures <34 °C [53,54]. Indeed, the association of coagulopathy with acidosis and hypothermia is underscored by the phrase, "Lethal Triad of Trauma." Complicating matters still further, patients may manifest a bleeding diathesis initially but subsequently convert within hours to a hypercoagulable state and acquire risk for thromboembolic complications [55].

Significant platelet dysfunction after trauma in the presence of an otherwise normal platelet count and standard clotting studies can be detected in a high percentage of seriously injured patients and even more frequently in head-injured patients [34]. Compromised platelet aggregation is observed in patients with traumatic brain injury (TBI), associated with diminished activity of the ADP receptor, $P2Y_{12}$ [33]. The mechanism responsible for TBI-induced ADP receptor down regulation is not clearly defined, and this type of platelet dysfunction is often overlooked in the TBI patient who is bleeding, particularly when the platelet count is normal. In addition, acidosis inhibits platelet aggregation [56], and hypothermia reversibly decreases platelet function [57]. Qualitative defects may be exacerbated by thrombocytopenia [58]. A platelet count less than 100×10^9/L with TBI has been reported as the strongest predictor of injury progression, a requirement for emergent neurosurgical intervention, and increased mortality [59]. For all trauma, every 50×10^9/L increase in admission platelet count is associated with an odds of death at 6 h decrease by 17% ($p = 0.03$, 95% confidence interval [CI], 0.70–0.99), whereas any platelet transfusion within the first 24 h is associated with a lower mortality in injured patients compared to patients who do not receive platelets ($p < 0.001$; 95% CI, 0.20–0.57) [58].

Shock-mediated injury of the vascular endothelium has been examined as a mechanism of TAC. This injury also includes disruption of the covering glycocalyx throughout the vascular space [60–64]. Negatively charged proteoglycans, glycoproteins, and glycolipids, including significant amounts of heparin-like molecules [65,66] of the glycocalyx have a dynamic role in a number of endothelial cell functions [67]. Glycocalyx damage is suggested by detection of circulating levels of a heparin sulfate proteoglycan, syndecan-1 [68], and is associated with so-called autoheparinization, which contributes to TAC in a small percentage of patients [69,70]. High levels of syndecan-1 are independently associated with increased mortality after trauma [69]. Detached endothelial cells circulating in blood, and detection of specific biomarkers indicating endothelial cell injury, including, angiopoietin-2, von Willebrand's factor antigen, ristocetin cofactor activity, sCD40L, and

soluble thrombomodulin suggest some form of disruption of vascular endothelium [63] as part of a dysfunctional hemostatic response to injury. The pathophysiology of endothelial cell dysfunction in patients after significant trauma has not been completely defined but likely involves, enhanced expression of the endothelial protein C receptor (EPCR) and of thrombomodulin (TM), which result in a substantial accumulation of activated protein C (aPC) and accelerated inactivation of FVa and FVIIIa [71]. Evidence also suggests that endothelial cell injury results in the release of substantial amounts of stored tPA from specific endothelial cell intracellular granules [63]. Furthermore, the concurrent activation of PC will also result in an increase in aPC-mediated degradation of plasminogen activator inhibitor-1 (PAI-1), which contributes to accumulation of tPA [64,68]. Thus, by more than one mechanism, excess expression of endothelial anticoagulation properties in the trauma patient destabilizes the balance between coagulation and fibrinolysis leading to a disproportionate amount of clot lysis over clot formation [63].

Because DIC involves unregulated thrombin and plasmin generation, the clinical manifestation of DIC in bleeding patients will be determined by the level of coagulation activity relative to the level of fibrinolytic activity. A deficiency of tissue factor pathway inhibitor (TFPI) increases susceptibility to the development of DIC [72], but possible TFPI dysregulation as a mechanism of bleeding-associated coagulopathy has not been investigated. Most often DIC is a hypercoagulable state characterized by diffuse non-specific deposition of microthrombi in smaller vessels causing a thrombotic microangiopathy, which obstructs microvascular flow, disrupts oxygen delivery to tissue, and results in organ system dysfunction or failure. [72] The coagulopathy that occurs from consumption of platelets and coagulation factors in microvascular thrombi exacerbates hemorrhage. Fibrinolysis may compensate for intravascular microthrombosis, and therefore antifibrinolytic therapy for bleeding-associated DIC is not recommended, except in rare cases when fibrinolysis dominates the clinical course (hyperfibrinolysis) [73].

Hyperfibrinolysis (HF) has been reported to develop in 2% to 20%, of trauma patients, increasing to 53% in a subgroup who progress to massive transfusion [49,74,75]. However, assessment of coagulation by viscoelastic technique demonstrates that clinically significant HF may actually occur less frequently, developing in under 3% of trauma patients [76,77]. HF in hemorrhaging patients, if determined by viscoelastic assay, can be categorized as fulminant, intermediate, or late, resulting in 100%, 91%, or 73% mortality, respectively [48]. Progressive hemodilution during resuscitation can decreases endogenous antifibrinolytic proteins including PAI-1, α_2-antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI), and contribute to the hyperfibrinolytic propensity associated with severe hemorrhage [78,48]. Both fibrin and fibrinogen degradation products in excess contribute to coagulopathy in bleeding patients by interfering with fibrin polymerization and clot stability [79], and by blocking ADP-induced platelet aggregation [80]. Also this bleeding diathesis is potentiated by diminished hepatic clearance of degradation products due to pre-existing liver disease, and hypoxic injury to the liver (shock liver). A decrease in α_2-plasmin in patients with TBI is suggested as an additional mechanism of unopposed plasmin formation that characterizes hyperfibrinolysis in this subgroup of trauma patients [81].

