10 Split Blood Products

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10.1 Plasma

10.1.1 Product Description and Selection for Transfusion

Plasma is the acellular fraction of blood, separated from the cellular blood components either by centrifugation of citrated whole blood or donor apheresis, with typical unit volumes averaging from 200 to 300 mL. There are several types of plasma products used for supplementation or replacement of soluble coagulation factors. The most widely recognized plasma component is fresh frozen plasma (FFP), which requires freezing at −18 °C within 6–8 h of collection (AABB 2013a). Plasma frozen within 24 h after phlebotomy (FP24) is similar to FFP in its preparation but differs in that it may be frozen at or below −18 C within 24 h after collection. Frozen plasma products prepared for transfusion requires thawing and warming to between 30 and 37 C. This takes 20–30 min, depending upon the equipment used for thawing and the unit volume. If the prepared plasma is not transfused within the initial 24-h post-thaw period, it can be relabeled as “thawed plasma” for use within 5 days after

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the initial thaw (AABB 2013a; Benjamin and McLaughlin 2012; Eder and Sebok 2007). The utility of thawed plasma is twofold: (1) it provides rapidly available plasma for the management of massive hemorrhage, and (2) it extends available plasma inventory by avoiding wastage of plasma suitable for transfusion (Downes et al. 2001). One rarely used plasma product, available in the USA, is liquid plasma. Unlike the previously described plasma products, liquid plasma has never been frozen; it is separated from a whole blood unit no later than 5 days before its expiration date and has a shelf life of 26 days from the date of the source blood collection (40 days if CPDA-1 is used as the anticoagulant for the parent component) (AABB 2013a; Benjamin and McLaughlin 2012).

Forms of pathogen-reduced plasma are widely available in Europe but until recently have not been available in the USA. Solvent/detergent-treated plasma (S/D plasma) is one of the most frequently used pathogen-reduced plasma products. Pooled plasma composed of a given ABO type undergoes viral inactivation with solvents (i.e., 1 % tri(n-butyl) phosphate) and detergents (i.e., 1 % Triton-X 100), which are subsequently extracted by oil and affinity ligand chromatography for selective binding of prion proteins (PrP^{Sc}). This treatment significantly inactivates lipid-enveloped viruses such as HIV and Hepatitis C as well as cellular pathogens such as bacteria and protozoa. While the pathogen inactivation process is ineffective against non-lipid-enveloped viruses such as hepatitis A (HAV) and parvovirus B19, product specifications identify minimum levels of B19 and hepatitis E virus (HEV) genetic material permissible, as well as minimum levels of neutralizing antibodies directed against HAV and B19 (Benjamin and McLaughlin 2012). This product had not been approved for use in the USA until January 2013, when the FDA approved *Octaplas*® (Octapharma, Austria) for transfusion (FDA 2013; Riedler et al. 2003; Ozier et al. 2011; Sachs et al. 2005; Sinnott et al. 2004).

Methylene blue (MB)-treated plasma is another pathogen-reduced product available in Europe. Methylene blue is an aniline dye which, upon light activation, generates reactive oxygen species that inactivate enveloped and some nonenveloped viruses, with lesser activity directed against protozoa and bacteria (Benjamin and McLaughlin 2012). Unlike S/D plasma, MB plasma is a single donor component.

Plasma contains ABO isoagglutinins, the naturally occurring antibodies directed against ABO antigens, and therefore must be ABO compatible with the recipient's red cells (see Table 10.1); however, cross-matching is not required. Group AB plasma, which lacks antibodies directed against A and B antigens, is compatible with all blood types and is used as emergency release plasma when there is insufficient time for determining the recipient's blood type (Wehrli et al. 2009). The Rh (D) type is not always matched because immunization to Rh (D) antigen has rarely been reported as a result of transfusion of Rh (D)-positive plasma to Rh (D)-negative individuals. Hemolytic reactions as a consequence of infusion of an undetected antibody directed toward recipient RBC antigens are rarely seen, as is alloimmunization to RBC antigens (Ching et al. 1991).

Table 10.1 ABO compatibility of blood components

Recipient blood group	Recipient alloantibodies	ABO-compatible blood components				
		Whole blood	Packed red cells	Plasma	Cryoprecipitate	Platelets
A	Anti-B	A	A or O	A or AB	A or AB (preferred)	A or AB (preferred)
B	Anti-A	B	B or O	B or AB	B or AB (preferred)	B or AB (preferred)
AB	Nil	AB	O, A, B, or AB	AB	AB (preferred)	AB (preferred)
O	Anti-A and anti-B	O	O	A, B, AB, or O	Any	Any

For platelet transfusions given to small pediatric or infant patients, the donor plasma should be ABO compatible with recipient red cells. Note the rare AB group is the universal plasma donor, while the common O group is the universal PRBC donor. ABO compatibility is required for plasma but may be waived in some circumstances for adult patients receiving cryoprecipitate or platelets

10.1.2 Indications

Notable variation exists in published guidelines for plasma transfusion (ASA 2006; Ferraris et al. 2011; Iorio et al. 2008; O'Shaughnessy et al. 2004; Fuller and Bucklin 2010; Roback et al. 2010), although there is agreement on its indication for replacement of coagulation factors in bleeding or surgical patients, particularly those suffering from disseminated intravascular coagulation (DIC) or undergoing massive transfusion. Many guidelines recommend using the international normalized ratio (INR) at or greater than 1.5 as an indication for plasma transfusion (O'Shaughnessy et al. 2004). However, a consensus on laboratory value "triggers" for plasma transfusion has not been reached. For massive hemorrhage, empiric transfusion of plasma in set ratios to RBC units is widely practiced in the USA (Holcomb et al. 2013; Dzik et al. 2011). Retrospective and observational studies on massive transfusion in military and civilian trauma have reported associations between higher plasma/RBC transfusion ratios and improved survival (Holcomb et al. 2013; Borgman et al. 2007; Shaz and Hillyer 2010), although definitive data on optimal use of plasma in this setting has yet to emerge (Holcomb et al. 2013).

