Blood transfusion management in the severely bleeding military patient

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Purpose of review
Hemorrhage remains the primary cause of preventable death on the battlefield and in civilian trauma. Hemorrhage control is multifactorial and starts with point-of-injury care. Surgical hemorrhage control and time from injury to surgery is paramount; however, interventions in the prehospital environment and perioperative period affect outcomes. The purpose of this review is to understand concepts and strategies for successful management of the bleeding military patient. Understanding the life-threatening nature of coagulopathy of trauma and implementing strategies aimed at full spectrum hemorrhage management from point of injury to postoperative care will result in improved outcomes in patients with life-threatening bleeding.

Recent findings
Timely and appropriate therapies impact survival. Blood product resuscitation for life-threatening hemorrhage should either be with whole blood or a component therapy strategy that recapitulates the functionality of whole blood. The US military has transfused over 10 000 units of whole blood since the beginning of the wars in Iraq and Afghanistan. The well recognized therapeutic benefits of whole blood have pushed this therapy far forward into prehospital care in both US and international military forces. Multiple hemostatic adjuncts are available that are likely beneficial to the bleeding military patient; and other products and techniques are under active investigation.

Summary
Lessons learned in the treatment of combat casualties will likely continue to have positive impact and influence and the management of hemorrhage in the civilian trauma setting.

Keywords
damage control resuscitation, transfusion, US military, whole blood

INTRODUCTION

Transfusion of the exsanguinating patient has come full circle and capitulates perfectly to the saying 'everything old is new again.' Over the last decade, there has been a paradigm shift in resuscitation and transfusion management of the severely bleeding military patient. The current best practice management can be summarized by the following statement: 'The indications for blood transfusion are based on the fact that transfused blood is the best substitute for blood lost in acute hemorrhages.' This is from the article *The Transfusion of Whole Blood: A suggestion for its more frequent employment in war surgery* in by Dr LB Robertson published in the *British Medical Journal* in 1918 [1]. A century later: two World Wars; the Korean and Vietnam Wars; Afghanistan and Iraq Wars; hundreds of articles; and thousands of combat casualties – what has been recognized for over a century is back in the spotlight.

DAMAGE CONTROL RESUSCITATION: EVOLUTION AND CLINICAL EXPERIENCE

Damage control resuscitation (DCR) is a term that popularized in the last decade when it was clinically recognized that whole blood-based resuscitation (hemostatic resuscitation) was independently associated with reduced death from hemorrhage [2–8].

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KEY POINTS

- Hemorrhage remains the number one cause of death on the battlefield and is a leading cause of preventable death in military and civilian trauma.
- Resuscitation of the bleeding patient should either be done with whole blood or component therapy ratios that mimic whole blood (1 : 1 : 1).
- Whole blood has over a century of efficacy and safety data; whole blood is likely the best resuscitation fluid for hemorrhage even though a prospective randomized trial has not been conducted to validate this.
- Whenever resuscitating a bleeding trauma patient, many factors should be considered: temperature, electrolytes, transfusion ratios, hemostatic adjunctions, TXA; crystalloid should be used judiciously if at all.
- Hemostatic adjuncts can be used with TEG or ROTEM goal-directed resuscitation or can be used empirically based on clinical bleeding; TXA, fibrinogen concentrates, PCCs, and lyophilized plasma have a role in hemostatic resuscitation; however, large prospective outcome data are needed.

A whole blood-based resuscitation is described as either the use of whole blood (fresh and warm or cold-stored) or the use of blood components in a 1 : 1 : 1 ratio for plasma : platelets : RBC units. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) randomized controlled trial supports the concept of hemostatic resuscitation [9]. Although the primary outcomes of 24-h and 30-day mortality were not statistically different between 1 : 1 : 1 and 2 : 1 : 1 ratio groups, the 1 : 1 : 1 ratio patients had reduced 24-h death from hemorrhage and reduced time to clinical hemostasis [9]. In addition to hemostatic resuscitation, principles of DCR include; rapid surgical control of bleeding, permissive hypotension, maintenance of normothermia, use of mechanical and intravenous hemostatic adjuncts, and minimal use of crystalloids and colloids [5,6,10–12] (Table 1). Although permissive hypotension was originally described as an integral aspect of DCR, the blood pressure threshold of at least 90 mmHg in nontraumatic brain injury requires further investigation. This is because of the increased transport time for military and civilian patients compared with transport times in the studies that supported hypotensive resuscitation [13,14]. In addition, as resuscitation has transitioned from crystalloid to blood-based methods, many hypothesize that increased blood pressure with improved cellular perfusion can be tolerated without 'popping the clot.' As a result, some experts in the field have suggested a slightly more liberal blood pressure goal with blood-based resuscitation [15▪▪].

