CRITICAL CARE

REVIEW

Clinical review: Fresh frozen plasma in massive bleedings - more questions than answers

Bartolomeu Nascimento[1], Jeannie Callum[2], Gordon Rubenfeld[3], Joao Baptista Rezende Neto[4,5], Yulia Lin[2] and Sandro Rizoli*[5]

Abstract

Fresh frozen plasma (FFP) is indicated for the management of massive bleedings. Recent audits suggest physician knowledge of FFP is inadequate and half of the FFP transfused in critical care is inappropriate. Trauma is among the largest consumers of FFP. Current trauma resuscitation guidelines recommend FFP to correct coagulopathy only after diagnosed by laboratory tests, often when overt dilutional coagulopathy already exists. The evidence supporting these guidelines is limited and bleeding remains a major cause of trauma-related death. Recent studies demonstrated that coagulopathy occurs early in trauma. A novel early formula-driven haemostatic resuscitation proposes addressing coagulopathy early in massive bleedings with FFP at a near 1:1 ratio with red blood cells. Recent retrospective reports suggest such strategy significantly reduces mortality, and its use is gradually expanding to nontraumatic bleedings in critical care. The supporting studies, however, have bias limiting the interpretation of the results. Furthermore, logistical considerations including need for immediately available universal donor AB plasma, short life after thawing, potential waste and transfusion-associated complications have challenged its implementation. The present review focuses on FFP transfusion in massive bleeding and critically appraises the evidence on formula-driven resuscitation, providing resources to allow clinicians to develop informed opinion, given the current deficient and conflicting evidence.

Introduction

Fresh frozen plasma (FFP) is a blood product that has been available since 1941 [1]. Initially used as a volume expander, it is currently indicated for the management and prevention of bleeding in coagulopathic patients [1-3]. The evidence on FFP transfusion is scant and of limited quality [4].

Estimates state that 25 to 30% of all critical care patients receive FFP transfusions [5,6]. Despite its commonality, only 37% of the physicians in a recent study correctly responded to basic questions about FFP, including the volume of one unit [7]. An audit on transfusion practices suggested that one-half of all FFP transfused to critical care patients is inappropriate [5].

Massive haemorrhage is among the most challenging issues in critical care, affecting trauma patients, surgical patients, obstetric patients and gastrointestinal patients [3,8,9]. In trauma, a recent series of retrospective clinical studies suggests that early and aggressive use of FFP at a 1:1 ratio with red blood cells (RBC) improves survival in cases of massive haemorrhage [10-19]. Because bleeding is directly responsible for 40% of all trauma-related deaths, this strategy – also known as haemostatic damage control or formula-driven resuscitation – has received substantial attention worldwide. This early formula-driven haemostatic resuscitation proposes transfusion of FFP at a near 1:1 ratio with RBC, thus addressing coagulopathy from the beginning of the resuscitation and potentially reducing mortality. Nevertheless, this strategy requires immediate access to large volumes of thawed universal donor FFP, which is challenging to implement.

Despite conflict with existing guidelines, early formula-driven haemostatic resuscitation use is expanding and is gradually being used in nontraumatic bleedings in critical care [20]. Both the existing guidelines and early formula-driven haemostatic resuscitation are supported by limited evidence, generating controversies and challenging clinical decisions in critical care (Table 1). The objective of the present article is to review the evidence on FFP in the management of massive traumatic haemorrhage and to critically appraise early formula-driven haemostatic resuscitation, providing the reader with resources to develop an informed opinion on the current controversy.

Plasma basics

'Fresh frozen plasma' is a confusing term as plasma cannot be fresh and frozen at the same time. Fresh refers

*Correspondence: Sandro.rizoli@sunnybrook.ca
[5]Surgery and Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Ave, H171, Toronto, ON M4N 3M5, Canada
Full list of author information is available at the end of the article

Table 1. Arguments for and against the adoption of early formula-driven haemostatic resuscitation in trauma

