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Review Article

Contemporary resuscitation of hemorrhagic shock: What will the future hold?

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ABSTRACT

Resuscitation of the critically ill patient with fluid and blood products is one of the most widespread interventions in medicine. This is especially relevant for trauma patients, as hemorrhagic shock remains the most common cause of preventable death after injury. Consequently, the study of the ideal resuscitative product for patients in shock has become an area of great scientific interest and investigation. Recently, the pendulum has swung towards increased utilization of blood products for resuscitation. However, pathogens, immune reactions and the limited availability of this resource remain a challenge for clinicians. Technologic advances in pathogen reduction and innovations in blood product processing will allow us to increase the safety profile and efficacy of blood products, ultimately to the benefit of patients. The purpose of this article is to review the current state of blood product based resuscitative strategies as well as technologic advancements that may lead to safer resuscitation.

Introduction

Trauma is the leading cause of death for individuals up to 45 years of age and is the fourth leading cause of death for people of all ages.[1,2] Hemorrhagic shock is the most common cause of potentially preventable death after traumatic injury in both the civilian setting and combat environment.[3] Furthermore, resuscitation of the critically ill patient with fluid and blood products is one of the most ubiquitous interventions in medicine. Blood product availability is dependent on blood donation and availability of appropriate storage conditions and thus is a potentially limited resource. Since traditional blood products are obtained from human donation, they also have the potential issues of immunologic reactions and vectors of blood borne illness. The study of the ideal resuscitative product for patients in shock has become an area of great scientific interest and investigation. The purpose of this article is to review contemporary resuscitation for hemorrhagic shock, with a focus on blood products and blood product components. Additionally, existing concerns with regard to the risks of blood product transfusion, and how those risks may be mitigated with scientific advancements, specifically pathogen reduction technologies, will be highlighted.

Brief history of crystalloid and colloid based resuscitation

Resuscitative fluids are generally classified into crystalloid and colloid solutions (see Table 1). Crystalloids are solutions of ions that are freely permeable, such as normal saline or lactated Ringer's.[4] Colloid solutions are suspensions of molecules within a carrier solution that are relatively incapable of crossing the semipermeable capillary membrane due to the molecular weight of the molecules.[5] Although it may be inferred that colloid solutions would be superior to crystalloids based on physiologic principles, they have not been shown to provide a substantial advantage.[5]

Normal saline, lactated Ringer's and PlasmaLyte are the primary crystalloid solutions used in clinical practice. Sodium chloride (normal saline) is the most commonly used crystalloid on a global basis.[5] Normal saline (0.9%) contains 154mMol of Na and Cl

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Table 1
Compositions of resuscitative fluids.

	Human Plasma	Crystalloids			Colloids		
		0.9% saline	Lactated Ringer's	PlasmaLyte	Hydroxyethyl starch	Gelatin	4% Albumin
Colloid Source					Maize or potato starch	Bovine Gelatin	Human Donor
Osmolarity (mOsm/L)	291	308	280.6	294	296–308	274–301	250
Sodium (mmol/L)	135–145	154	131	140	137–154	145–154	148
Potassium (mmol/L)	4.5–5.0		5.4	5.0	3.0–4.0	0–5.1	
Calcium (mmol/L)	2.2–2.6		2.0		0–5.0	0–6.25	
Magnesium (mmol/L)	0.8–1.0			3.0	0–1.5		
Chloride (mmol/L)	94–111	154	111	98	110–154	120–145	128
Acetate (mmol/L)				27	0–34		
Lactate (mmol/L)	1–2		29		0–28		
Gluconate (mmol/L)				23			
Bicarbonate (mmol/L)	23–27						
Octanoate (mmol/L)							6.4

*Adapted from Myburgh, JA, Mythen MG.[5]

respectively, thus making it isotonic when compared with extracellular fluid. The strong ion difference of normal saline is zero, which leads to hyperchloremic metabolic acidosis when administered in large volumes. Adverse immune and renal effects have also been attributed to this phenomenon.[6] As a result of these potentially harmful effects, the use of "balanced" salt solution crystalloids such as Ringer's lactate and PlasmaLyte that are thought to be more physiologic are now being increasingly utilized. Balanced salt solution crystalloids are in fact crystalloid solutions that contain a buffer (such as lactate) to maintain the acid-base status as well as additional electrolytes (magnesium, potassium, calcium). The use of buffered solutions is associated with less metabolic derangement, hyperchloremia and metabolic acidosis and as a result, their use has been favored in the clinical setting. Although these balanced salt solutions are thought to be superior to normal saline, they are not without issues. Despite having fewer effects on pH, balanced salt solutions have been shown to lead to coagulopathy, tissue edema (particularly problematic in the setting of traumatic brain injury and acute lung injury), and other detrimental physiologic effects.[7–9]