The old paradigm of trauma resuscitation supported the use of 2 l of crystalloids followed by the subsequent use of red blood cells (RBCs) if bleeding continued, then followed by plasma and platelets only if lab values suggested they were needed. It is now well recognized that for patients with life-threatening haemorrhage, the above approach should be abandoned and is no longer considered optimal care [4,9,16–20]. The detrimental effects of crystalloid are multifactorial and occur secondary to the development of a dilutional coagulopathy and anemia; injury to the endothelium secondary to the pro-inflammatory effects of crystalloid; and hyperchloremic metabolic acidosis. It has been shown that even small volumes (1.5 l) of crystalloid increase morbidity and mortality [9,18,21–26]. Crystalloid resuscitation has been associated with increased rates of respiratory distress syndrome, resuscitation morbidities such as abdominal and extremity compartment syndromes, and surgical site infections – these morbidities occur in a dose-dependent fashion [18]. In patients undergoing trauma laparotomies, higher volumes of crystalloid administered was an independent predictor of mortality prior to the adoption of DCR principles [27▪].

ALL ROADS LEAD TO WHOLE BLOOD

Whole blood has a long history of use in the battlefield; it was the primary resuscitation fluid for hemorrhage during World War I (WWI), WWII, the Korean War, and early in the Vietnam War. There are two main forms of whole blood: warm fresh whole blood and cold-stored whole blood (CWB). Warm fresh whole blood is collected 'on scene' and transfused immediately; as a result, formal and complete transfusion-transmitted disease screening cannot be accomplished. Ideally, whenever warm fresh whole blood is transfused, it is from prescreened donors and rapid testing is performed for HIV, hepatitis B and C. CWB is typically collected and tested using formal, Food and Drug Administration (FDA)-approved techniques and then stored at 2–6 °C for up to 21 days (even though it is licensed for up to 35 days) based on in-vitro studies of platelet hemostatic function and RBC storage lesion concerns [28]. Whenever used in military settings, this product is most commonly collected in the United States and then transported to overseas military treatment facilities.

In the 1970s, a transformation occurred from resuscitation of hemorrhage with whole blood to the primary use of crystalloid and then the sequential initiation of component therapy. Although this resuscitation strategy lacked support

Table 1. Damage control resuscitation principles

Pre-hospital
Rapid recognition of life-threatening hemorrhagic shock
Point-of-care devices: near infrared spectroscopy; INR; lactate level may be of value
Prevent hypothermia
Hemorrhage control with mechanical hemostatic adjuncts:
Tourniquet/junctional tourniquet
Pressure dressings/thrombin and fibrin-impregnated gauze
REBOA
Intraabdominal foams (investigational)
Hemostatic resuscitation
Whole blood is optimal
Component therapy with plasma (dried, liquid, or thawed), RBCs, and platelets in 1 : 1 : 1 ratio
Permissive hypotension for patients without traumatic brain injury[a]
Avoid crystalloid resuscitation
Consider TXA administration if less than 3 h from time of injury[b]
Consider source of fibrinogen (fibrinogen concentrate or cryoprecipitate)
Avoid hypocalcemia
In prolonged evacuations, empiric calcium administration for every 4–6 units of RBCs or WB
Hospital
Rapid surgical correction of bleeding
Hemostatic resuscitation
Whole blood is optimal
Component therapy: plasma (dried, liquid, thawed, FFP/FP24), RBCs, platelets in 1 : 1 : 1 ratio
Shift from empiric whole blood based resuscitation to goal-directed resuscitation whenever feasible
Permissive hypotension prior to surgical control of bleeding for patients without TBI[a]
Intravenous hemostatic adjuncts
Consider TXA administration indicated either empirically or guided by functional viscoelastic studies demonstrating LY30 more than 3%[b]
Source of fibrinogen for reduced fibrinogen function
PCC for patients taking vitamin K antagonist
Avoid crystalloid resuscitation
Blood pressure goals after hemorrhage control
MAP at least 60; SBP greater than 100 mmHg and evidence of improved end organ perfusion
Monitor CBC, electrolytes, and blood gas hourly
Calcium administration for every 4–6 units of RBC or WB; follow ionized calcium concentration
Treat hypomagnesaemia
Avoid/treat hyperkalemia