	Pros	Cons
Mortality	Retrospective studies suggesting a reduction in mortality from exsanguination	Data limited by survivorship bias
		Increase in FFP and platelet use might increase the risk of acute lung injury, multiple organ failure, thrombosis, sepsis and death
Coagulopathy	Prevention and treatment of coagulopathy due to transfusion of clotting factors	Difficult to identify patients early on who will develop coagulopathy and in fact need transfusion of FFP and platelets
	Minimize crystalloid use (decrease the risk of dilution)	Uncertainty about the ideal dose of FFP in the trauma situation
Laboratory tests	No need for coagulation tests	Unnecessary exposure to AB plasma (in some countries, a higher risk of transfusion-related acute lung injury due to higher proportion of female donors)
	Avoid the delay of waiting for blood test results	
Blood bank systems	More timely issuing of blood components	The waste of FFP will increase (shortage of AB plasma)
	No time needed to thaw FFP (AB plasma available at all times)	May increase the complications associated with FFP and platelet transfusion
	Decrease the need for communication between blood bank and the medical team	

FFP, fresh frozen plasma.

to timing from collection to freezing, and frozen refers to the long-term storage condition. FFP transfusion must be ABO compatible, with AB being the universal type, lacking anti-A and anti-B antibodies. Only 4% of the population is AB, resulting in chronic shortage of this blood type [21].

Preparation and composition

FFP is prepared from either single units of whole blood (a whole blood-derived unit is approximately 250 ml) or plasma collected by apheresis (usually 500 ml) [1,2,22]. FFP is collected in citrate-containing anticoagulation solution, frozen within 8 hours and stored at –30°C for up to 1 year. FFP contains all of the clotting factors, fibrinogen (400 to 900 mg/unit), plasma proteins (particularly albumin), electrolytes, physiological anticoagulants (protein C, protein S, antithrombin, tissue factor pathway inhibitor) and added anticoagulants [1,2].

Plasma frozen within 24 hours of collection is termed frozen plasma (PF24), containing 15 to 20% lower factor VIII levels than FFP [23,24]. PF24 is common in countries using the buffy-coat method, in which RBC and plasma are extracted after hard spin from whole blood and platelets recovered after a second soft spin within 24 hours of collection. PF24 has similar clinical indications as FFP [2,23,24].

FFP is commonly thawed in a water bath over 20 to 30 minutes, but US Food and Drug Administration-approved microwaves can thaw 2 units of plasma in 2 to 3 minutes [1]. After thawing, the activity of labile clotting factors such as factor V and factor VIII decline gradually, and most countries recommend FFP use within 24 hours [25,26]. In some countries, FFP is used up to 5 days after thawing. The consequences of transfusing stored, thawed 5-day-old plasma is not completely understood, but the activity of factor VIII is expected to drop by >50%, and the activity of factor V and factor VII drops to about 20% 5 days after thawing [27].

Photochemically treated FFP and solvent detergent FFP are approved methods of inactivating pathogens in some jurisdictions. Both methods cause loss of clotting factors, particularly factor VIII. Some solvent detergent FFP preparations have reduced activity of protein S and α_2-antiplasmin, and have been associated with thromboembolic complications [28,29]. These solvent detergent preparations are extensively used in some European countries, while solvent detergent FFP was withdrawn in North America due to concerns of Parvovirus transmission [1].

Risks

FFP can transmit infectious diseases, albeit rarely. Screening and pathogen inactivation reduced transmission rates of HIV to 1:7.8 million, of hepatitis C virus to 1:2.3 million and of hepatitis B virus to 1:153,000 units transfused [30]. In the UK, concerns over Creutzfeldt–Jakob disease – a rare but rapidly progressive spongiform encephalopathy – led to leukocyte depletion in all blood products and recommendations to use FFP from areas of low epidemicity [31,32].

Other important complications relate to blood immunogenicity, increasingly recognized over the past two decades, particularly transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload [33,34]. TRALI is the commonest cause of transfusion-related death [33,34]. Two mechanisms have mostly been implicated in TRALI. Donor plasma antibodies react with human leukocyte antigens, causing

complement activation, endothelial damage, neutrophil activation and lung capillary leak. Anti-human leukocyte antigens and anti-neutrophil antibodies are commonly found in plasma from multiparous female donors, and the TRALI frequency is higher in recipients from female donors [35-37]. To minimize the risk of TRALI, a male-only plasma policy has been adopted in many countries – with marked reductions in TRALI [35]. Another potential mechanism involves interactions of biologically active mediators in stored plasma and lung endothelial cells. Other important transfusion-related complications include acute haemolytic reaction from anti-A and anti-B antibodies, and anaphylaxis [22].