Colloid solutions are typically salt solutions that also contain proteins or polysaccharides. Albumin is the most commonly used colloid and much of its clinical use is based on its capacity to act as a plasma expander as a result of increased intravascular oncotic pressure. However, broad usage of albumin as a resuscitative fluid has not been supported by clinical and scientific evidence. Albumin has been shown to be an ideal fluid for resuscitation of patients with liver cirrhosis and other conditions related to liver failure, and is generally considered safe for resuscitation of critically ill patients, except those with traumatic brain injury.[10] The use of hydroxyethyl starch solutions has been associated with increased rates of renal-replacement therapy, bleeding, and mortality, and has largely fallen out of favor as a result.[11] Until recently, Hextend® (6% hetastarch in lactated salt solution) was the preferred resuscitative fluid in the absence of blood products by the United States military due to its smaller volume and potential for prolonged evacuations.[12] However, the newest Damage Control Resuscitation Clinical Practice Guideline has removed Hextend® from the guideline.[13] Gelatins are another synthetic colloid solution, however, they have not been widely adopted due to safety concerns.[14]

Brief history of blood product based resuscitation

In more recent years, the use of blood products and more commonly, blood components, have become the preferred method of resuscitation for patients in hemorrhagic shock.[15] Whole blood transfusions historically were the principal resuscitative fluid for hemorrhagic shock, beginning as early as World War I. During the Korean and Vietnam wars low titer Group O whole blood (LTOWB) was used extensively (along with some cases of non-Group O blood as requirements for blood increased).[16] However, after the Vietnam era, blood was replaced by crystalloids and colloids as the primary resuscitative fluid for hemorrhagic shock, in both the military and civilian setting.[17] This was partially due to the risks associated with blood transfusion, such as transmission of infectious disease, but also related to research indicating that the interstitial compartment or "third space" required resuscitation with crystalloid for adequate tissue perfusion.[17,18] By the early 1970s, whole blood had virtually disappeared from use. Instead, patients who received blood transfusions received unbalanced component therapy, in which red blood cell (RBC) to plasma ratios often reached 10:1, with platelets given even less frequently. Many patients during this era also were resuscitated with large volumes of crystalloid fluid before receiving any blood products. Perhaps unsurprisingly, this resulted in dilutional coagulopathy, interstitial edema, abdominal compartment syndrome, acute respiratory distress syndrome, and multiple organ failure in many patients.[16,19] Today, the pendulum has swung back towards a blood-based resuscitation strategy for patients with life threatening hemorrhagic shock. Bleeding patients are now recommended to receive minimal crystalloid and the results of the PROPPR trial have encouraged a 1:1:1 use of RBCs, plasma, and platelets, attempting to recreate whole blood with balanced component transfusion (Fig. 1).[20]

Whole blood

Following the military's lead, a number of civilian centers have now instituted whole blood programs, both in the pre-hospital and hospital environments. In military settings, in which formal testing for transfusion transmitted diseases is often not possible, whole blood is collected from pretested donors (tested every 90 days during deployment) and stored at 22 °C for up to 8 h and then at 4 °C for a maximum of another 24 h; this is termed warm fresh whole blood.[16] In the civilian setting, whole blood can be stored without agitation at 2–6 °C for up to 35 days if collected in the proper citrate solution. A number of studies have shown that transfusion of whole blood is safe, feasible, and may increase survival for some patients in hemorrhagic shock.[16,19,21–23] Whole blood also offers a logistical advantage in that it allows for simplification and streamlining of the massive transfusion process and may even decrease administrative errors that occur during the chaos of massive component transfusion. However, transfusion of