FFP, fresh frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrates; RBC, red blood cells; REBOA, resuscitative endoscopic balloon occlusion of the aorta; SBP, systolic blood pressure; TBI, traumatic brain injury; TXA, tranexamic acid; WB, whole blood.
[a]Conventional goal is SBP greater than 90 mmHg. Recent concept indicates a higher goal of 90–110 mmHg because of shift towards blood-based resuscitation and concern for prolonged hypoperfusion especially for patients with long transport times.
[b]Military policy currently is to empirically administer 1 g of TXA for severe bleeding in both prehospital and in-hospital settings.

from high-quality clinical evidence, it was nevertheless widely adopted until recent data supported a paradigm shift back to using a whole blood-based strategy for traumatic hemorrhage [29–31].

Early in the recent wars in the Middle East, whole blood use was in the form of walking blood banks and was most commonly warm fresh whole blood. In a large retrospective review of patients who received whole blood without platelet transfusion compared with those who received balanced resuscitation to include platelet transfusion, those who received whole blood had a higher survival at 24 h and 30 days [31].

In 1991, a randomized control trial demonstrated that CWB in children requiring cardiac surgery reduced bleeding and had improved platelet function compared with blood components in a 1 : 1 : 1 unit ratio [32]. The increased coagulation efficacy of cold stored whole blood may be a result of the platelets being stored at 4 °C compared with 22 °C as is standard with platelet units. CWB is also a more concentrated product with less anticoagulants and additives compared with whenever blood components are mixed in a 1 : 1 : 1 unit ratio [33▪▪,34▪▪].

Multiple factors make cold-stored low-titer group O whole blood (LTOWB) well tolerated and

an efficacious alternative to reconstituted whole blood: reconstituted whole blood includes platelets stored at 22 °C, which increases the risk of bacterial contamination; LTOWB confers a lower risk of hemolysis compared with type A plasma (no titer testing) and nonmatched platelets whenever transfused; additionally, LTOWB can be transfused to a patient of any ABO blood type thereby decreasing the dreadful potential of a potentially fatal ABO incompatibility transfusion reaction. The definition of 'low-titer' has not been definitively established. The threshold of less than 1 : 256 has been used by the US military since WWII and remains the current standard [33▪▪,35]. An additional method to further improve the safety of LTOWB is leukoreduction, which can reduce febrile reactions, CMV transmission, and human leukocyte antigen (HLA) alloimmunization [36,37].

The logistic benefits of cold-stored LTOWB are based on increased availability because of the increased storage duration of up to 21 days, and increased timeliness and simplicity of transfusing an optimal product. As of September 2017, 10 568 units of whole blood have been transfused during the wars in Iraq and Afghanistan (see Figs. 1–2). These transfusions have predominantly occurred in the 'hospital' setting: Role 2 (Forward Surgical Teams) or Role 3 (Combat Support Hospitals). Point-of-injury whole blood transfusion does occur and is an active area of investigation and implementation to improve its efficacy and safety amongst special operations and conventional military forces [38,39].

Blood product availability currently exists in many of the rotary wing evacuation platforms; the capability did not exist, until recently, at point of injury [40–42]. Currently, special operations forces medics carry LTOWB on select missions. This strategy is becoming more common as the lifesaving value of prehospital transfusion continues to be established [41,43,44▪▪]. Whole blood transfusion – fresh whole blood or cold whole blood – in the prehospital environment (at point of injury or en route to a hospital) is not only feasible but also is also logistically sound. Most importantly, this strategy is associated with improved outcomes in combat casualties with life-threatening hemorrhage [41,44▪▪,45▪,46].