Massive bleeding

Massive bleeding is defined as the loss of one blood volume within 24 hours, or as 50% blood loss within 3 hours or a bleeding rate of 150 ml/minute [38]. The physiological derangements and complications are proportional to the blood loss and to the time to correct shock. Loss of one blood volume and replacement with RBC only results in clotting factor levels dropping to approximately 30%, the minimal level thought to be required for adequate haemostasis [3,39]. Lower levels significantly prolong the prothrombin time and the activated partial thromboplastin time above 1.5x normal [1]. FFP transfusion to replace clotting factors is often recommended for these patients but no studies exist supporting this practice [4]. Replacing one blood volume or more without FFP results in dilutional coagulopathy, diffuse microvascular bleeding and increased mortality [40,41].

Current guidelines for FFP in massive bleeding

The principles of managing massive haemorrhage include rapid control of bleeding; replenishing the intravascular volume with crystalloid followed by RBC and, once coagulopathy is present or suspected, then adding FFP, platelets and cryoprecipitate; along with correction of acidosis and hypothermia. Most current guidelines [1,39,42-44], including the European and US guidelines, recommend transfusing FFP, platelets and cryoprecipitate only when laboratory assays detect a deficit. The goal is to correct the assays as follows: FFP to correct the prothrombin time/activated partial thromboplastin time to <1.5x normal, platelets to raise the count to ≥50 x 10^9/l and cryoprecipitate to raise fibrinogen to ≥1.0 g/l [1,42-44]. Where a laboratory is not available, these products are recommended after large infusions of crystalloid and RBC. The usual FFP dose in massive bleeding is 15 to 20 ml/kg or 3 to 6 units, which aims to raise clotting factors levels above 30% [3,38,39].

Current crystalloid-based resuscitation guidelines initiate FFP transfusion late, often after more than one blood volume is lost and the patients have clinically overt coagulopathy [40,41]. Most recommendations are based on observations and expert opinion, often lacking high-level evidence. Many recommendations originated in studies conducted in nontrauma settings and when RBC units had 150 to 300 ml plasma [1]. Currently, RBC preparations contain only minimal residual plasma (≤30 ml). Despite worldwide acceptance of similar resuscitation principles, bleeding remains the second overall cause of death in trauma – becoming the first cause of death following hospital admission [45-47].

Trauma-associated coagulopathy

Haemorrhage is directly responsible for 40% of all trauma-related deaths [45,46], and many deaths are potentially preventable. Current resuscitation strategies invariably fail to prevent coagulopathy in massive bleedings. Multiple causes have traditionally been implicated in trauma coagulopathy, including clotting factor consumption and dilution, hypothermia and acidosis – all linked to large-volume crystalloid infusion and late replacement of clotting elements [40,41]. The management of massive trauma bleeding started changing when Brohi and MacLeod and colleagues separately described that trauma coagulopathy occurs early, and is present on hospital admission in 25% of all severely traumatized patients [48,49]. Further studies suggest that early coagulopathy is initiated by shock and the amount of tissue destruction, independent of clotting factor consumption or dilution (Figure 1), and is associated with a threefold mortality increase [48,49].

A unique coagulopathy in traumatic brain injury has long been suspected, where the release of brain tissue factor causes systemic activation of coagulation (disseminated intravascular coagulation), exhaustion of clotting elements and hyperfibrinolysis [50,51]. While coagulopathy is common and critically important in traumatic brain injury, the controversial existing evidence suggests it may not differ from trauma coagulopathy in general [51].

The early trauma coagulopathy concept has challenged the current crystalloid-based resuscitation that ignores coagulopathy until it becomes overt. Over the past 2 years, a haemostatic blood-based resuscitation – commonly termed damage control resuscitation – proposes a series of early and aggressive strategies to treat or prevent early trauma-associated coagulopathy [52,53]. This resuscitation entails the use of thawed plasma as the primary resuscitation fluid, limited use of crystalloid, targeted systolic blood pressure at approximately 90 mmHg to prevent renewed bleeding, early activation of a massive transfusion protocol with fixed ratios of FFP: platelets:cryoprecipitate:RBC (approximately 1:1:1:1), liberal use of recombinant activated factor VII (rFVIIa)