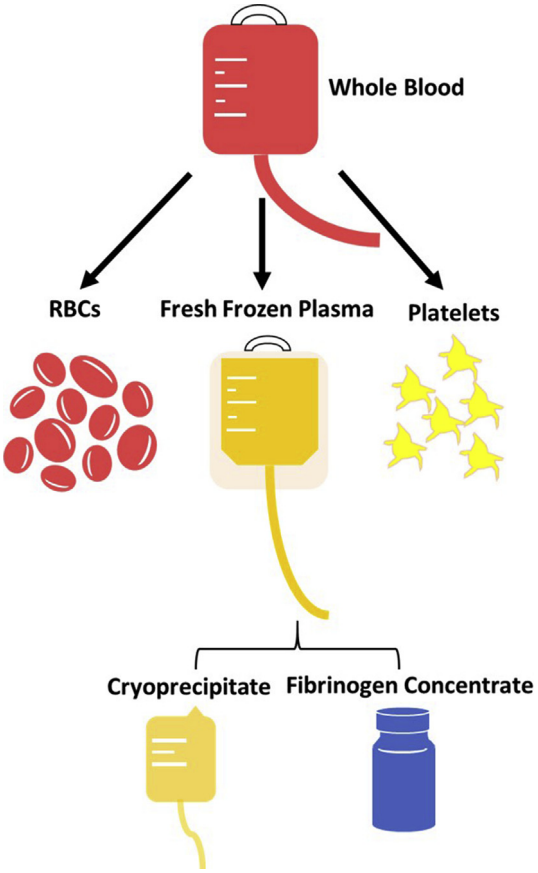

Fig. 1. Whole blood can be given or split into components: red blood cells, plasma and platelets. Specific factors from plasma can be given as cryoprecipitate or fibrinogen concentrate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

whole blood is not without risks. Only about 8% of the US blood donor population is group O-, making these "universal donor" whole blood units scarce.[24] A number of studies have shown that it is feasible and safe to transfuse O+ whole blood, however, the risk of alloimmunization remains a concern.[23,25,26] However, only a small number of women of childbearing age are transfused. Furthermore, the risk of becoming alloimmunized to the D antigen (+/− blood type) is approximately 22% and the risk is smaller yet for hemolytic disease of the newborn in future pregnancies.[24] In contrast, the mortality rate for patients in hemorrhagic shock who require a laparotomy is 40% and the mortality rate for combat causalities requiring blood transfusion is 16%.[19,24] It is also possible to leukoreduce whole blood, which may decrease the risk of alloimmunization. Leukoreduction does deplete total platelet count and it is currently unclear whether leukoreduction leads to a change in platelet hemostatic function post filtration, however, leukoreduced whole blood may be a viable resuscitation option for select patients in hemorrhagic shock. This data suggests that although the risk of alloimmunization should remain a consideration, there is probably a larger potential benefit of having O + LTWB available for all hemorrhagic shock patients, male and female.

Red blood cells

The current practice in most trauma centers is to transfuse RBCs, plasma and platelets in combination for patients in hemorrhagic shock. Even with this shift in practice, red blood cells remain the most commonly requested transfusion product worldwide.[27] RBCs are most commonly transfused for acute blood loss, symptomatic anemia and sickle cell crisis. Red blood cell units are prepared from donated whole blood by removing the plasma fraction after centrifugation. Preservative solutions are then added to the RBCs to improve their quality and shelf life. Currently, the Food and Drug Administration (FDA) has approved storage of red blood cells for up to 42 days at 2–6 °C.[28] However, despite preservative solutions, storage time influences the quality of the RBC unit as it ages, which has been termed the storage lesion. Several studies have shown that RBC storage lesion may lead to potential unwanted clinical outcomes such as acute lung injury and a higher mortality rate.[27,29] Cryopreservation of RBCs may be one way to circumvent the storage lesion, allowing for preservation of RBCs for up to ten years when stored at −80 °C. Several studies have recently shown that cryopreserved RBCs may even be superior to traditionally stored RBCs in regards to inducing inflammation and fibrinolysis.[30–32] However, Chang et al. reported that cryopreservation accelerated the red cell storage lesion.[33] Finally, red blood cells have an associated universal donor type, O-, meaning that they lack the A and B antigens as well as the Rh antigen on the surface of the cells; thus allowing for transfusion to a patient with any blood type.