2.2. Massive transfusion

2.2.1. Fixed ratio protocols

DCR focus specifically on restoration of venous return to the right heart before the patient's physiologic reserve is exhausted in concert with expedient correction and subsequent prevention of coagulopathies by hemostatic resuscitation with plasma and platelets. Crystalloid infusion is tightly restricted and colloid volume expanders are avoided [18]. In military settings [82], fresh whole blood is often utilized for resuscitation. DCR is carried out most effectively if directed by a specific protocol or algorithm that delineates authority and clinical criteria for activation, outlines the responsibilities of various members of the resuscitation team, lists how and at what time points the patient is assessed, directs the timing and coordination of certain interventions, suggests resuscitation endpoints to monitor, and specifies under what circumstances a DCR is deactivated. Examples of MT prediction scores are shown in Table 2. Scores with a greater number of variables that have been weighted appear to be more accurate. The efficiency of a protocol-directed process decreases the time to transfusion, which may be a significant factor in observed reductions in organ failure, other post-injury complications, and mortality associated with DCR [10,83,84]. Protocols also direct transfusion of blood components either in fixed ratios or as a goal-directed strategy.

Analyses of blood component transfusion during fixed-ratio-based DCR protocols indicate improved survival with high ratios of plasma and platelet transfusions to RBC transfusions [10,85–88], as first suggested in 2005 (referred to as "balanced transfusion therapy") [89] and consistent with data subsequently reported by the U.S. Military [90]. The optimal fixed ratio of units of plasma, platelets and RBCs for non-military DCR remains incompletely defined [91–93], although likely falls between 1:1:3 and 1:1:1. (plasma:platelets:RBCs). Data from PROMMTT were used to design the recently completed Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR; NCT01545232) trial, which examined a 1:1:1 component transfusion ratio compared to a lower ratio (1:1:2) [8] with survival as the primary endpoint. Of note, the survival benefit from a high plasma:PRBC ratio appears to be similar for any massively transfused patient even if the patient does not have a coagulopathy [94] (for which high plasma:RBC ratios were originally implemented).

A reduction in the time to first plasma transfusion during DCR significantly reduces mortality [95]. However, fresh frozen plasma (FFP) and FP24 require up to 60–75 min preparation that significantly delays plasma availability [96]. In contrast, stored thawed plasma, which retains acceptable levels of all coagulation factors for up to 5 days [97–100] can be transfused immediately. Immediate transfusion of plasma is associated with an overall reduction in the amount of plasma and other blood components transfused during DCR and with reduced plasma wastage [4,13,83]. Also, plasma separated from whole blood and stored at 4 °C for 21 days, and referred to as liquid plasma, retains close to 90% coagulation factor activity, and is the primary source of plasma in many European DCR strategies [101]. Reconstituted lyophilized plasma (LP) is another source of this blood component that may be used immediately for a recipient of any blood type because of dilution and neutralization of anti-A and anti-B hemagglutinins. LP, which contains coagulation factor levels equivalent to FFP, has been used by the French Army since 1994 [102]. Presently, LP is utilized by medics of the Israeli Defense Force for resuscitation of combat casualties in hemorrhagic shock [9], and previously LP was carried for a similar purpose by U.S. Special Operations Forces in Afghanistan [103].

Hemostatic resuscitation for massive hemorrhage will necessitates extensive use of AB plasma until a recipient blood type can be determined. However, the requirement for AB plasma is not as stringent as the requirement for group O blood. To prevent exhaustion of an AB plasma supply by DCRs, group A plasma has been used in DCR before blood type is known without significant transfusion reactions or detrimental effects on outcomes and is now advocated [104–106]. Concern is mitigated by the fact that the most commonly encountered blood group in a recipient will be group A. Also, anti-B titers are generally low in group A plasma donated by males, hemolytic transfusion reactions in non-group A recipients after transfusion of platelets that have been suspended in group A plasma are rare, and DCR patients typically receive several units of group O RBCs with plasma, which decreases the risk of hemolysis due to ABO group mismatch [107].

Bleeding-associated coagulopathy may occur secondary to the rapid development of hypofibrinogenemia [27,108–112], although the fibrinogen concentration below which hemostasis may no longer be effective has not been established [113]. Fibrinogen is depleted in the process

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Table 2
MT prediction scores.