Plasma is also indicated as a replacement fluid in therapeutic apheresis for thrombotic thrombocytopenia purpura (TTP) (Szczepiorkowski et al. 2010) and for coagulation factor replacement in patients with congenital deficiencies of single factors (such as FV and FXI), but should not be used for factor replacement in congenital factor deficiencies if factor concentrates are readily available (i.e., FVIII concentrates in hemophilia A patients). Additional indications include rapid warfarin reversal in an actively bleeding patient, although guidelines are emerging preferentially recommending prothrombin complex concentrates as a first-line agent (Ageno et al. 2012; Keeling et al. 2011; Morgenstern et al. 2010; Ansell et al. 2008). Plasma is not appropriate to use as a nutritional supplement or as a source of immunoglobulin and

should not be used as a volume expander when blood volume can safely and adequately be replaced with other agents such as colloids (AABB 2013).

10.1.3 Dose and Therapeutic Effect

In a nonpregnant individual, 1 mL of plasma contains approximately 1 unit of coagulation factor activity. Nonpathogen-reduced plasma products contain slightly less than 1 U/mL clotting factors due to approximately 10 % dilution from anticoagulant solution and naturally occurring variability in factor levels between individual donors (Benjamin and McLaughlin 2012; Eder and Sebok 2007). Administration of a 10–20 mL/kg dose of plasma typically increases circulating coagulation factor levels by 20–30 % (Spector et al. 1966). Standardization of clotting factors in S/D plasma manufacturing allows for more precise dosing; a dose of 12–15 mL/kg should raise most coagulation factors levels by up to 25 %. Plasma doses exceeding 15 mL/kg present increasing risks for volume overload in the recipient unless given in context of ongoing blood loss or therapeutic plasmapheresis (Murad et al. 2010; Popovsky 2004). Standard dosing protocols are appropriate for FFP and FP24, as well as for liquid plasma as these three products are considered essentially hemostatically equivalent for almost all clotting factors except for FV and FVIII—despite slight variations between clotting factors existing between these products (Benjamin and McLaughlin 2012; Eder and Sebok 2007; Downes et al. 2001; Sidhu et al. 2006; Yazer et al. 2008, 2010; Gosselin et al. 2013) (see Table 10.2). The process of solvent detergent treating of plasma also results in a decrease in FV and FVIII (Buchta et al. 2004). While remaining within regulatory requirements, declines in procoagulant levels may be clinically significant and require patient monitoring (Benjamin and McLaughlin 2012; Buchta et al. 2004).

Liquid plasma dosing is the same as that for FFP and FP24. Additional recommendations in the literature are that liquid plasma should be used in conjunction with either thawed FFP or FP24 and limited to a shelf life less than 15 days. A study by Gosselin et al. demonstrated significant drops in the levels of FV, FVIII, vWF, protein S, and endogenous thrombin activity (the thrombin generation potential of the product) at 30 days (Gosselin et al. 2013). Because of the decreased levels of both clotting and antithrombotic factors, liquid plasma is recommended only for massive transfusion support in patients with life-threatening hemorrhage and significant coagulation factor deficiencies (AABB 2013a).

In the USA, earlier forms of S/D plasma retained clotting factor levels close to those in other licensed plasma products, though reductions in protein C, protein S (Flamholz et al. 2000), antiplasmin, and antitrypsin activity were noted (Theusinger et al. 2011; Pock et al. 2007). In the early 2000s, reports of thrombotic adverse events and increased fibrinolysis after the use of S/D plasma prompted withdrawal of the product from the US markets (Flamholz et al. 2000; de Jonge et al. 2002). Currently, the manufacturer of FDA-approved Octaplas® claims to have all coagulation factors within their known references ranges and the same hemostatic activity as FFP (Heger et al. 2006). The only exception is the inhibitor α-2 antiplasmin, which is below the cited reference range. Protein S levels are lower in S/D plasma

Table 10.2 Average values of coagulation factors found in different plasma and cryoprecipitate preparations

Factors	Thawed plasma from FFP (Downes et al. 2001)		Thawed plasma from FP24 (Yazer et al. 2008)		Cryo from FP24 (cryo24) (Yazer et al. 2010)		Liquid plasma (Gosselin et al. 2013)		
Ref. range (U/mL)	Day 1	Day 5	Day 1	Day 5	Standard	Cryo24	Day 1	Day 15	Day 30
Factor V (0.70–1.50)	0.70	0.66	1.40	0.87			1.10	0.77	0.50
Factor VII (0.60–1.60)	0.90	0.72	1.09	0.96			0.97	0.78	1.08
VWF:Ag (340–820)					448.1	505.9	0.73	0.50	0.40
Factor VIII (0.60–1.50)	1.07	0.63	0.60	0.69	2.16	2.52	0.72	0.56	0.50
FX	0.85	0.80					1.10	1.11	1.12
FIX (0.60–1.50)			1.20	1.26			0.86	0.84	0.76
Antithrombin III (0.80–1.20)			0.89	0.92					
Protein C (0.70–1.40)			1.05	0.96			0.88	0.89	0.86
Protein S (0.58–1.28)			0.70	0.52			0.90		0.91
Protein S activity (0.76–1.35 IU/mL)							0.90	0.48	0.22
Fibrinogen (150–350 mg/dL)	225	225	320	318	455.8	575.8	2.92	2.76	2.75

Further details including the variability of these levels can be found in the individual references (Downes et al. 2001; Yazer et al. 2008; Gosselin et al. 2013; Yazer et al. 2010)

as compared with FFP; as such, the use of S/D plasma is not recommended for use in patients with severe protein S deficiency (Theusinger et al. 2011).

MB-treated plasma, however, may have markedly reduced hemostatic (Pock et al. 2007) and antithrombotic (Alvarez-Larran et al. 2004) efficacy; other photochemical pathogen reduction treatments of plasma, such as amotosalen, are also being evaluated and appear more equivalent to FFP (de Alarcon et al. 2005; de Valensart et al. 2009; Mintz et al. 2006a, b).