Fresh frozen plasma

Fresh frozen plasma (FFP), another commonly used blood product, has been available since the 1940s. FFP can be prepared from either a single unit of whole blood or via apheresis. It is collected in citrate-containing anticoagulation solution, frozen within 8 h and stored at −30 °C for up to one year.[34,35] FFP contains all of the clotting factors, fibrinogen, proteins, electrolytes and physiologic anticoagulants such as protein C, protein S, and antithrombin. FFP is currently the most commonly used plasma-based product. Indications for transfusion of FFP include hemorrhagic shock, correction of coagulopathy (both clinical and laboratory), and plasma exchange. FFP is also currently being investigated as a potential resuscitative fluid for non-hemorrhagic shock.[7,36–38] FFP must be thawed between 30 and 37 °C in a water bath over 30 min or by FDA approved microwaves in 2–3 min. FFP should be transfused as soon as possible after thawing, but can be used within 24 h if stored at 4 °C.[35]

Alternatively, plasma may be frozen within 24 h of collection and is termed FP24. It must be stored at −18 °C or colder and has a shelf life of one year. FP24 contains lower levels of factor VIII than FFP, but has similar indications for use, with the exception of those indications specifically requiring replacement of factors V and/or VIII.[39] Liquid plasma is produced from whole blood within five days of the whole blood expiration date and is maintained at 1–6 °C for up to 30 days.[39] Clotting factors and proteins within liquid plasma are labile, however, the vitamin K-dependent factors are relatively stable and thus it is typically used to reverse the effects of warfarin.[39] Thawed plasma can be prepared from either FFP or FP24 by thawing the unit at 37 °C and then storing it at 1–6 °C for up to five days.[39] Like whole blood and packed red blood cells, FFP transfusion must be ABO compatible. AB is the universal donor type for plasma, as it lacks anti-A and anti-B antibodies. However, only 4% of the population is AB, resulting in a chronic shortage of universal donor plasma.[34] Transfusion of plasma has also been associated with transfusion-related acute lung injury (TRALI). TRALI is the most common cause of transfusion related death. TRALI has been associated with antibodies found in the plasma of multiparous females and thus, many countries have eliminated or restricted the use of plasma from female donors, resulting in decreased incidence of TRALI.[40] In fact, recent trauma studies

report a near absence.[20,41]

Platelets

Since the 1960s, platelets have been transfused in patients for a number of indications, including but not limited to severe thrombocytopenia, functional platelet defects, patients undergoing surgery, and to prevent or treat hemorrhage. Platelet concentrates can be isolated from donated whole blood or obtained by apheresis, in which platelets are harvested but all other cells are returned to the donor. The viability of stored platelets is dependent on temperature, pH, constant agitation, and the gas-permeability of the storage bags.[42] Traditionally, platelets have been stored at 22 °C in an effort to preserve function. However, storage at this temperature facilitates bacterial growth, leading to a short shelf life, typically five days. Some settings have instituted pathogen screening and reduction technologies, extending the shelf life to seven days.[43] Recently, data in the trauma population has raised the question of the optimal storage temperature for platelets.[44] Exposure of platelets to 4 °C versus 22 °C has been known to result in poor recovery and shorten platelet life span.[45] However, recent work has shown that aggregation and adhesion seem equivalent or better with refrigerated platelets, and cold platelets form stiffer clots in both in vivo and in vitro studies.[42] Refrigerated platelets therefore may become a viable transfusion therapy for patients undergoing surgery or suffering from hemorrhagic shock, conditions in which hemorrhage control is of greater importance that prolonged platelet survival. In 2017, the FDA approved cold storage for apheresis platelet concentrates for use in active hemorrhage.[42] Newer platelet-derived products are being investigated such as platelet-derived extracellular vesicles, which in a preclinical study by Miyazawa et al. demonstrated equivalent control of blood loss as traditional platelets.[46]

Cryoprecipitate

Fibrinogen is a key component of both FFP and cryoprecipitate. Fibrinogen is also often the first factor to reach critically low levels during hemorrhage, and low fibrinogen has been shown to be an independent predictor of mortality in trauma patients.[47,48] Fibrinogen concentrate offers an appealing alternative for hemostasis control as it allows for purification, viral inactivation, and rapid delivery of a standardized quantity of fibrinogen without the risk of hemodilution and volume overload.[47] A systematic review of the use of fibrinogen concentrate found that it was generally associated with improved outcomes when used for perioperative bleeding, although more studies are needed.[49]

Fibrinogen has recently been shown to be a key protein in FFP that modulates its endothelial protection, via a novel PAK1 mediated endothelial cell pathway.[50] Yu et al. also identified fibrinogen as a key anti-apoptotic factor in FFP that further contributes to its endothelial protection.[51]