Prediction score	Clinical criteria	Lab criteria	Imaging criteria	Comment
Trauma Associated Severe Haemorrhage (TASH) Score [244,245]	▪ SBP ▪ HR ▪ Male gender ▪ Unstable pelvic FX ▪ Femur FX	▪ Hgb ▪ BE	FAST	Variables are weighted to yield a possible score between 0 and 28; TASH scores are transformed into a probability of MT by a logistic function; for example TASH ≥ 16 points indicates a probability of MT > 50% [246].
Assessment of Blood Consumption (ABC) Score [247]	▪ SBP ▪ HR ▪ Penetrating mechanism	None	FAST	One point given to defined abnormalities for each variable; possible score 1 to 4; MT prediction threshold ≥ 2
Cincinnati Individual Transfusion Trigger Study (CITT) [248]	▪ SBP ▪ Temp	▪ Hgb ▪ INR ▪ BE	None	INR most predictive (odds ratio, 16.7) for any transfusion and highly predictive for the need for MT (odds ratio, 11.3).
Massive Transfusion Score (MTS) [249][a]	▪ SBP ▪ HR ▪ Temp ▪ Penetrating mechanism	▪ INR ▪ Hgb ▪ BE	FAST	Validates variables in other scores using the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study cohort.
Emergency Transfusion Score [250]	▪ SBP ▪ Age ▪ Unstable pelvic FX ▪ Mechanism[a]	None	FAST	Variables weighted; also considers admission from scene as a criteria; risk of E.D. transfusion Low < 3, intermediate risk = 3; >3.
Prince of Wales Hospital/Rainer (PWH/Rainer) Score [251]	▪ SBP ▪ HR ▪ GCS ▪ Displaced pelvic FX	▪ Hgb ▪ BE	CT or FAST	Variables weighted to yield possible score between 0 and 18; MT prediction threshold is score ≥ 6
Vandromme [252]	▪ SBP ▪ HR	▪ Lactate ▪ Hgb ▪ INR	None	Only predictive model that incorporates lactate. All variables equally weight for possible score 0 to 5; all combinations or clinical measures alone yielded lower predictive probability.
Schreiber [253]	▪ Penetrating mechanism	▪ Hgb ▪ INR	None	Based on military databases; each variable equally weighted
Larsen [254]	▪ SBP ▪ HR	▪ Hgb ▪ BE	None	Based on military databases; each variable equally weighted

Hgb, hemoglobin; BE, base excess; FX, fracture; SBP, systolic blood pressure; HR, heart rate; FAST, focused abdominal sonography for trauma.
[a] Traffic accident or fall from height (>3 m).

of clot formation, while fibrinogen synthesis may be diminished by pre-existing liver disease or hypothermia. Furthermore, depletion of fibrinogen will be compounded by plasmin-mediated degradation of fibrinogen. Although fibrinogen is resistant normally to plasmin, hyperfibrinogenolysis can develop as plasmin reaches abnormally high levels during DCR [40]. Also, plasmin-mediated fibrinogen degradation is accelerated by the acidosis that frequently complicates DCR [114,115]. Cryoprecipitate is the principal component transfused during DCR to manage suspected hypofibrinogenemia (or possibly acquired fibrinogen dysfunction). A 200 mL–10 unit dose of cryoprecipitate will deliver 2.5 g of fibrinogen and will elevate fibrinogen levels in a 70 kg adult by approximately 70 mg/dL. Four units of plasma (600 mg fibrinogen/unit) is equivalent to a 10-unit dose of cryoprecipitate [116]. If resuscitation with plasma is initiated early and transfusion of these components is continued at a high plasma:RBC ratio, then a quantity of fibrinogen will be infused that approaches the amount of a standard dose of cryoprecipitate [117]. In the course of DCR, cryoprecipitate may then be used if fibrinogen repletion is still required, but further volume expansion is not.

2.2.2. Goal-directed protocols

Patients treated empirically for hemorrhage-associated coagulopathy with blood components in fixed ratios may receive blood products they do not need, or in excess of what was required to correct a bleeding diathesis, creating exposure to unnecessary or excessive risk [118,119]; and other patients may not receive a product that was indicated, or may not receive it in a timely manner [120]. Routine evaluation of the coagulation system by standard laboratory test of coagulation are performed on platelet-poor plasma and do not reflect the important contribution of cellular elements to coagulation [121]. Moreover, these tests have not been validated for accuracy in bleeding patients [122]. Prothrombin fragment 1.2 and thrombin-antithrombin complexes have been used as markers of thrombin generation in the setting of hemorrhage, but these may be unpredictably influenced by other variables [123]. Measures of coagulation more relevant to DCR may include assessment of specific physical properties such as rate of clot formation, clot strength, and the resistance of the newly formed clot to lysis. The use of systems to assay these properties and to monitor and guide transfusion therapy in hemorrhaging trauma patients is referred to as goal-directed DCR. Three systems, SONOCLOT®, thromboelastography (TEG®; Haemonetics Corp, Niles, IL, USA), or rotational thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany), are used in clinical laboratory or point-of-care (POC) coagulation testing as an integrated assessment of the kinetics of clot formation and lysis, and the physical properties of clot strength and elasticity in vitro, which more accurately reflect hemostasis in vivo.