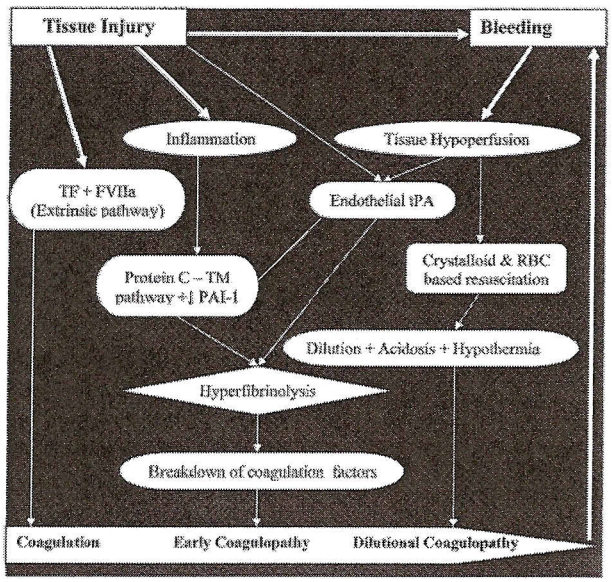

Figure 1. Recently proposed mechanism for coagulopathy in trauma. Tissue trauma activates the coagulation process via tissue factor (TF) and activated factor VII (FVIIa), formerly named the extrinsic pathway, to stop bleeding. Concomitantly, endothelial damage/ischaemia leads to release of physiologic anticoagulants and antifibrinolytics (that is, thrombomodulin (TM), protein C and tissue plasminogen activator (tPA)) due to inflammation and tissue hypoperfusion, to prevent thrombosis. Early coagulopathy develops when there is an imbalance in this process, with excessive anticoagulation, hyperfibrinolysis and consumption of clotting factors. Resuscitation with crystalloid and red blood cells (RBC) can cause/worsen dilution, acidosis and hypothermia. PAI-1, plasminogen activator inhibitor 1.

and the use of fresh whole blood for the most severely injured combat casualties [52,53].

Critical appraisal of the evidence on early formula-driven haemostatic resuscitation

The first reports suggesting aggressive FFP transfusions were computer simulation models. In 2003, Hirshberg and colleagues published a haemodilution model of exsanguination, calculated the changes in coagulation and predicted an optimal FFP:RBC ratio of 2:3 to adequately replenish clotting factors [54]. Ho and colleagues predicted 1 to 1.5 units FFP to each RBC to prevent dilutional coagulopathy in mathematical models [55].

Since 2007, growing numbers of retrospective military and civilian papers have studied early formula-driven haemostatic resuscitation with different FFP:RBC ratios (mostly near 1:1) and mortality [11-20,56,57]. Overall, these studies demonstrate a significant association between higher ratios and lower mortality in massive traumatic bleedings, with absolute mortality reductions ranging between 15 and 62% [11-20]. These figures surpass any predictions of potentially preventable deaths in trauma [47]. While the survival advantage of early and aggressive FFP transfusion in early formula-driven resuscitation cannot be ignored, the evidence behind it has limitations that are discussed next.

Survival advantage

Borgman and colleagues reviewed 246 massively transfused (≥10 units RBC/24 hours) combatants and analysed mortality at three different FFP:RBC ratios (1:8, 1:2.5 and 1:1.4) [11]. A 55% absolute reduction in mortality occurred between the highest and lowest ratios. While mortality reduction was impressive, patients with a higher FFP:RBC ratio (1:1.4) had a longer median time to death (38 hours) than those with a lower ratio (2 hours). These data suggest that lower ratio patients may not have lived long enough to receive FFP. Another study by the same group on civilian trauma patients reported a similarly impressive survival advantage for higher ratios than lower ratios, but also a markedly dissimilar time to death (35 hours versus 4 hours) [58]. Both studies disclose survivorship bias, where arguably patients had to survive long enough to receive FFP, thus questioning their conclusions.

Addressing survivorship bias

Two studies specifically addressed the survivorship bias in high-FFP:RBC studies. Scalea and colleagues used stepwise logistic regression analysis on 806 patients, demonstrating no survival benefit for higher ratios when early deaths were excluded [56]. This study has its own limitations, however, including a failure to report the time to intensive care unit admission, an inability to include major factors (acidosis and coagulation) in the statistical model and a surprisingly low mortality (6%) for massive transfusions. Snyder and colleagues also attempted to correct for survivorship bias in another study where mortality in high (>1:2) and low (<1:2) ratios was compared in regression models [57]. Using the FFP:PRBC ratio as a fixed value at 24 hours, as in many studies on this topic, the high ratio resulted in better survival. This survival advantage was lost, however, when the ratio was treated as a time-dependent variable (relative risk = 0.84, 95% confidence interval = 0.47 to 1.5). These two studies dispute the survival advantage suggested by the previous studies with such bias.