Currently, fibrinogen concentrate is not FDA approved for traumatic bleeding in the US, but is being used widely in Europe. Early clinical data suggest that fibrinogen supplementation improves clot strength, reduces blood loss and increases survival.[52] Cryoprecipitate, which is prepared from plasma and contains fibrinogen, von Willebrand factor, factor VIII, factor XIII, and fibronectin, is used to replenish fibrinogen in the US. Traditionally, however, transfusion of cryoprecipitate has been relegated too late in the resuscitative process in hemorrhaging patients.[53] Currently, the CRYOSTAT-2 trial is underway in the United Kingdom. This study will evaluate whether early fibrinogen supplementation in the form of cryoprecipitate during traumatic hemorrhage will reduce mortality.[54]

Prothrombin complex concentrate (PCC) is composed of the clotting factors II, IX, and X (as well as factor VII in four factor PCCs) along with protein S, protein C, anti-thrombin II and other proteins. It is most commonly used to reverse the effects of warfarin in the setting of bleeding or need for surgical intervention. PCC is derived from pooled, virus-inactivated human plasma products. Early studies have shown that PCC may also be a useful tool in the reversal of trauma-induced coagulopathy, however, more research is needed.[55–57] *In vitro* data also suggests that four factor PCC has endothelial protective effects similar to FFP.[58]

Transfusion risks

Although it is clear the transfusion of blood products are beneficial, they are not without risk. Blood products can lead to transfusion reactions and transmission of pathogens. Transfusion reactions are defined as "adverse events associated with the transfusion of whole blood or one of its components.".[59] The majority of transfusion reactions are minor; however, they must be evaluated promptly, as some may be life threatening or fatal. The timing of transfusion reactions is variable, and they may occur acutely or days to weeks later. Transfusion reactions may or may not be immunologic and include hemolytic, febrile non-hemolytic, anaphylactic, simple allergic, septic, TRALI, and transfusion-associated circulatory overload (TACO).[59,60] Mild allergic reactions are due to hypersensitivity to a foreign protein present in the donor blood product. Anaphylactic reactions are similar but a more severe hypersensitivity reaction. They can sometimes occur in an IgA deficient patient who receives blood products containing IgA. Febrile non-hemolytic reactions are thought to be caused by cytokines released from donor leukocytes.[59] Septic reactions are caused by blood products that have been contaminated by bacteria or bacterial products such as endotoxin. Acute hemolytic transfusion reactions are often due to the presence of recipient antibodies to blood donor antigens. TRALI is thought to be caused by antibodies in the donor product, specifically human neutrophil antigen or human leukocyte antigen, which react with recipient antigens. The recipient immune system responds to these antibodies and this ultimately leads to pulmonary edema. TACO may occur when the volume of transfused blood product leads to hypervolemia. Careful testing for compatibility, monitoring of patients during transfusion and restriction of certain blood product donors has helped to mitigate these risks.[40,60]

Pathogen reduction

Over the past several decades, the primary source of transfusion-associated mortality has shifted towards non-infectious complications, such as hemolytic reactions, TRALI, and TACO. Nonetheless, transfusion transmitted infections make up approximately 10–15% of transfusion associated mortality.[61] Bacterial contamination of platelets and septic transfusion reactions remain a major source of transfusion related morbidity and mortality, as up to 1:1000 units of platelets are bacterially contaminated.[62] Additionally, the possibility remains that emerging pathogens may contaminate the supply of blood products and pose yet unknown risks to patients. During an outbreak of Zika virus in 2013 and 2014 in French Polynesia, the potential for transmission via blood transfusion was revealed when 3% of blood donors were found to test positive for the disease.[63] In fact, at this time it is unknown whether the novel coronavirus SARS-CoV-2, which causes the disease COVID-19, can be transmitted via blood transfusion.[64,65] Until recently, the medical community has dealt with infectious threats to the safety of the blood product supply reactively, which inevitably has led to years-long delays in effectively

containing such pathogens and mitigating these risks.[66] As a result, emerging pathogens pose a major threat to the supply of safe blood products. However, newer blood product technologies aim to reduce these risks in a more proactive manner. Specifically, researchers are working to develop technologies that would allow for the empiric reduction of pathogens in blood components used for transfusion. Two products are currently FDA approved (INTERCEPT® and OctaplasLG®), while another is currently seeking FDA approval (Mirasol®) (see Table 2).

OctaplasLG®

OctaplasLG® (Octapharma), which is currently FDA approved, is an alternative to fresh frozen plasma. The pathogen reducing technologies used to generate OctaplasLG® have the potential to benefit patients, especially those who are critically ill or otherwise immunosuppressed. Plasma is treated with solvent/detergent to inactivate both non-enveloped and enveloped viruses.[63] Studies have shown the robustness of solvent/detergent treated blood products to inactivate viruses like Human Immunodeficiency Virus (HIV), Hepatitis C, Chikungunya virus, and Ebola virus.[67–70] With

Table 2
Selected clinical studies involving pathogen reduced blood products.