POC viscoelastic coagulation tests do not, in fact, provide critical data at the immediate onset of a DCR and without modification may not provide data any sooner than conventional tests [124]. However, as a DCR progresses these assays permit a more specific determination of the blood product required and a more exact, usually less estimate of the amount needed to reverse any identified defect in hemostasis rather than transfusions of plasma, cryoprecipitate and platelets in a fixed ratio to empirically and non-specifically treat coagulopathy. In the TEG system, goal-directed resuscitation involves the use of rapid-TEG (r-TEG®) to diagnose and describe post-injury coagulopathy and to guide blood product replacement. For r-TEG tissue factor is added with kaolin to activate coagulation, and recent data suggest that r-TEG can identify coagulation abnormalities very early after injury [125]. Blood products may be transfused in a fixed ratio initially for patients presenting with uncontrolled hemorrhage, with subsequent focused intervention based on r-TEG data, as it becomes available. The next component transfusion based on the r-TEG data may include additional thawed plasma (10–20 mL/kg) for a prolonged R value (designated TEG-ACT for a r-TEG assay) (>1 min) indicating coagulation factor deficiency or depletion, or if markedly prolonged (>1.5 min), 30 mL/kg of thawed plasma. However, 1 U apheresis platelets would be transfused instead if the MA < 50 mm or 2 U apheresis platelets if MA < 45 mm,

whereas cryoprecipitate (3–5 mL/kg) would be transfused for a functional fibrinogen MA < 14 mm, or an α-angle < 52° suggesting fibrinogen deficiency. Ly30 > 8% suggests hyperfibrinolysis for which an antifibrinolytic agent, started at the time of admission, would be continued, or if a Ly30 > 8% occurs in association with elevated α-angle or MA (reactive fibrinolysis), would be immediately discontinued [126].

Goal-directed DCR has been reported to reduce bleeding, significantly diminish transfusion requirement, and substantially improve outcomes [96,127]. Additional potential benefit of a specific and rapid correction of coagulation abnormalities is a more effective and complete restoration of physiological homeostasis, which improves outcomes due to attenuation of an auto-inflammatory response [128]. Implementation of POC viscolastography-based protocols for management of hemorrhage in cardiovascular surgical patients has been associated with a reduction in perioperative transfusion requirements and transfusion-related adverse events, a decreased incidence of thromboembolic complications, and improved patient outcomes, including increased 6-month survival [129]. However, a recent systematic review of 55 studies on POC viscoelastic assays for trauma patients, not all including patients undergoing DCR, concluded that the effect of this approach on blood product transfusions, mortality, and other patient outcomes remain unproven in randomized trials [130]. Presently, a prospective, randomized study (NCT01536496 [131]) comparing viscoelastic assay with conventional coagulation testing (aPTT, INR, platelet count, fibrinogen level, D-dimer) for diagnosis of post-injury coagulopathy and to guide resuscitation has recently completed enrollment of subjects. A viscoelastic assay-based strategy, in fact, is now endorsed by several relevant international societies and incorporated into transfusion guidelines from these groups [132–134].

2.2.3. *Coagulation factor concentrates*

Because coagulation factor concentrates do not require time to thaw, are not restricted serologically, and obviate transfusion-related complications, they have been considered as an alternative to blood components for hemostatic resuscitation during DCR [135]. Plasma-derived or recombinant products available in many countries include, fibrinogen concentrate (RiaSTAP®; CSL-Behring), 3-factor prothrombin complex concentrate (PCC; Profilnine SD®; Grifols Biologicals Inc), 4-factor PCC (unactivated Kcentra®; CSL-Behring or activated FEIBA NF®; Baxter Healthcare Corp), FXIII concentrate (Corifact®; CSL-Behring), and recombinant activated FVII (NovoSeven RT®; Novo Nordisk A/S).

Fibrinogen concentrate given during resuscitation to patients experiencing massive blood loss effectively and rapidly controls hemorrhage-associated coagulopathy, which correlates with significant improvement in coagulation viscoelastographic parameters, and substantially reduces the requirements for RBC, FFP, and platelet transfusions. Fibrinogen concentrate improves diminished clot strength thought to be caused by impaired platelet-fibrinogen interactions, which can be readily detected by viscoelastic assay. However, at very high fibrinogen concentrations an opposite effect may occur [136], which must be considered during DCR. A vial of lyophilized fibrinogen concentrate is stored at room temperature and typically contains 1.0 g of fibrinogen that is reconstituted in 50 mL sterile water for infusion. Controlled prospective comparisons of cryoprecipitate and fibrinogen concentrate in management of hemorrhagic shock are lacking [137]. The Fibrinogen in Trauma Induced Coagulopathy Trial (FI in TIC Trial; ClinicalTrials.gov Identifier: NCT01475344) is a multicenter, double-blind, placebo controlled, randomized pre-hospital pilot study in Europe that will examine the efficacy of pre-hospital administration of fibrinogen concentrate [138]. In Europe, fibrinogen concentrate is now used in place of allogeneic blood products as a first-line treatment for hypofibrinogemia [139–144]. Fibrinogen concentrate is commercially available in the U.S. and approved by the FDA to treat hereditary fibrinogen disorders. However, fibrinogen concentrate to correct acquired fibrinogen deficiency complicating hemorrhagic shock has not been approved by the FDA [145],

An association between low FXIII levels and increased bleeding has been noted in cardiac surgery and other clinical settings [146]. Supra-physiological concentrations of factor XIII ranging from 150% up to 600% have been shown to increase clot firmness, accelerate clot formation, and increase clot stability in vitro [147]. Administration of FXIII concentrate with fibrinogen concentrate has been considered in the management of massive hemorrhage [148,149]. In some patients undergoing DCR, an acquired FXIII deficiency is suggested by persistent coagulopathy and diminished clot strength despite adequate fibrinogen levels and platelets, and administration of FXIII concentrate may prove effective for this clinical state [135].