10.2 Cryoprecipitate and Plasma, Cryoprecipitate Reduced

10.2.1 Product Description and Selection for Transfusion

Cryoprecipitated antihemophilic factor (cryoprecipitate) is the cold-precipitated protein fraction collected by centrifugation from a frozen plasma component thawed at 1–6 °C. A single 10–15 mL cryoprecipitate unit is enriched in high-molecular-weight proteins including vWF, FVIII, fibrinogen, fibronectin, and FXIII (AABB 2013a).

Cryoprecipitate is stored at −18° C or below, and preparation time prior transfusion includes 30 min or more to thaw and pool individual units into one dose. Unlike plasma, cryoprecipitate cannot be stored in a thawed form and causes the longest preparation delay when used as a component of a massive transfusion protocol. Cryoprecipitate administration in adults does not need to be ABO compatible; however, the transfusion of large volumes of ABO-incompatible cryoprecipitate in to any single recipient may cause positive direct antiglobulin test results and, rarely, mild hemolysis (Dzik et al. 2011; Nascimento et al. 2011). Rh compatibility does not need to be considered for pre-transfusion product selection (Downes and Schulman 2011).

The stability of FVIIIC, vWF antigen, and fibrinogen between standard cryoprecipitate and cryoprecipitate made from FP24 plasma has been demonstrated (Yazer et al. 2010). Cryoprecipitates derived from pathogen-inactivated plasma treated with psoralens, however, contain significantly reduced levels of fibrinogen, FVIII, and ADAMTS-13 (an enzyme degrading vWF), although the vWF quantity and quality are well preserved (Cid et al. 2013).

The plasma supernatant remaining after the preparation of cryoprecipitate is termed "plasma, cryoprecipitate reduced" also known as "cryo-poor plasma" or cryosupernatant. Compared with other plasma products, this blood fraction is depleted of vWF, FVIII, FXIII, and fibrinogen. However, many of the remaining clotting factors are found in levels similar to that in FFP or FP24, including factors II, V, VII, IX, X, and XI (AABB 2013a; Benjamin and McLaughlin 2012; Wehrli et al. 2009).

10.2.2 Indications, Dosage, and Therapeutic Effect

Cryoprecipitate was originally developed as a FVIII concentrate for the treatment of hemophilia A, but the availability of safer, purified, or recombinant FVIII concentrates has largely supplanted its use in these patients. The primary indication for cryoprecipitate in modern transfusion practice is as a fibrinogen concentrate (Callum et al. 2009). Cryoprecipitate is the most frequently used fibrinogen concentrate in the USA and is the only one approved for use in the USA for treatment of acquired fibrinogen deficiency such as surgical blood loss, trauma, or postpartum hemorrhage. Pasteurized fibrinogen concentrates are increasingly replacing cryoprecipitate for treatment of both congenital and acquired fibrinogen deficiencies (Franchini and Lippi 2012; Kozek-Langenecker et al. 2013; Wikkelso et al. 2013). In the USA, each unit of cryoprecipitate is expected to contain >80 IU FVIII and >150 mg fibrinogen, with typical adult doses ranging from 6 to 10 pooled units. The following formula is recommended for calculating cryoprecipitate dosage: body weight (in kg) × 0.2 = number of cryoprecipitate units to raise fibrinogen by 50–100 mg/dL (AABB 2013a). Therapeutic recovery of transfused fibrinogen from cryoprecipitate may be reduced by consumption in ongoing hemorrhage or fibrinolysis. A recent retrospective review of plasma fibrinogen increments following cryoprecipitate transfusion in the setting of trauma found a mean increase of 55 mg/dL after an

average transfusion of 8.7 units (±1.7) (Stanworth 2007). Cryoprecipitate remains a second-line therapy for von Willebrand disease and hemophilia A, as well as bleeding secondary to uremia (Hedges et al. 2007). Additionally, the 2013 European Society for Anaesthesia perioperative bleeding guidelines suggest that the use of cryoprecipitate for the treatment of hypofibrinogenemia is indicated if fibrinogen concentrates are not available (Kozek-Langenecker et al. 2013).

The depletion of FVIII, fibrinogen, vWF, and FXIII in cryosupernatant limits its utility and renders it unsuitable as a substitute for other forms of plasma. Cryosupernatant has been used most widely as a replacement fluid during therapeutic apheresis for the treatment of thrombotic thrombocytopenic purpura (AABB 2013a). Both cryosupernatant and cryoprecipitate have potential utility for treating acquired coagulation factor deficiency in Jehovah's Witness (JW) patients. While typically refusing transfusion, the JW community leadership has allowed for individuals to consider accepting "processed" fractions of blood products as a matter of individual conscience (Hughes et al. 2008; Sniecinski et al. 2007).

10.3 Platelet Concentrates

10.3.1 Product Description

Platelets are small (2–3 μm in diameter) anucleate cell fragments which bind to sites of injury, providing the phospholipid surface for coagulation enzymes to assemble and generate thrombin (Hoffman and Monroe 2001). In addition, they contribute key protein and molecular elements for fibrin clot formation as well as exerting a contractile force that draws together the margins of injury. Platelet concentrates are obtained either from whole blood or by collection from donors via apheresis. Platelet concentrates derived from a single 450–500 mL whole blood collection contain greater than 5.5×10^{10} platelets per unit, with a typical adult dose formed by pooling 4–6 concentrates (AABB 2013a). Apheresis platelets contain over 3×10^{11} platelets per unit, and contrary to other platelet concentrates, they have the advantage that they represent only a single donor exposure per transfusion, reducing the risk of transfusion-transmitted infections. While some *in vitro* differences have been observed between platelets derived from the different collection methods (Vasconcelos et al. 2003), these have little clinical consequence, and these products are interchangeable (Slichter 2007; Chambers and Herman 1999).