Study	Product	Design	Study Population	Primary Endpoints	Outcome
VIPER-OCTA[82]	OctaplasLG® plasma	RCT	Adult patients undergoing emergency surgery for thoracic aortic dissection	Endothelial injury, bleeding, transfusion requirements	Reduced glycocalyx and endothelial injury, reduced bleeding, transfusions, use of prohemostatics, and time on ventilator after surgery compared to standard FFP
Plasma Transfusions in Critically Ill Children[83]	Solvent detergent plasma including OctaplasLG®	Secondary analysis of prospective, observational study	Critically ill pediatric patients	INR reduction and ICU mortality	No difference in INR reduction. Solvent detergent plasma transfusion was independently associated with reduced ICU mortality.
Plasma transfusion for acquired coagulopathy of liver disease[107]	INTERCEPT® plasma	RCT	Patients with acquired coagulopathy due to liver disease (with and without liver transplantation)	Changes in PT and PTT in response to first FFP transfusion	No difference in reduction of PT and PTT with first transfusion. No difference in recovery of Factor VII or number of blood components transfused between INTERCEPT® plasma and conventional FFP
Plasma transfusion for congenital factor deficiency[92]	INTERCEPT® plasma	Single-arm, Phase III, open-label, multi-center, intent-to-treat study	Patients with congenital factor deficiencies	Coagulation factor kinetics, hemostatic efficacy, safety	Replacement coagulation factors in INTERCEPT® plasma exhibited kinetics (PT and PTT) and therapeutic efficacy consistent with conventional FFP
Plasma for therapeutic plasma exchange[108]	INTERCEPT® plasma	RCT	Patients with Thrombotic Thrombocytopenic Purpura	Remission within 30 days	Time to remission, relapse rates, time to relapse, total volume and number of FFP units exchanged were similar between INTERCEPT® and conventional FFP
SPRINT[94]	INTERCEPT® platelets	RCT	Patients with thrombocytopenia	WHO grade 2 bleeding	Incidence of grade 2, 3 and 4 bleeding were similar between groups. Fewer transfusion reactions for treated platelets.
Follow up to SPRINT[109]	INTERCEPT® platelets	Post hoc analysis of RCT	Patients with thrombocytopenia	Platelet dose	Lower CCIs and shorter transfusion intervals for INTERCEPT® platelets. Suggests some platelet injury may occur during pathogen reduction, however this did not result in detectable increases in bleeding.
Follow up to SPRINT[110]	INTERCEPT® platelets	Post hoc analysis of RCT	Patients with thrombocytopenia	Acute Lung Injury	No difference was found between the treated and untreated groups with regard to acute lung injury. Patients receiving treated platelets were more likely to be ventilated sooner.
Follow up to SPRINT[111]	INTERCEPT® platelets	Post hoc analysis of RCT	Patients with thrombocytopenia	Adverse event profile	Overall adverse events, thrombotic adverse events and deaths were similar between groups. Minor adverse events, fecal occult blood and skin rashes were more frequent in the treated platelet group.
Hemovigilance at multiple sites[112,113]	Mirasol® plasma and platelets	Observational	Patients with various hematologic disorders requiring transfusion of platelets or plasma	Increases in reported adverse events	No increase in rate of adverse reactions after introduction of Mirasol® system into routine blood component production.
PREPAReS[114]	Mirasol® platelets	RCT	Thrombocytopenic patients	Number and % episodes of bleeding $\geq$ WHO grade 2	Non-inferior to standard platelets in intention to treat analysis
IPTAS[115]	Mirasol® platelets	RCT	Thrombocytopenic patients needing $\geq$2 platelet transfusions	% patients with bleeding $\geq$ WHO grade 2	Conclusions on non-inferiority could not be drawn due to low statistical power. No significant differences in mortality.
Safety and Performance of Mirasol® Treated Platelet Transfusion Products[116]	Mirasol® platelets	RCT	Patients with chemotherapy-induced thrombocytopenia	CCI	Failed to show non-inferiority with regards to the CCI. Platelet and RBC utilization not significantly different suggesting this may not be a clinically significant difference.
AIMS[117]	Mirasol® whole blood	RCT	Adult patients who required up to two WB transfusions within 3 days	Prevention of transfusion transmitted malaria	Reduced incidence of transfusion transmitted malaria with Mirasol® treated whole blood.