Prothrombin complex concentrates (PCCs) include vitamin K-dependent factors. FII. FVII. FIX. and FX. PCC products are considered either three-factor PCCs (containing a negligible concentration of FVII) or four-factor PCCs (with a higher concentration of FVII); also products differ in whether FVII is activated or requires entry into a functioning coagulation system for activation after injection [150]. Technically, newer PCC products should be considered 6-factor PCCs as most contain two additional vitamin K covalently modified factors, protein C and protein S. Also, measureable amounts of other proteins, including albumin and, in particular, antithrombin may be present.. Thromboembolic complications associated with PCCs include deep venous thrombosis, DIC, microvascular thrombosis and myocardial infarction [151]. Inclusion of protein C and protein S prevents excessive thrombin generation and thereby mitigates these thrombotic risks. Reversal of Trauma Induced Coagulopathy Using Coagulation Factor Concentrates or Fresh Frozen Plasma (RETIC Trial; NCT01545635) is a prospective open-label, parallel-group, monocentric study that evaluates 200 severely traumatized patients (ISS > 15) randomized to treatment of coagulopathy detected by ROTEM with FFP alone, fibrinogen concentrate alone, or either one combined with prothrombin complex concentrate, or FXIII concentrate [152]. Administration of PCC with fibrinogen concentrate to cardiovascular surgical patients has been associated with decreased incidence of blood transfusion and thrombotic/thromboembolic events [153].

Recombinant FVIIa was initially developed and utilized for management of hemophilia A or B with inhibitors to FVIII or FIX. Off-label use of rFVIIa in the U.S. significantly increased approximately 10 years ago, particularly in cardiovascular surgery such that by 2008, one in four uses of rFVIIa was in response to bleeding during open heart surgery [154]. At that time the cost of one-time administration of rFVIIa (assuming a weight of 70 kg) was $25,712 USD [155]. In trauma patients, a large manufacturer-sponsored trial (CONTROL Trial) involving 150 international sites, designed to assess the potential for mortality and morbidity benefits associated with use of rFVIIa for refractory bleeding after injury, was terminated when an interim data analysis predicted a low likelihood of observing a significant difference in the primary mortality end point [117,155]. From a further analysis of a large and comprehensive cohort involved in placebo-controlled trials of rFVIIa, it was reported that treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial thromboembolic events (e.g., coronary artery thrombosis), especially among the elderly [156]. Also, effectiveness of rFVIIa for hemostatic control in the setting of spontaneous intracranial hemorrhage, liver transplantation or hepatobiliary surgery, or for gastrointestinal hemorrhage in patients with end-stage liver disease remains unproven and is associated with increased risk of thrombotic complications [157].

2.2.4. *Antifibrinolytics*

Tranexamic acid (TXA) has been shown to decrease the need for blood transfusion by one-third in patients undergoing high-risk elective surgery [158], diminish post-partum hemorrhage following vaginal delivery and Cesarean section [159], and reduce chest tube drainage and blood component transfusion in cardiac surgery patients [160], although the association of TXA with thromboembolic complications remains uncertain [161]. Currently, a large pragmatic randomized

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double-blind, placebo controlled trial, (World Maternal Antifibrinolytic Trial [WOMAN]; NCT00872469 [162]), expecting to enroll 15,000 subjects by February 2015, will further examine the effectiveness of TXA in obstetrical hemorrhage. Also, TXA has been evaluated in trauma patients in a large international randomized placebo-controlled trial, the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH 2) trial [163]. CRASH-2 involved 274 centers located in 40 countries and enrolled 20,211 subjects who either had significant hemorrhage or were at risk for significant hemorrhage. All-cause 28-day mortality was reduced 1.5% in the TXA-treated group (14.5%) compared to the placebo group (16.0%), while death due to hemorrhage was 4.9% in the TXA group compared to 5.7% in the control group (RR, 0.85; 95% CI, 0.76–0.96; $p = 0.0077$) [163,164]. These data yield a number needed to treat of 67 to save one life. In a much smaller sub-group of patients presenting with SBP ≤ 75 mm Hg, all-cause 28-day mortality was 30.6% for the TXA group compared to 35.1% for the placebo group (RR, 0.87; 99% CI 0.76–0.99).

CRASH-2 inclusion criteria were based on a systolic blood pressure < 90 mm Hg or heart rate > 110 beats/min. However, of the very large number of patients screened for eligibility (20,255), an unusually small number of patients were excluded (14; 0.0.07%) [165]. Moreover, 90% of all deaths related to trauma occurred in countries where standardized trauma care or advanced resuscitation protocols generally do not exist [166]. In addition, approximately half of the patients receiving TXA were not actually bleeding, which possibly explains why there was no reduction in the amount of blood transfused in the TXA group compared to the control group. Also the modest injury profile of the CRASH-2 cohort may have introduced a conservative bias against the TXA effect [167]. Other limitations identified in the CRASH-2 study include the absence of a description of injury severity in treatment and control groups and omission of coagulation testing, particularly with regard to identification of hyperfibrinolysis [168]. More importantly, an absolute increase in mortality was observed if TXA was begun 3 h after injury [164]. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage Intracranial Bleeding Study (CRASH-2 IBS) was a prospective randomized controlled trial nested within the CRASH-2 trial. One hundred and thirty-three patients fulfilled the inclusion criteria for the CRASH-2 trial and also had TBI indicated by GCS ≤ 14 and a CT scan compatible with TBI. Data here suggest TXA significantly reduces extension of intracranial hemorrhage compared to controls [169]. To further examine the effects of TXA in TBI, the Tranexamic Acid for the Treatment of Significant Traumatic Brain Injury: an International Randomised, Double Blind Placebo Controlled Trial (CRASH-3; NCT01402882 [170]) was begun in September 2011 with a planned enrollment of 10,000 patients with TBI and estimated to be completed by January 2017.