One notable characteristic of platelet components is their cold intolerance. The exposure of platelet concentrates to temperatures of 4 °C or less results in platelet shape change, functional defects, and increased circulatory clearance rates (Hoffmeister et al. 2003; Rao and Murphy 1982). Platelets also have the shortest shelf life of any transfused product: the time from collection to expiration is 5 days; attempts to extend the approved storage time have failed (Dumont et al. 2010). This is due in part to the relatively short functional life of platelets (7–10 days in the circulation) but also to the risks of bacterial proliferation due to storage at room temperature (Palavecino et al. 2010).

Platelets, whether in the form of platelet concentrate or apheresis platelets, are a plasma-rich product and should, ideally, be ABO compatible with the recipient to avoid the infusion of ABO isoagglutinins. However, inventory shortages often prompt the use of ABO-incompatible platelets; these are typically well tolerated, but hemolytic transfusion reactions have been reported in rare instances (Slichter 2007; Fung et al. 2007; Josephson et al. 2010). The highest risk ABO-incompatible platelet transfusions are those from group O single donor products administered to group A or B recipients, due to the tendency of group O individuals to form high titer anti-A and anti-B antibodies (Chambers and Herman 1999). Lastly, although platelets do not bear RhD antigens, trace red blood cell content in platelet products has driven the practice of transfusing RhD-negative donor platelets to RhD-negative recipients to avoid alloimmunization. Should inventory shortages necessitate transfusion of RhD-positive platelets to RhD-negative recipients—particularly women of child-bearing age or female pediatric patients with child-bearing potential—treatment with anti-RhD immunoglobulin is recommended to avoid RhD alloimmunization (British Committee for Standards in Haematology 2012).

10.3.2 Indication, Dose, and Therapeutic Effect

Platelet transfusion is indicated (1) as prophylaxis against hemorrhage in severely thrombocytopenic patients (most widely defined as $<10 \times 10^9$/L platelets) and (2) for the treatment of bleeding in patients with thrombocytopenia or platelet dysfunction (AABB 2013a; ASA 2006; Slichter 2007; Slichter et al. 2010). Therapeutic platelet transfusion in the context of massive transfusion or DIC should be administered with the aim of keeping the recipient's platelet count at $>50 \times 10^9$/L (British Committee for Standards in Haematology 2012). The transfusion of one unit of platelets typically increases platelet count by $20–40 \times 10^9$/L.

The majority (86 %) of platelets are given to patients with hematologic malignancies; 68 % are given for bleeding prophylaxis and 32 % to treat acute bleeding episodes (McCullough et al. 1988). Other indications include dilutional thrombocytopenia after massive transfusion, qualitative platelet disorders, rare congenital disorders of platelet function such as Glanzmann thrombasthenia, or drug-induced platelet dysfunction. Aspirin-, clopidogrel-, abciximab-, or prasugrel-related platelet dysfunction should respond to platelet transfusion although high circulating plasma levels of eptifibatide or clopidogrel also render transfused platelets dysfunctional (Vilahur et al. 2007). Little data are available for ticagrelor, but due to its reversible binding to the P2Y12 receptor, transfused platelets can be inhibited by redistribution of ticagrelor from native to the transfused platelets.

The current recommended transfusion trigger for prophylaxis in oncology patients is 10×10^9/L (Rebulla et al. 1997). For patients who are bleeding or undergoing invasive procedures the trigger is typically higher (National Institutes of Health Consensus Conference 1987; ASA 2013). While the American Society of Anesthesiologists (2006) proposes a platelet count of 50×10^9/L as a trigger for platelet transfusion prior to an invasive procedure (ASA 2013), a target closer to $>100 \times 10^9$/L is often favored for neurosurgical interventions as historically

bleeding time was shown to steadily increase below this level (Slichter and Harker 1978).

Pathogen-inactivated, photochemically treated (PCT) platelets offer the promise to minimize transfusion-related infection with a broad range recognized and emerging bacteria, viruses, and protozoa (McCullough et al. 2004). Synthetic psoralens intercalate with microbial DNA or RNA and, upon exposure to ultraviolet light, cross-link pyrimidine bases to prevent microbial replication. While equivalent hemostatic efficacy was seen in clinical trials of standard versus PCT platelets (McCullough et al. 2004; Cid et al. 2012), the in vivo recovery of PCT platelets was lower and others dispute their efficacy (Kerkhoffs et al. 2010). PCT platelets are approved for use in Europe, but not in the USA.

Platelets require a supportive milieu derived from the plasma they are stored in; most apheresis units are stored in 100 % plasma with ACD-A anticoagulant. Reduction of plasma volume allows diversion of the plasma for other uses and may reduce the risk of plasma-associated TRALI occurring on transfusion of plasma-containing platelets. The use of platelet additive solutions (PAS) such as InterSol® (Fenwal Inc., Zurich, IL) allows plasma reduction to be tolerated by supplementing electrolytes and buffers. PAS platelets demonstrate in vivo recovery and survival that exceed FDA requirements (van der Meer et al. 2010; Dumont et al. 2013).

Future developments in available platelet products include reconstituted, cryopreserved platelets. The in vivo survival of transfused thawed, resuspended, cryopreserved platelets met FDA criteria (Dumont et al. 2013), and in vivo hemostatic activity appears adequate (Khuri et al. 1999). However, while the relevance to hemostasis is unclear, adequate 24-h in vivo recovery remains a regulatory hurdle.

10.3.3 Whole Blood as a Source of Platelets

While fresh whole blood may be viewed as ideal treatment for trauma resuscitation, there are several logistical and functional limitations. First, it would limit availability of other blood components, and second, if not used when fresh, how long could it be stored and how rapidly do storage lesions develop? The longer whole blood remains in storage, the more platelets and white cells aggregate in the product, increasing the risks of adverse reactions following transfusion. Erythrocytes promote aggregation and activation of platelets within the product, thereby defeating one of the therapeutic benefits of using whole blood. Although some *in vitro* measures support the hemostatic function for whole blood refrigerated for up to 21 days (Pidcoke et al. 2013). Many issues would have to be addressed before whole blood can be licensed by the FDA and readily available for transfusion.

10.4 Complications of Transfusion

Transfusion-related complications originate from immunologic complications or contamination with infectious agents (Eder and Chambers 2007; Kleinman et al. 2003). A comprehensive review of all adverse transfusion reactions is beyond the

scope of this chapter, particularly the infectious complications, but will be reviewed briefly.