Time to intervention

The delay to thaw and initiate FFP transfusion leads to another important limitation: timing to initiate and reach the high FFP:RBC ratio. Early formula-driven resuscitation proposes that FFP should be initiated early, ideally with the first RBC unit at the start of resuscitation [52,53]. Considering that even laboratory-guided resuscitation eventually results in a high FFP:RBC ratio, a

critical difference in formula-driven resuscitation is the early implementation of a high ratio. No studies to date have reported on transfusing pre-thawed FFP along with the first RBC units or on the time to reach the 1:1 ratio. Snyder and colleagues stated that the median time to the first RBC was 18 minutes from arrival, while the first FFP was transfused more than 1 hour later [57].

The commonly used definition of massive bleeding as transfusions over 24 hours ignores the fact that 80% of all massive transfusions occur within the first 6 hours of hospitalization, at which point either bleeding reduces substantially or the patient dies [59]. A multicentre study involving 16 trauma centres, 452 massively bleeding trauma patients and transfusion rates within 6 hours of hospitalization (rate <1:4, rate of 1:4 to 1:1 and rate ≥1:1) concluded that early high FFP:RBC and platelet:RBC ratios improved survival [19]. Despite limitations, including significant differences in the baseline Glasgow coma scale and therefore the severity of head injuries between groups, the study provides better evidence that reaching high FFP:platelet:RBC ratios within the first hours of admission is associated with mortality reduction.

Missing data, co-interventions and heterogeneity

Data on timing to initiate FFP transfusions, on timing to reach the 1:1 ratio and on transfusions during the first 6 hours are equally missing in the studies supporting early formula-driven haemostatic resuscitation and in existing guidelines, limiting comparisons between the different strategies.

Spinella and colleagues reported in 708 military patients transfused with ≥1 units RBC that FFP transfusion was associated with increased survival (odds ratio = 1.17, 95% confidence interval = 1.06 to 1.29; P = 0.002) [12]. Missing data on the International Normalized Ratio, not measured in one-half of the patients, and heterogeneity with nonsurviving patients being significantly more coagulopathic than that for surviving patients, International Normalized Ratio 2.06 versus 1.4 (P <0.001) on admission, however, challenge their conclusion.

Aggressive and early FFP transfusion is part of damage control resuscitation, which also proposes crystalloid restriction, rFVIIa and other interventions. A small study on 40 combat casualties resuscitated with a package containing whole blood, rFVIIa, crystalloid restriction and a high FFP:RBC ratio illustrates the complexity of analysing multiple co-interventions [52]. Combatants receiving the package had better survival compared with historical controls managed with similar FFP:RBC ratios but not rFVIIa, whole blood and significantly less blood transfusion [60]. In this study, multiple co-interventions make it impossible to establish the contribution of any of them.

Two other studies analysed survival before and after implementation of massive transfusion protocols [13,17]. Both studies demonstrated better survival with the protocol despite no difference in 24-hour FFP transfusion before and after protocol implementation and despite FFP:RBC ratios other than 1:1. The results could be interpreted as the protocol, and not the high FFP:RBC ratios, leading to better survival.

Potential harm

In a study demonstrating the survival advantage of aggressive FFP transfusion in the intensive care unit, Gonzalez and colleagues reported an unusual high incidence of early and lethal acute respiratory distress syndrome [10]. The aggressive FFP transfusion was aimed at correcting the International Normalized Ratio to ≤1.3, probably an unattainable goal given that the International Normalized Ratio of FFP is near 1.3 [61-63]. Considering that the deaths might represent transfusion-associated circulatory overload or TRALI, the study raises concerns on the aggressive FFP transfusion strategy. In a separate study of 415 trauma patients [64], early acute respiratory distress syndrome (before day 4) occurred significantly more among those patients transfused more FFP. Some studies, however, suggest that the adoption of early and aggressive FFP transfusion in fact reduces the overall exposure to blood and blood products [19]. Here also, the evidence is conflicting and precludes definitive conclusions.

Ethical and logistical considerations

In many countries, blood transfusion requires written informed consent, which is deferred only in life-threatening situations, including massive bleeding. The proposal to transfuse FFP early and aggressively raises important ethical considerations. First, traumatic massive bleeding carries upm to 40% mortality even when current resuscitation guidelines are strictly followed, and early coagulopathy increases mortality threefold. The marked reduction in mortality recently reported with early and high FFP:RBC resuscitation has prompted many trauma centres to adopt this strategy. The evidence behind early formula-driven haemostatic resuscitation is concordant with recent advances in the understanding of early trauma coagulopathy, but they also have methodological flaws and bias that seriously question the survival benefit.