IT IS NOT JUST WHAT IS GIVEN BUT WHEN IT IS GIVEN

Combat casualties requiring massive transfusion have a mortality rate up to 39% and will likely have the most benefit from a balanced whole blood-based resuscitation [10,29,42,47–49,50▪]. The most common cause of preventable death after traumatic injury is hemorrhage. The vast majority of these deaths in both military and civilian practice occur in the prehospital phase of resuscitation. In the United States, it is estimated that there are 30 000 deaths a year that are preventable after injury because of hemorrhage, and 25 000 of these deaths occur prehospital [51▪▪]. Death from traumatic hemorrhage also occurs very fast, typically within 2 h

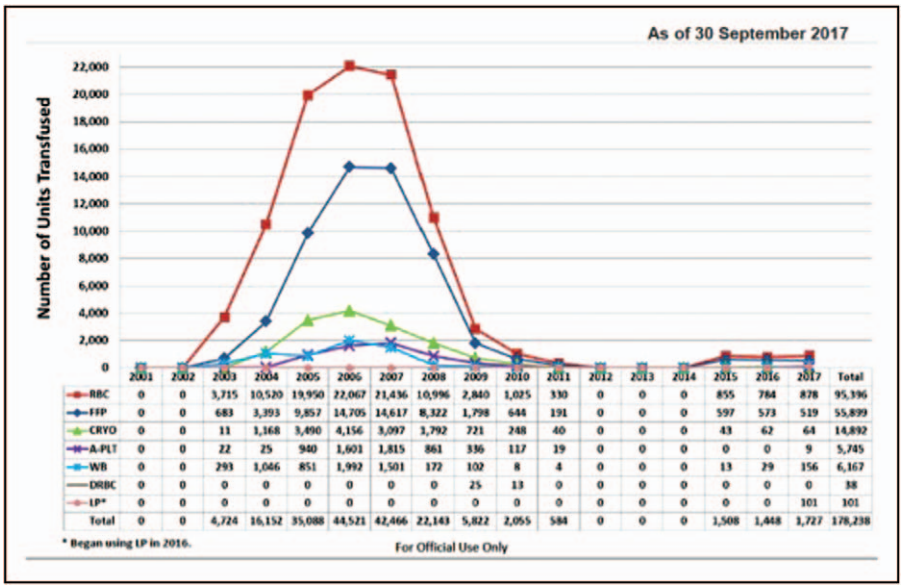
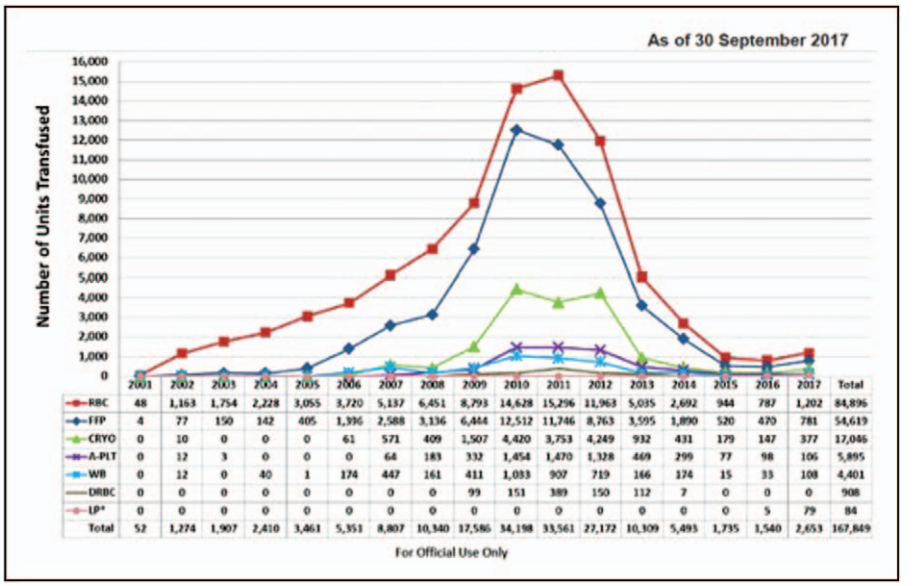


FIGURE 1. Blood products transfused in the Iraq Theater of Operations 2003–2017. Data from the Armed Services Blood Program (ASBP) demonstrating the total number of packed red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate (CRYO), apheresis platelets (A-PLT), whole blood (WB), and deglycerized red blood cells (DRBC) transfused per year. Information and data provided with courtesy of the ASBP with permission.