Abbreviations: Randomized controlled trial (RCT), fresh frozen plasma (FFP), international normalized ratio (INR), intensive care unit (ICU), prothrombin time (PT), partial thromboplastin time (PTT), World Health Organization (WHO), Corrected count increment (CCI), red blood cell (RBC), whole blood (WB).

the use of solvent/detergent treated products, transfer of pathogens has reduced dramatically.

Pooled plasma is another method utilized to increase the safety profile of OctaplasLG®. Fresh frozen plasma samples are obtained from 630 to 1520 donors and pooled before solvent/detergent treatment.[71–73] TRALI is one of the leading causes of transfusion related complications. Antibodies to human neutrophil antigens (HNA) and human leukocyte antigens (HLA) as well as bioactive lipids in blood products can lead to TRALI in recipients of these blood products.[74,75] By pooling blood products, anti-HLA and anti-HNA are diluted to not clinically significant amounts, thereby preventing immune responses like TRALI.[76,77] Several studies have also shown that granulocyte and lymphocyte-reactive antibodies are undetectable in solvent/detergent plasma thereby representing a potential alternative to reduce the risk of TRALI associated with transfusion of FFP.[76,78]

The manufacturing of Octaplas® requires three phases. In the first phase, fresh frozen plasma donations are pooled and thawed. A one-micron filter removes cells and debris. In the second phase, the sample is treated with a solvent/detergent at 30 °C for 1–1.5 h. The solvent/detergent used for Octaplas® contains 1%Tri n-butyl phosphate (TNBP) and 1% Octoxynol-9 (TRITON).[71] Solvent extraction is used to remove TNBP from the rest of the sample.[67] After removal of TNBP, the sample is filtered in decreasing amounts starting with 1.0 μm until reaching a 0.45-μm filter. Solid phase extraction is then used to remove TRITON from the sample.[71] The last step of the second phase involves affinity chromatography for prions ensuring no contamination of the sample.[71,73] The third phase involves additional filtering through a 0.45-μm filter as well as a 0.2-μm filter. The sample is then packaged, frozen at −60 °C and stored at −30 °C until ready for distribution.[71]

In vitro studies have demonstrated that Octaplas® does not have a decrease in clotting factors but may have a decrease in unwanted cytokines.[67,79–81] More importantly, Octaplas® has shown success in the clinical setting. Octaplas® has been trialed with success in cardiac surgery, liver transplantation, and the critically ill pediatric population.[82–84] The most recent study completed was a single group assessment to determine the safety of Octaplas® in pediatric patients needing coagulation factor replacement.[85] Out of 50 patients, five experienced a significant adverse event and one of these resulted in death. There are currently two trials recruiting patients to test the safety of Octaplas® in both the adult and pediatric patient populations.

INTERCEPT® Blood System

The FDA has recently approved another technology for pathogen-reduction, the INTERCEPT® Blood System (Cerus Corporation). This system utilizes amotosalen-HCl, an ultraviolet light activated compound, to remove a variety of pathogens such as viruses (both enveloped and non-enveloped) and bacteria (gram negative and gram positive), as well as inactivation of leukocytes.[86] Amotosalen-HCl works by intercalating between pyrimidine bases in nucleic acids.[86] The ultraviolet light crosslinks amotosalen-HCl with the pathogen nucleic acids preventing further replication.[86] This mechanism prevents proliferation of pathogens within blood products. Many studies have demonstrated the success of amotosalen-HCl in inactivating Middle East respiratory syndrome-coronavirus, Chikungunya virus, *K. pneumoniae*, and decreasing T cells involved in transfusion-associated graft-versus-host disease.[87–90]

The three-step process of INTERCEPT® treatment begins with obtaining a single donor plasma sample or platelet concentrate. First, the sample is mixed with a solution of amotosalen-HCl.[86] Next, the sample is placed within an ultraviolet illuminator used to deliver ultraviolet light at the proper dose and activate the crosslinking of amotosalen to nucleic acids.[86] The first two steps take around 10 min to treat two plasma units. During the final step, the sample flows through a compound adsorption device (CAD).[86] The CAD removes amotosalen-bound nucleic acids from the sample.[86] This step takes an additional 10 min.[86] After the third step is complete, the sample is stored until ready for use.