2.3. *Complications associated with DCR*

2.3.1. *Acidosis*

Lactic acidosis (pH ≤ 7.20 [171]) decreases cardiac contractility and provokes dysrhythmias, which, in effect, impose cardiogenic shock on hypovolemic shock in the exsanguinating patient. Acidemia also desensitizes peripheral vasculature adrenergic receptors to endogenous catecholamines disabling compensatory mechanisms in response to hemorrhagic shock [172–174], stimulates inflammation, and suppresses immunity [174]. Other adverse effects of severe acidemia include, in particular, inhibition of platelet activation, diminished coagulation factor activity [50,175], and accelerated breakdown of fibrinogen [114]. Crucial phospholipid-coagulation factor complex interactions are destabilized by excess H^+ ions thereby drastically reducing factor activity [176]. Thus, mortality increases predictably with successive increases in base deficit. Moreover, most all of the detrimental effects of acidemia are compounded, and survival is further reduced by hypothermia (core temperature < 34 °C) [177].

Unlike bicarbonate administration, Tris(hydroxymethyl)-aminomethane (THAM) more effectively corrects the deep acid–base imbalance of lactic acidosis associated with hemorrhagic shock without lowering intracellular pH, reducing serum ionized calcium, or affecting serum osmolality [174]. The initial loading dose of a 0.3 mol/L-solution of THAM acetate = lean body-weight (kg) × base deficit (mmol/L); maximum 24 h-dose is 15 mmol/kg, or 3.5 L for a 70 kg patient [178]. Treatment of acidosis with THAM will distort the anion gap, reducing the usefulness of this number in determination of different treatment strategies during DCR.

2.3.2. *Hypothermia*

A decrease in core body temperature increases mortality of patients in hemorrhagic shock. The enzymatic specificity constants of coagulation factors in hemostatic pathways and platelet activity are negatively affected to a significant degree by hypothermia. Coagulation factor activity is reduced approximately 10%–15% for each 1 °C drop in temperature, which is exacerbated by factor depletion secondary to dilution or consumption [54,179]. However, the activity of endogenous anticoagulants, tissue factor pathway inhibitor, antithrombin, and protein C, are also modified by hypothermia [176]. Hypothermia has a more important clinical effect on coagulation by inhibiting von Willebrand factor-platelet glycoprotein Ib-IX-V interactions [180]. TEG or ROTEM can be performed at the patient's actual core temperature, in contrast to standard assays performed after serum has been warmed to 37 °C. TEG for example, may reveal a prolonged r-time (enzymatic reaction time), lower K value (rate of clot formation), and lower α-angle (clot formation time) [181,182]. Hypothermic-mediated inhibition of clotting times and clotting rate synergize with hemorrhage-mediated reduction in clot strength (MA by TEG determination), which explains in part the significant worsening of hemorrhage-associated coagulopathy caused by reduced core body temperature [182]. Hyperfibrinolysis has been suggested as a potential mechanism of hypothermia-mediated coagulopathy [183], but accelerated clot lysis does not appear to be involved in this process when interrogated by viscoelastography [54].

In the hypovolemic patient, mild hypothermia may increase cardiac output and oxygen demand, whereas moderate or severe hypothermia can depress myocardial contractility and reduce cardiac output [184]. The reduction in cardiac output is often exacerbated by arrhythmias from cold-induced conduction abnormalities [185], such as hypothermia-induced Osborn waves that may precede ventricular fibrillation [186]. More commonly hypothermic patients develop supraventricular arrhythmias, and atrial fibrillation is frequently the arrhythmia observed in patients with severe hypothermia [187].

Metabolism is significantly diminished in hemorrhaging patients and consequently heat production is reduced limiting passive rewarming [188]. Furthermore, external rewarming methods help to prevent heat loss, but transfer virtually no heat to the patient. Hypothermia is perpetuated or made worse by infusion of room-temperature fluids or cold blood components. For example, a patient will need to generate an additional 16 kcal to warm 1 L of room temperature (21 °C) crystalloid to 37 °C. If the patient cannot generate this additional heat because of diminished oxygen consumption due to shock, then infusion of room temperature-fluids is equivalent to a 16 kcal/L-heat loss, which will decrease the body temperature of a mildly hypothermic patient approximately 0.3 °C for every 2 L of infused crystalloid [189]. Counter-current fluid warmers enable the infusion of up to 800 mL of saline, or 1 unit of blood, per minute at a temperature of 37 °C–40 °C, equivalent to transfusing 5–8 kcal of heat per liter, or 18 kcal to 28 kcal of heat/12 units transfused [188,190].