10.4.1 Transfusion-Transmitted Infections

All blood components bear the risk of transmitting infectious diseases, despite careful screening of blood donors and (in many countries) universal testing of the blood supply for infectious disease markers. Pooled products such as pooled platelets or cryoprecipitate, which have not undergone pathogen inactivation, present increased risks due to the multiple donor exposures. Existing and emerging infectious agents are of greatest local or regional importance in endemic areas, but international travel increases exposure to pathogens. If all pathogens are not included in existing screening mechanisms in a traveler's native country, travel may increasingly limit suitable blood donors. Rigorous donor screening, serologic testing, and nucleic acid amplification testing have proven extremely effective in reducing the risk of transfusion-transmitted infections in developed nations (Bowden and Sayers 1990), but transfusion-transmitted infection remains a serious concern throughout the developing world.

In 2009, the American Association of Blood Banks Transfusion-Transmitted Diseases Committee made up of volunteer members with expertise in infectious disease convened to publish a supplement to the journal *Transfusion* on the threat to the North American blood supply from emerging infectious diseases (Stramer et al. 2009). They prioritized specific agents into categories: red agents had the highest priority, followed by orange, yellow, and white. For further understanding of the classification system, readers are directed to the reference (Stramer et al. 2009).

Red agents include human variant Creutzfeldt-Jakob disease, dengue viruses, and *Babesia* species. Orange agents include Chikungunya virus, St. Louis encephalitis virus, *Leishmania* species, *Plasmodium* species, and *T. cruzi*. Yellow agents include chronic wasting disease prions, human herpes virus 8, HIV variants, human parvovirus B19, influenza A virus subtype H5N1, simian foamy virus, *Borrelia burgdorferi*, and hepatitis A virus. White agents include hepatitis E and *Anaplasma phagocytophilum* (Stramer et al. 2009).

10.4.2 Bacterial Contamination

Bacterial contamination of blood components can be asymptomatic or induce sepsis with a high mortality. It is especially relevant to platelet products as they are the only component to not undergo refrigerated storage. Incidences approximate 5–30 in 10,000 units of random donor-pooled platelets, 0.5–23 in 10,000 units of apheresis platelets stored at room temperature, 0.25 in 10,000 units of packed RBCs stored at 4 °C, and, rarely, in FFP or cryoprecipitate contaminated during thawing in water baths (Kleinman et al. 2003). Bacterial contamination of platelet products is acknowledged as the most frequent infectious risk from transfusion (Blajchman and Goldman 2001; Brecher and Hay 2005). Along with TRALI and clerical errors

resulting in ABO mismatch, it is considered one of the most common causes of death from transfusion, with mortality rates ranging from 1:20,000 to 1:85,000 donor exposures (Hillyer et al. 2003).

Clinically recognized septic reactions have been reported at a rate of 1 in 2,500 to 1 in 11,400 for whole blood-derived platelet concentrate pools and 1 in 15,400 for apheresis platelets. Symptoms occurred after 17–42 % of contaminated platelet transfusions, with a 17 % mortality rate (Kleinman et al. 2003; Brecher and Hay 2005). The incidence of severe septic episodes has not been clearly established but is probably approximately 200/million platelet units transfused (50 % sensitivity) (Blajchman and Goldman 2001; Walker 1987). Given the 5-day storage life and the persistent risk of platelet shortage, in September 2005, the FDA trialed the use of 7-day apheresis platelets under the surveillance program PASSPORT to determine the safety of extending the storage life. The study was discontinued early after 2 true-positive cultures were detected in 2,571 day 8 platelets (778/million) (Dumont et al. 2010). However, based on risk modeling, overall recipient risk may not have been improved by the reduced inventory caused by withdrawal of 7-day apheresis platelets. From an inventory management standpoint, platelet pools would have replaced them, potentially increasing infection risk and delaying a TRALI risk reduction strategy (Kleinman et al. 2009). Pathogen reduction strategies may further renew enthusiasm for 7-day storage.

10.4.3 Acute Hemolytic Transfusion Reaction

Acute hemolytic transfusion reactions are one of the most serious complications of transfusion and remain as one of the leading causes of transfusion-related mortality worldwide (Eder and Chambers 2007; Vamvakas and Blajchman 2010). These reactions result from RBC lysis or accelerated clearance by the reticuloendothelial system resulting from RBC transfusion into a recipient with preformed antibodies directed against donor erythrocytes. Rarely, plasma-rich blood products have been implicated in hemolytic reactions by passive transfer of antibodies directed against recipient erythrocytes (Fung et al. 2007). Antibodies directed against ABO antigens are the most frequent source of incompatibility (Ching et al. 1991; Josephson et al. 2010), for example, transfusion of O platelets containing anti-A and anti-B. Pre-transfusion plasma reduction and ABO matching easily avoid this complication.

10.4.4 Febrile Nonhemolytic Transfusion Reaction

Febrile nonhemolytic transfusion reactions (FNHTR) represent an essentially benign, albeit unpleasant, transfusion reaction most notable for development of fever, defined as a temperature elevation of >1 °C above pre-transfusion temperature. Patients may also experience chills, rigors, nausea, and vomiting. Occasionally patients will manifest such signs and symptoms in the absence of fever. FNHTRs are caused by pyrogenic cytokines, such as IL-1, Il-6, or TNF-α, which accumulate in blood products during storage. The onset of symptoms usually occurs during

transfusion but may present toward the end of the transfusion process or even within 1–2 h afterward due to the increasing level of cytokine exposure. The diagnosis of FNHTR is one of exclusion, having ruled out other causes of febrile reactions such as hemolytic transfusion reactions, septic reactions, or contributions from comorbidities or medications. Treatment is supportive, including antipyretics such as acetaminophen (Heddle 2007).