INTERCEPT® plasma

Since INTERCEPT® targets nucleic acids, proteins remain unaffected in plasma samples. Studies show no significant decrease in proteins such as antithrombin and protein S that are integral to the clotting cascade.[91] It has been shown that for patients with congenital coagulation factor deficiencies, replacement of coagulation factors in INTERCEPT® plasma exhibited kinetics and therapeutic efficacy similar to conventional FFP.[92] Additionally, liver transplant and therapeutic plasma exchange studies have shown success for the INTERCEPT® system.[91,93]

INTERCEPT® platelets

Amotosalen/UVA treated platelets have shown comparable results in the treatment and prevention of bleeding in randomized controlled clinical trials primarily in hematology/oncology patients.[94,95] A more recent retrospective study in 306 bleeding patients requiring massive transfusion (of which 51 were trauma patients), again demonstrated efficacy of amotosalen/UVA treated platelets when compared to traditional platelets.[96] Another observational study was completed on 90 patients to determine the efficacy of INTERCEPT® to decrease the risk of transfusion-transmitted infections by the Chikungunya and Dengue viruses.[97] Of the individuals treated, only 3% had an adverse reaction to the INTERCEPT® platelet components, while 30% had a reaction unrelated to the platelet components. Currently, trials are recruiting to study the safety of utilizing INTERCEPT® on red blood cells for patients undergoing cardiac procedures and patients at risk for transfusion-transmitted Zika virus.

Mirasol®

Mirasol® Pathogen Reduction Technology (Terumo BCT) is applicable to platelets, plasma and whole blood. Similar to the INTERCEPT® system, Mirasol® uses ultraviolet light to inactivate pathogens. The differences stem from the use of riboflavin (vitamin B2) to induce the pathogen reduction effects and blood components are immediately ready for use after ultraviolet light treatment.[98] Riboflavin damages the nucleic acids of pathogens, rendering them unable to proliferate.[98] Since riboflavin is a harmless compound, blood products are ready for immediate use after this treatment. Mirasol® targets viruses (enveloped and non-enveloped), bacteria (gram negative and gram positive), parasites, and white blood cells to reduce pathogens and the immunological complications often associated with transfusion.[98] Studies have shown effective inactivation of many bacteria like *Plasmodium falciparum* and *Trypanosoma cruzi*. Research has also shown Mirasol® to be effective in inactivating Human Immunodeficiency Virus.[99–102] Studies in a mouse model revealed that Mirasol® is an effective method to prevent xenogeneic graft-versus-host disease.[103] The most recent clinical trial completed studied the survival of red blood cells after Mirasol® treatment and determined that red blood cells in Mirasol®-treated whole blood had decreased red blood cell survival compared to non-treated whole blood.[104] More studies are needed to determine the efficacy of Mirasol® in human subjects and the company is currently seeking FDA

approval.

Cost effectiveness

Very little information is currently available with regard to the costs of implementing widespread use of pathogen reduction technology to the blood product supply in the United States.[105] Compared to current practices, the additional costs of pathogen reduction may be considerable and would lead to an increase in the cost of blood products. However, the potential savings that may be subsequently realized from improved safety of blood transfusions and other downstream reductions in healthcare expenditures are unknown. Pathogen reduction technologies may allow for reductions in adverse transfusion events and decreases in laboratory screening interventions. Additionally, current donor selection criteria, which is both complex and costly, reduces the available blood product supply substantially. Pathogen reduction technologies may allow for additional safety and subsequent loosening of donor selection criteria as well as elimination of some existing donor screening assays and product modifications.[106] Finally, as emerging pathogens such as the recent SARS-CoV-2 virus may affect the supply of blood products, pathogen reduction technologies may allow for continued safe transfusion of these products, even in the absence of available and reliable nucleic acid testing for emerging viruses and other pathogens. Moving forward, more studies are needed to evaluate the cost effectiveness of pathogen reduction technologies along with careful accounting of what adverse events can be prevented and what healthcare costs can be diminished with their implementation.[105]

Conclusion

Blood product usage for the treatment of patients in hemorrhagic shock and with other disorders requiring transfusion is one of the most common medical interventions worldwide. However, pathogens, immune reactions, and the limited availability of this resource remain a challenge for clinicians. Technologic advances in pathogen reduction and innovations in blood product processing will continue to allow us to increase the safety profile and efficacy of blood products, ultimately to the benefit of patients.

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Authors' contributions

A.M.C. and C.J. wrote and edited the article. F.W. and R.A.K. provided additional input, critical revisions, and review. R.A.K. obtained funding support. All authors approved the final version.

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