2.3.3. *Divalent cation deficiencies*

Reduced circulating concentrations of calcium and magnesium due to citrate toxicity are common adverse events in DCR. High transfusion rates often exceed the liver's capacity to clear the infused citrate,

or citrate metabolism may be reduced secondary to pre-existing liver disease or impaired hepatic function from hypothermia [191]. Citrate accumulation during DCR and citrate-mediated hypocalcemia are often made worse by dilution of calcium. Hypocalcemia reduces myocardial contractility and impairs maintenance of vasomotor tone. Hypomagnesemia also develops during DCR due to citrate accumulation and dilution. Hypomagnesemia and hypocalcemia are associated with disruption of myocardial repolarization characterized by a prolonged a QT interval and a risk for development of *torsades de pointes* [192,193].

Intravenous calcium gluconate or calcium chloride may be administered empirically for every 4–8 units of PRBCs or plasma transfused to prevent the development of severe hypocalcemia, although this has not been evaluated in clinical trials. A 10 mL-ampule of calcium chloride has 3-times the amount of calcium (270 mg) and 3-times the osmolarity (2,000 mOsm/L), as a 10-mL ampule of 10% calcium gluconate (90 mg; 680 mOsm/L). Magnesium for i.v. injection is supplied as 50% or 12.5% solutions of magnesium sulfate containing 500 mg/mL (4 mEq/mL) or 120 mg/mL (1 mEq/mL) of elemental magnesium, respectively.

2.3.4. Storage lesion

The length of time blood is stored before it is transfused correlates with an increase in multiple organ failure, systemic inflammatory response syndrome, increased infection, and increased mortality [194–198]. The progressive deterioration in many erythrocyte biophysical and metabolic properties, collectively referred to as red cell storage lesion [196,199–202], develops largely as a result of suppression of RBC metabolic activity. Exhaustion of energy (ATP) leads to intracellular acidosis, 2,3-DPG depletion, membrane Na^+/K^+-ATPase failure, band 3 damage (responsible for chloride shifts and the transport of CO_2 by RBCs), accumulation of reactive oxygen intermediates, lipid peroxidation, depletion of nitric oxide, and loss of parts of the plasma membrane with deformation of erythrocyte shape [203,204]. [203] This collection of changes reduces the capacity of stored RBCs to carry and deliver oxygen to tissue and also indirectly promotes a systemic proinflammatory state by inducing innate immune activation [205], and by generating procoagulant bioactive phospholipids that are pro-inflammatory and associated with an increased risk of acute lung injury.

Metabolism in stored blood is restored rapidly after transfusion, but the capacity initially of transfused RBCs to efficiently transport oxygen to recipient tissue may be significantly impaired [206]. For example the length of time required to regenerate 2,3-DPG is in vivo, although typically of minimal clinical consequence may not be within the brief time frames and extreme conditions of DCR. In addition a higher affinity of hemoglobin for oxygen due to low levels of 2,3-DPG is exacerbated by hypophosphatemia [207,208], a common electrolyte abnormality induced by hemorrhagic shock. Also, incomplete reduction of accumulated methemoglobin in stored blood [209] that has been transfused [210] contributes to potentially a significant fall in P_{50} during DCR. Thus a patient could remain acidotic despite apparent adequate perfusion because of the high affinity of hemoglobin for oxygen and a reduction in offloading of oxygen in the periphery [211]. This storage lesion-related defect in oxygen delivery is compounded by hypothermia, which shifts the oxyhemoglobin dissociation curve to the left (Bohr affect) increasing the affinity of hemoglobin for oxygen still further. In addition to these metabolic abnormalities, morphologic change in stored erythrocytes from flexible biconcave discs to rigid echinocytes and spheroechinocytes decreases microvascular flow due to obstruction of capillaries. Furthermore, RBC-mediated regulation of microvascular blood flow mediated by release of nitric oxide (NO) and adenosine triphosphate (ATP), is abolished by storage [212].

2.3.5. Acute lung injury

Improved early survival associated with high plasma:RBC ratio resuscitations to preemptively treat hemorrhage-associated coagulopathies may be abrogated by an increase in late hospital mortality secondary to multisystem organ failure [213]. The leading cause of transfusion-related mortality is acute lung injury (TRALI) that develops during or within 6 h after transfusion of one or more units of blood or blood components, including platelets [214]. TRALI represented 38% of confirmed transfusion-related fatalities reported to the FDA in the past five fiscal years, although there has been a decrease in TRALI fatalities, from 17 (45% of confirmed transfusion-related fatalities) in FY2012, to 14 (37%) in FY2013 [215]. The risk of TRALI develops due to a dose-dependent exposure to anti-HLA class II, or anti-human neutrophil antigen (HNA) antibodies in donor plasma. Platelet transfusion carries the risk of a plasma-mediated TRALI by content of the transfusion alone, but because platelets are stored at room temperature complications secondary to pathogen contamination are more problematic.