10.4.5 Allergic Reactions/Anaphylaxis

Allergic transfusion reactions are one of the most common adverse transfusion reactions, with incidence rates estimated between 1 and 3 % (Vamvakas 2007; Domen and Hoeltge 2003). Clinical presentation varies, but most manifests solely with cutaneous symptoms such as urticaria, pruritus, erythema, and angioedema (Domen and Hoeltge 2003). These minor allergic reactions are thought to be most often mediated by preexisting recipient IgE or IgG targeting plasma protein antigens. Passive transfer of IgE directed against recipient plasma allergens or other environmental allergens has also been observed. Accordingly, allergic reactions occur most frequently with plasma-rich products (including platelets) but may also occur in plasma-deplete products such as red cell units. Antihistamines such as diphenhydramine or famotidine form the cornerstone for treatment of minor allergic transfusion reactions with corticosteroids reserved for more severe reactions.

Rarely, severe allergic reactions may rapidly progress to anaphylactic shock within minutes after symptom onset. These reactions are characterized by bronchospasm, hypotension, nausea and vomiting, chest pain, and tachycardia. IgA-deficient patients who have developed class-specific anti-IgA are at risk; however, this group only represents a fraction of anaphylactic transfusion reactions (AABB 2013a). Causative agents vary widely from anti-haptoglobin antibodies to passive transfer of allergens to which a patient is already sensitized, such as recently ingested foods (i.e., peanuts) (Jacobs et al. 2011). Ultimately, anaphylaxis is an unpredictable and potentially fatal transfusion outcome requiring swift action to prevent an adverse outcome. Severe allergic reactions or anaphylaxis should be managed in a similar fashion to anaphylaxis from other causes, with administration of epinephrine (with or without other vasopressors as needed) and corticosteroids, maintenance of a patent airway, and volume infusion to maintain hemodynamic stability. Testing for associated DIC and postponing procedures requiring further transfusion should also be considered.

10.4.6 Transfusion-Related Acute Lung Injury (TRALI)

10.4.6.1 Pathophysiology

Transfusion of plasma-containing blood products—which include all blood products other than washed cellular blood products—may result in a syndrome of noncardiogenic pulmonary edema and acute respiratory distress. Clinical findings defining TRALI include (1) onset during or within 6 hours of transfusion; (2) severe hypoxemia,

such as less than 90 % oxygen saturation on room air; (3) diffuse bilateral pulmonary infiltrates on chest x-ray; (4) absence of volume overload; and (5) no preexisting acute lung injury (Kleinman et al. 2004). TRALI may also be associated with fever, chills, hypotension, and transient leukopenia. The primary pathophysiologic mechanism is believed to be a reaction between donor anti-leukocyte antibodies and recipient leukocytes, which results in leukocyte activation (Marques et al. 2005), sequestration, and infiltration into the pulmonary capillary bed (Fung and Silliman 2009). Leukocyte activation results in pulmonary microvascular injury and capillary leakage with an influx of proteinaceous fluid into the alveolar space (Bux and Sachs 2007). A "two-hit" hypothesis for the pathogenesis of TRALI holds that the first hit is due to recipient neutrophils primed for activation by virtue of the patient's underlying clinical condition. The second hit involves activation of these neutrophils by anti-leukocyte antibodies or biological response modifiers contained in the transfused product (Silliman 2006). In rare cases, the transfused product may provide both hits (Kelher et al. 2009).

Female donors sensitized to human leukocyte antigens (HLA) by pregnancy are most frequently implicated as the source of blood products which have been linked to TRALI cases (Densmore et al. 1999; Powers et al. 2008; Triulzi et al. 2009). The frequency of anti-HLA antibodies ranges from 1.7 % for never pregnant females to 32.2 % for four or more pregnancies, whereas males and previously transfused donors all showed very low frequency of anti-HLA antibodies (in the range of 1–2 %) (Triulzi et al. 2009; Kakaiya et al. 2010). As a result, many blood collection agencies in the USA and Europe limit or prohibit collection of plasma-rich blood products from female donors (Eder et al. 2010; Funk et al. 2012; Jutzi et al. 2008; Keller-Stanislawski et al. 2010; Lucas et al. 2012; Middelburg et al. 2010; van Stein et al. 2010).

The best available, current TRALI incidence estimate comes from a prospective study surveilling hypoxemia after transfusion of over 450,000 units between 2006 and 2009. Ninety-one TRALI cases were identified with an incidence of 1 in 3,141 in 2006 compared with 1 in 12,346 in 2009 after the introduction of gender-based mitigation strategies (Toy et al. 2012).

10.4.6.2 Diagnosis and Management

The diagnosis of TRALI is clinical and not based on the results of laboratory investigations for the presence of anti-leukocyte antibodies in the donor (Popovsky and Moore 1985; Goldberg and Kor 2012). Although cognate leukocyte antibody-antigen matches are often seen in TRALI cases, their absence does not rule out TRALI (Kopko et al. 2003; Stafford-Smith et al. 2010). Careful patient evaluation of suspected TRALI should involve both the clinical team and the transfusion service and include posttransfusion chest x-rays, measures of oxygenation, and evaluation for volume overload. Once TRALI is suspected, the transfusion must be immediately discontinued and the blood bank informed (Su and Kamel 2007). The details of the transfusion workup are beyond the scope of this chapter. Briefly, following all cases of TRALI and some cases of possible TRALI, the blood bank and the blood collection facility should investigate all donors associated with TRALI or possible TRALI cases for the presence of antihuman leukocyte antigen (HLA) and possibly antihuman neutrophil antigen (HNA) antibodies (Reil et al. 2008). Few laboratories (mostly

in Europe) also perform leukocyte cross-matching as part of the evaluation. The extent of these investigations varies depending upon the availability of donor samples (usually not a problem), the availability of neutrophil antibody testing, and the availability of a recipient sample for HLA antigen typing (Kopko et al. 2001, 2003). A donor with HLA antibodies matching an affected recipient is classified as an implicated donor and is deferred from future plasma apheresis or platelet apheresis donation. If a donor has the highly morbid anti-HNA 3a antibodies, most blood banks will defer the donor from any type of blood donation (Davoren et al. 2003).