Many trauma centres keep thawed AB plasma (universal donor) available at all times for resuscitation. In countries that have implemented policies favouring male-only plasma to minimize the risks of TRALI, supplying AB plasma becomes an even greater challenge. Other ethical, logistical and financial considerations include the potential waste of unused thawed FFP, a so far untouched issue, plus the financial costs of haemostatic protocols,

Table 2. Challenges and proposed solutions to future clinical trials on haemostatic resuscitation

Most important challenges	Proposed solutions
Avoid survivorship bias	Exclude patients not expected to live long enough to receive plasma
	Precise documentation of the time of transfusions and death
	Perform analysis of transfusion as a time-dependent variable
Avoid contamination of the control arm and avoid delay in initiating 1:1 transfusions in the intervention arm	Transfusion guidelines for both arms clear and easy to follow
	Close cooperation between blood bank, trauma, anaesthesia and critical care
	Thawed AB plasma 24/7 or rapid thawing (microwave)
	Minimize time for results of laboratory tests – consider point-of-care testing
Multiple interventions concomitantly tested	Standardize all aspects of resuscitation (that is, amount and type of intravenous fluid; procoagulant drugs) in control and intervention groups
	Measure clotting factor levels
Discriminate coagulopathic from mechanical bleeding	Measure indicators of coagulopathy:
	• Thromboelastography
	• Clotting factor assays
	• Markers of hyperfibrinolysis
	• Tissue hypoperfusion (lactate, base deficit)
	• Progression of bleeding by computerized tomography scan (that is, progression brain contusion, retroperitoneal haematomas)
	• Ask the physician's opinion (that is, surgeon, anaesthetist, intensivist)
Immediate cessation of component therapy	Evidence that bleeding has stopped
	Consider ending by 6 hours
Outcome	Consider restoration of haemostasis competence
Need for large samples	Consider a feasibility trial prior to a large multicentre trial to identify major challenges
Consent	Need for delayed consent

and the use of AB plasma on non-AB patients (potential increased risk from exposure to female FFP).

The answer to these challenges is not readily available or intuitive, particularly contrasting with the high mortality and lack of evidence supporting the existing guidelines. For now, the clinical decision continues to be based on observations, judgement and evidence transplanted from other fields. Definitive answers will only come from better understanding the pathophysiology of coagulation and prospective clinical trials, which may be years away. The challenges to such clinical trials are summarized in Table 2.

Conclusion

The current knowledge regarding coagulopathy and FFP precludes the development of evidence-based guidelines. Existing guidelines for the management of massive bleeding recommend late FFP transfusion, based on conventional coagulation assays, which correlate poorly with clinically bleeding.

Early formula-driven haemostatic resuscitation has challenged this approach and has proposed early and aggressive FFP transfusion at a FFP:RBC ratio near 1:1, thus treating or preventing early trauma coagulopathy. Initial studies have reported significant reductions in mortality, but are uncontrolled and methodologically flawed, particularly by survivorship bias. Presently, clinical decisions should be based in assessing the pros and cons of both strategies while considering local resources and individual clinical context.

Prospective clinical trials are urgently needed to determine whether early formula-driven haemostatic resuscitation should be adopted or forgotten, to better understand trauma-associated coagulopathy and to

develop evidence-based massive transfusion guidelines. Other areas for future research include improving the diagnosis of coagulopathy and evaluating novel products such as thawing microwaves for faster release of blood products.

Abbreviations

FFP = fresh frozen plasma; RBC = red blood cells; rFVIIa = recombinant factor VII activated; TRALI = transfusion-related acute lung injury.

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Author details

[1]Transfusion Medicine, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Ave, C160, Toronto, ON M4N 3M5, Canada
[2]Pathobiology and Laboratory Medicine, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Ave, B204, Toronto, ON M4N 3M5, Canada
[3]Trauma, Emergency and Critical Care Program, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Ave, D503, Toronto, ON M4N 3M5, Canada
[4]Department of Surgery, Universidade Federal de Minas Gerais, Ave Alfredo Balena 190, Belo Horizonte, Minas Gerais 30-130-100, Brazil
[5]Surgery and Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Ave, H171, Toronto, ON M4N 3M5, Canada

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