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
RBC	48	1,163	1,754	2,228	3,055	3,720	5,137	6,451	8,793	14,628	15,296	11,963	5,035	2,692	944	787	1,202	84,896
FFP	4	77	150	142	405	1,396	2,588	3,136	6,444	12,512	11,746	8,763	3,595	1,890	520	470	781	54,619
CRYO	0	10	0	0	0	61	571	409	1,507	4,420	3,753	4,249	932	431	179	147	377	17,046
A-PLT	0	12	3	0	0	0	64	183	332	1,454	1,470	1,328	469	299	77	98	106	5,895
WB	0	12	0	40	1	174	447	161	411	1,033	907	719	166	174	15	33	108	4,401
DRBC	0	0	0	0	0	0	0	0	99	151	389	150	112	7	0	0	0	908
LP*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	79	84
Total	52	1,274	1,907	2,410	3,461	5,351	8,807	10,340	17,586	34,198	33,561	27,172	10,309	5,493	1,735	1,540	2,653	167,849

FIGURE 2. Blood products transfused in the Afghanistan Theater of Operations 2003–2017. Data from the Armed Services Blood Program (ASBP) demonstrating the total number of packed red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate (CRYO), apheresis platelets (A-PLT), whole blood (WB), and deglycerized red blood cells (DRBC) transfused per year. Information and data provided with courtesy of the ASBP with permissions.

from admission [9,52]. Recent data indicates that the rapid availability of blood products is independently associated with improved survival of combat casualties. Kotwal *et al.* [45▪,53] demonstrated that decreased transport times and time to capability improved survival in military casualties. A recently published article by Shackelford *et al.* demonstrated that prehospital blood product transfusion in combat casualties improved early and 30-day survival. This analysis was unique compared with other prehospital transfusion studies in that all deaths in this military population were captured; this is important because early hemorrhagic deaths are the cohort of patients predicted to most benefit from prehospital transfusion. The study demonstrated that the median time to initiation of transfusion, 36 min after injury, or 7 min after MEDEVAC arrival significantly improved survival and it supports sustainment of a military trauma system with prehospital transfusion capability [44▪▪].

The recent wars in the Middle East have spawned a generation of military providers who have witnessed the clinical benefits of whole blood transfusion; this century's old approach is being validated by multiple military and civilian-ongoing studies. Although there has not been a prospective randomized clinical trial definitively comparing whole blood to balanced component therapy, the existing historical, and current, evidence challenges the necessity of for a prospective randomized investigation.

ADJUNCTS TO HEMOSTATIC RESUSCITATION

The empiric use of whole blood-based resuscitation strategy should be followed by a goal-directed resuscitation strategy whenever possible. Goal-directed therapy and the use of point-of-care technology to facilitate early diagnosis of shock and coagulopathy may have a role in resuscitation and possibly be superior to empiric ratio-based component therapy [54▪]. Mechanical and intravenous hemostatic agents may also be helpful to reduce morbidity and mortality in traumatic hemorrhagic shock.

Adjuncts to hemostatic resuscitation: goal-directed hemostatic resuscitation

Thromboelastography (TEG) or thromboelastometry (ROTEM) are laboratory methods that can facilitate goal-directed hemostatic resuscitation in the bleeding patient. These point-of-care tests provide global and qualitative information regarding the dynamics of clot development, stabilization, and dissolution that reflect aspects of in-vivo hemostasis; however, definitive outcome benefits for this approach are still under investigation [55,56]. It is now well recognized that plasma-based studies, such as activated partial thromboplastin time (aPTT) and international normalized ratio (INR), fail to predict coagulopathy of trauma, given that these assays were designed to evaluate defects in patients who were known to have a bleeding diathesis [57]. A

recent Cochrane Review reported improved survival in nontrauma patients who were resuscitated according to TEG or ROTEM compared with conventional coagulation tests [58▪]. One small randomized controlled trial (RCT) in adult trauma patients published after the Cochrane Review indicated improved survival with TEG-directed resuscitation [54▪]. Larger multicenter studies are needed to confirm these results.