The management of the patient with TRALI/possible TRALI is supportive, with oxygen supplementation for the correction of hypoxemia and hemodynamic support for hypovolemia and associated hypotension (Wallis 2007). Most patients who develop TRALI or possible TRALI will require endotracheal intubation and ventilatory support (approximately 70–80 %) (Popovsky and Moore 1985; Vlaar et al. 2010; Gajic et al. 2007a; Wallis 2003). Early reports described a mean duration of ventilatory support of approximately 40 h (Popovsky and Moore 1985), while more recent evidence points to longer period of respiratory support (approximately 3–10 days) (Vlaar et al. 2010; Gajic et al. 2007a). TRALI is not responsive to diuretics, and the role of corticosteroids remains unclear (Peter et al. 2008); the majority of patients recover with supportive care.

10.4.6.3 Prevention

It has been well established that donors implicated in TRALI cases are more likely to be female and multiparous (Toy et al. 2012; Gajic et al. 2007b). While not all studies support the benefit of avoiding female plasma (Welsby et al. 2010), the overwhelming evidence supports the implementation of gender-based policies for reducing TRALI incidence from plasma transfusion. These factors resulted in the implementation of a new TRALI risk mitigation policy during the mid- to late 2000s throughout most of Europe and the USA, in which plasma units were predominantly obtained from male donors, thereby avoiding the transfusion of plasma units from female donors. This policy is feasible for plasma transfusion because the number of plasma units collected from whole blood or apheresis collections meets, or is in excess of, demand. In contrast, this policy is challenging for group AB platelet and plasma components (Reesink et al. 2012), where restriction of units to male donors jeopardizes supply (see Table 10.3). Despite that, in 2013 the AABB announced new TRALI risk mitigation standards requiring high-plasma volume components come from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy to rule out the presence of anti-HLA antibodies, regardless of ABO group. These new standards are to go into effect in 2014 (AABB 2013b).

Some blood centers have implemented a policy of testing selected populations of platelet apheresis donors for anti-HLA antibodies or resuspending apheresis platelets in platelet additive solution (PAS) (Lucas et al. 2012; Reesink et al. 2012; Kleinman et al. 2010) although there are inadequate data to evaluate its effect on the incidence of TRALI following platelet transfusion (Kakaiya et al. 2010; Reesink et al. 2012).

Table 10.3 Following implementation of the American Red Cross TRALI mitigation strategies, the incidence of TRALI cases 2008–2010 fell for all but group AB plasma where female donors still comprise 40 % of the group AB donor pool

Component	Cases (*n*)	TRALI rates per 10^6
A, B, O plasma	9	1.9
AB plasma	12	24.9
RBC	39	2.2
Apheresis platelets	19	8

Adapted from Reesink et al. (2012)

The use of solvent/detergent-treated plasma has also been promoted as a TRALI risk reduction strategy. In contrast to a TRALI incidence from single donor plasma units of 1 in 31,000 units, observational data (Riedler et al. 2003) and hemovigilance data from France between 2007 and 2008 (Ozier et al. 2011) identify a zero incidence of TRALI with this product with undetectable HLA antibodies (Sachs et al. 2005).

While hemovigilance data may be subject to biased reporting, these international data present compelling evidence supporting the global implementation of gender-based TRALI risk reduction strategies, provided inventory or organizational impediments are not restrictive.

10.4.7 Volume Overload

10.4.7.1 Pathophysiology

Transfusion-associated circulatory overload (TACO) will cause transfusion-related respiratory insufficiency and is thought to occur when the rate of transfusion exceeds the recipient's cardiovascular adaption to the additional workload. The rapid infusion of excessive volume can result in dyspnea, hypoxemia, elevated central venous pressure, and pulmonary edema (Eder and Chambers 2007).

TACO is typically reported in elderly patients and small children, due to their relatively small circulating volume but can occur in all age ranges. Compromised cardiac function, positive fluid balance, and rapid blood product administration are additional risk factors for TACO, which appears to occur more frequently in operative or intensive care settings, where large fluid volumes and blood are administered (Li et al. 2011).

While the primary mechanism of TACO centered around fluid overload (Popovsky 2004; Li et al. 2010), this has recently been questioned as the median transfusion volume in patients who develop TACO is only 3 (2–7) units (Li et al. 2011) and a large proportion of reported TACO cases occur after a single blood unit exposure (Popovsky et al. 1996). Similarly, Roubinian et al. reported no statistically significant differences in hourly fluid balance or the number of blood component units transfused in the 24-h interval preceding the TACO or TRALI episode (Roubinian et al. 2012).

TACO is also typically associated with increased systemic blood pressure (Popovsky 2010; Klein and Anstee 2006), which exceeds that expected from the

volume challenge alone, suggesting a possible effect of vasoconstricting substances in the transfused blood product (Donadee et al. 2011). While most likely associated with RBC transfusion, a sudden increase in the systemic vascular resistance has the clear potential to compromise left ventricular function resulting in the elevated left atrial pressures and ultimately hydrostatic pulmonary edema characteristic of TACO.

10.4.7.2 Diagnosis and Management

Distinguishing TRALI from TACO is important but often difficult (Skeate and Eastlund 2007; Popovsky 2009). Generally, TRALI is more likely to be associated with fever, hypotension, and exudative pulmonary infiltrates and less likely to respond to diuresis, whereas TACO is more likely to be associated with volume overload (e.g., positive fluid balance, elevated jugular venous pressure) or poor cardiac function (e.g., history of congestive heart failure, reduced left ventricular ejection fraction, or diastolic dysfunction). Similarly, elevated systolic blood pressures near the time of dyspnea onset, cardiomegaly, and/or increased circulating levels of brain natriuretic peptide (BNP) or N-terminal (NT)-pro-BNP support a diagnosis of TACO rather than TRALI (Popovsky 2009; Zhou et al. 2005; Tobian et al. 2008; Li et al. 2009; Rice et al. 2011; Ely et al. 2001).