Transfusion of plasma also imparts higher risk for development of transfusion-associated circulatory overload (TACO). TACO during DCR occurs by infusion of blood components at a high rate, in large volumes, or both, and is characterized by the acute onset of hypoxia, tachypnea, tachycardia, and rapidly falling SpO_2 [216]. The rate of TACO caused by all blood products ranges from approximately 1% to 8% [217,218], but may actually be higher than recognized [219]. Predictably, TACO is also associated with a history of congestive heart failure, coronary artery disease, previous coronary bypass surgery, and atrial fibrillation [220]. Differentiating between TACO and TRALI is primarily based on determining whether transfusion-related pulmonary edema is due to increased hydrostatic pressure (TACO) or is caused by an alveolar fluid accumulation due auto-inflammatory pathology (TRALI) [220]. Elevation of BNP or NT-proBNP has been shown to be both sensitive and specific markers of TACO [221].

2.3.6. Ischemia–reperfusion injury

Rapid restoration of normal blood flow to hypoperfused tissue by DCR can be complicated by a distinct pathologic process referred to as reperfusion injury. The pathogenesis of reperfusion injury involves regional and systemic autoinflammatory reactions [222,223] due to non-specific activation of the coagulation/fibrinolysis system as well as activation of innate immune processes, in concert with down regulation of endogenous anticoagulants [224] and inhibitors of inflammation [225,226]. This process is mediated by dissemination of constitutive intracellular molecules released from disrupted cells in areas of severe ischemia and damaged tissue. Several unrelated and multifunctional intracellular and extracellular molecules, as well as certain interleukins, heat shock proteins, and others exhibit these properties [227–229]. All possess similar molecular component structures referred to as DAMPs (or, damage-associated molecular pattern). DAMPs are recognized by a family of receptors associated with innate immunity known as pattern recognition receptors (PRRs). Of note, a significant portion of RBCs stored for long periods release free heme that is recognized by PRRs as a DAMP ligand resulting in activation of the recipient's innate immune system and creating the potential for systemic autoinflammatory tissue damage and organ failure [199].

Serum levels of HMGB1, the prototype DAMP molecule, increase in hemorrhagic shock [230–232]. HMGB1 binds to a specific PRR, toll-like receptor 4 (TLR4) that is expressed on several cell types such as dendritic cells, neutrophils, macrophages, lymphocytes, endothelial cells, and platelets. A HMGB1-TLR4 interaction induces proinflammatory activities [233,234] which mediate, in part, an autoinflammatory response expressed clinically as a systemic inflammatory response syndrome (SIRS) [235,236]. HMGB1 also demonstrates specific interactions with the hemostatic system, specifically upregulation of TM expression and activation of PC leading to aPC-mediated inhibition of thrombin generation and consumption of PAI-1 [49]. These activities may contribute to modulation of coagulation by hypoperfusion.

The consequences of a systemic autoinflammatory syndrome are diffuse interstitial edema and cellular swelling. Marked splanchnic hypoperfusion is a characteristic feature of the compensatory mechanisms that operate in response to massive blood loss. Subsequent

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reperfusion of hypoperfused gut mucosa during DCR produces significant bowel edema [237] and may also lead to hepatic dysfunction [236] (so-called, shock liver). Bowel edema during reperfusion occurs early [237] leading to intraabdominal hypertension (IAH) that may progress to intra-abdominal compartment syndrome, defined as IAH associated with organ failure. Right ventricular (RV) preload is also diminished by IAH-mediated reductions in inferior vena cava blood flow [238,239]. Moreover, in response to increased RV afterload, acute RV dilatation may develop causing a decrease in ejection fraction. Also, RV dilatation impinges on the ventricular septum, which due to ventricular interdependence decreases left ventricular preload and consequently further reduces cardiac output [240,241].

3. Conclusion

MT for catastrophic blood loss is a rare event. Also, an exact definition of MT, uniform guidelines that specify for whom MT is indicated, in what manner this complex intervention is accomplished, and the meaningful outcomes that should be expected from MT all remain incompletely defined. Paradoxically, an increase in mortality has been associated with increasing number of units transfused, and the administration of massive amounts of this expensive and limited resource is associated with substantial risk for several non-lethal, yet still formidable complications. Also, among patients who do survive, MT is independently associated with an unfavorable long-term outcome, and a substantial proportion of post-resuscitation patients endure significant functional deficits one year after injury [242]. In contrast to this bleak perspective, however, is the fact that continued advances in resuscitation practices and incorporation of MT into comprehensive DCR protocols have led to progressive improvement in survival for patients in profound hemorrhagic shock. Indeed, before 1990 resuscitation of patients with severe acute blood loss resulted in low survival rates, on the order of 10% to 40%, while survival currently, with implementation of comprehensive DCR programs, is reported from 65% to as high as 92% [243].

The success of current DCR strategies is founded on advances from laboratory and clinical investigations that have more thoroughly elucidated the pathogenesis of hemorrhagic shock and clarified the mechanisms of hemorrhage-induced coagulopathy. New paradigms such as hemostatic resuscitation have fundamentally redefined the management of catastrophic blood loss. To continue to refine the principles of resuscitation, additional high-quality prospective randomized intervention studies, guided by initial acquisition of prospective observational data, will be necessary. And, whereas in previous decades the management of exsanguinating hemorrhage required clinicians to possess simply a passing familiarity with MT, effective resuscitation practices now mandate an understanding of a significantly more complex and considerably more comprehensive strategy for care of the bleeding patient.

Conflict of interest statement

None.

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