Adjuncts to hemostatic resuscitation: tranexamic acid

Tranexamic acid (TXA) is a long-established antifibrinolytic drug that has historical use for decreasing blood loss in patients with congenital coagulopathies and elective surgery. It was first evaluated for use in trauma in 2010 and has been shown to decrease transfusion requirements and possibly improve survival in both military and civilian trauma patients [59,60]. If a bleeding trauma patient receives TXA, it should not be more than 3 h after injury because of the higher risk of thromboembolic events and mortality [59,61–63]. Initial military data supported the use of TXA in combat trauma indicating that whenever used with blood component-based resuscitation, it improved measures of coagulopathy and survival [59]. Two very recent articles demonstrated the increased risk for venous thromboembolism with TXA use in the combat casualty population [64▪,65]. Additionally, a large retrospective review of TXA use in the combat trauma population demonstrated no mortality benefit [64▪]. Current military recommendations endorse the empiric use of TXA within 3 h of trauma that results in significant bleeding [61]. The use of TXA has not gained widespread empiric use in civilian trauma centers in patients with traumatic bleeding [64▪,65,66]. In patients who have viscoelastic testing (TEG or ROTEM) demonstrating hyperfibrinolysis, subsequent administration of TXA likely has therapeutic value and may improve outcomes.

Adjuncts to hemostatic resuscitation: lyophilized (freeze-dried) plasma

If component therapy is being transfused instead of whole blood, plasma is essential. Fresh frozen plasma (FFP) can be impractical on the battlefield, given its weight and its temperature requirements [67–69]. The US Army developed freeze-dried plasma (FDP) to resuscitate combat casualties during WWII, but it is not currently licensed in the United States [67]. FDP is produced in Germany and France and used in a few countries in Europe. FDP is preferred in the tactical environment compared with thawed FFP because it is rapidly able to be reconstituted, stable at different temperatures, easy to carry, and does not require refrigeration [70]. Until recently, only US Army Special Operations Forces were fielded with FDP. Given its practicality, feasibility, and long history of use by European allies, the US military liberalized FDP use prior to full FDA approval and in September 2017, Marine and Air Force units deployed with FDP [69,71,72]. The Israeli Defense Force has evaluated FDP as a potential adjunctive therapy for traumatic hemorrhage [67,73]. Studies evaluating efficacy and the safety of FDP are ongoing [72,74]. Multiple FDP products are in development for licensure in the United States [75▪].

Adjuncts to hemostatic resuscitation: fibrinogen concentrates and cryoprecipitate

In traumatic hemorrhage, fibrinogen levels fall precipitously and this hypofibrinogenemia is associated with worse outcomes [76▪▪,77]. In a single-center retrospective analysis, early fibrinogen supplementation improved outcomes in patients with severe pelvic fractures who required massive transfusion [76▪▪]. Fibrinogen can also be obtained from cryoprecipitate. Advantages of fibrinogen concentrates over cryoprecipitate include: no requirement for ABO group matching; administration does not involve the time delay for thawing; and higher amounts of fibrinogen are dissolvable in small volumes enabling rapid delivery without as much potential for fluid overload [78▪,79,80]. Advantages of cryoprecipitate include that it contains vWF, factors VIII and XIII, each of which are important for hemostasis. Targeted fibrinogen concentration in resuscitation for trauma-induced coagulopathy is usually set at more than150 mg/dl [81–84]. Fibrinogen supplementation either as a concentrate or within cryoprecipitate requires further evaluation for indications of use and goals of therapy for patients with traumatic injury and hemorrhagic shock.

Adjuncts to hemostatic resuscitation: prothrombin complex concentrates

Prothrombin complex concentrates (PCCs) rapidly reverse coagulopathy associated with the administration of vitamin K agonists [85,86]. In animal models, administration of three and four-factor PCCs improved individual clotting factors with transient improvement of prothrombin time, but there was no lasting improvement in the consumptive coagulopathy of hemorrhage [87]. Currently PCCs are used primarily for the management of bleeding in patients taking vitamin K antagonists [86].

CONCLUSION

The rate of preventable deaths after traumatic injury because of hemorrhage is high in military casualties. The vast majority of these preventable deaths occur in the prehospital phase of resuscitation. The use of blood products prehospital reduces this risk of death from hemorrhage. Whole blood has increased efficacy, safety, and logistical benefits for both prehospital and in-hospital use. Whenever whole blood is not available, blood components should be used in ratios that emulate whole blood. Additionally, dried plasma is a valuable resuscitative solution. Agents that still require additional investigation include TXA, cryoprecipitate, fibrinogen concentrates, and PCCs.

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