Differentiating TRALI from TACO can be a significant challenge, particularly as both may coexist (Popovsky 2009, 2010; Gajic et al. 2006). Related to this, approximately 30 % of ALI/ARDS patients show evidence of left atrial hypertension (Wheeler et al. 2006), increasing the difficulties of differential diagnosis and explaining a degree of diuretic responsiveness associated with TRALI.

While chest x-ray findings of bilateral infiltrates are similar to TRALI, TACO shows symptomatic improvement with diuresis. Patients with suspected TACO should have any ongoing transfusion paused to establish the diagnosis, with diuretics and supportive care given as indicated before attempting further transfusion. Resumption of transfusion should be approached with a slower infusion rate and careful vigilance for recurrent symptoms.

10.4.8 Metabolic Complications and Hypothermia

As all blood products are collected and stored in citrate-based anticoagulants, large volume transfusions may be complicated by hypocalcemia (Eder and Chambers 2007). Citrate binds divalent cations such as calcium and magnesium and is rapidly metabolized by the liver. Whereas citrate is easily cleared during nonurgent transfusions, citrate load during massive transfusion may overwhelm this clearance mechanism (Sihler and Napolitano 2010). In the awake patient, hypocalcemia presents initially with chills, tingling, dizziness, and tetany; continued progression of citrate toxicity can lead to prolonged QT interval, decreased left ventricular function, and cardiac arrhythmias. While hypocalcemia can be managed by slowing the rate of transfusion, in ongoing massive transfusion, and in patients with liver dysfunction or under general anesthesia, calcium replacement therapy should be guided by the patient's ionized calcium concentration.

Hypothermia can lead to multiple systemic derangements, including peripheral vasoconstriction, cardiac dysfunction, acidosis, and coagulopathy (Moffatt 2013). The effects of hypothermia and acidosis on coagulation have been observed both clinically and in vitro. Decreases in core temperature <34 °C and pH <7.1 after massive transfusion are predictive for the development of coagulopathy (Eder and Chambers 2007). The activity of tenase (FVIIa/tissue factor) and prothrombinase (FXa/FVa) complexes is directly dependent on temperature, with both showing a 1.1-fold loss of activity at 33 °C as compared to 37 °C (Meng et al. 2003). Even more dramatically, FVIIa/tissue factor and FXa/FVa show sharp decreases in activity in acidic environments, with activity decreasing by 55 and 70 % at pH 7.0, respectively (Viuff et al. 2008). Blood products transfused in this setting may be less effective, and, similarly, transfusion of chilled blood products especially in large volumes is absolutely contraindicated.

References

AABB (2013) Circular of information for the use of human blood and blood components. In: Cross AR (ed) Bethesda. http://www.aabb.org/resources/bct/Documents/coi_ct1013.pdf. Last accessed 19 May 2014

AABB (2013) AABB Revises and Clarifies TRALI Risk Reduction Requirements. http://www.aabb.org/sa/standards/Pages/revised-trali-risk-reduction-requirements.aspx. Accessed 1 Oct 2013

Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G (2012) Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e44S–e88S

Alvarez-Larran A, Del Rio J, Ramirez C, Albo C, Pena F, Campos A, Cid J, Muncunill J, Sastre JL, Sanz C, Pereira A (2004) Methylene blue-photoinactivated plasma vs. fresh-frozen plasma as replacement fluid for plasma exchange in thrombotic thrombocytopenic purpura. Vox Sang 86:246–251

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G (2008) Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133:160S–198S

ASA (2006) Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology 105:198–208

ASA. American Society of Anesthesiologists practice guidelines for perioperative blood transfusion and adjuvant therapies. http://www.asahq.org/publicationsAndServices/practiceparam.htm#blood. Accessed 1 Oct 2013

Benjamin RJ, McLaughlin LS (2012) Plasma components: properties, differences, and uses. Transfusion 52(Suppl 1):9S–19S

Blajchman MA, Goldman M (2001) Bacterial contamination of platelet concentrates: incidence, significance, and prevention. Semin Hematol 38:20–26

Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB (2007) The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 63:805–813

Bowden R, Sayers M (1990) The risk of transmitting cytomegalovirus infection by fresh frozen plasma. Transfusion 30:762–763

Brecher ME, Hay SN (2005) Bacterial contamination of blood components. Clin Microbiol Rev 18:195–204

British Committee for Standards in Haematology. Guidelines for the use of prophylactic anti-D immunoglobulin. www.bcshguidelines.com/documents/Anti-D_bcsh_07062006.pdf. Accessed 9 Feb 2012

Buchta C, Felfernig M, Hocker P, Macher M, Kormoczi GF, Quehenberger P, Heinzl H, Knobl P (2004) Stability of coagulation factors in thawed, solvent/detergent-treated plasma during storage at 4 degrees C for 6 days. Vox Sang 87:182–186

Bux J, Sachs UJ (2007) The pathogenesis of transfusion-related acute lung injury (TRALI). Br J Haematol 136:788–799

Callum JL, Karkouti K, Lin Y (2009) Cryoprecipitate: the current state of knowledge. Transfus Med Rev 23:177–188

Chambers LA, Herman JH (1999) Considerations in the selection of a platelet component: apheresis versus whole blood-derived. Transfus Med Rev 13:311–322

Ching EP, Poon MC, Neurath D, Ruether BA (1991) Red blood cell alloimmunization complicating plasma transfusion. Am J Clin Pathol 96:201–202

Cid J, Escolar G, Lozano M (2012) Therapeutic efficacy of platelet components treated with amotosalen and ultraviolet A pathogen inactivation method: results of a meta-analysis of randomized controlled trials. Vox Sang 103:322–330

Cid J, Caballo C, Pino M, Galan AM, Martinez N, Escolar G, Diaz-Ricart M (2013) Quantitative and qualitative analysis of coagulation factors in cryoprecipitate prepared from fresh-frozen plasma inactivated with amotosalen and ultraviolet A light. Transfusion 53:600–605

Davoren A, Curtis BR, Shulman IA, Mohrbacher AF, Bux J, Kwiatkowska BJ, McFarland JG, Aster RH (2003) TRALI due to granulocyte-agglutinating human neutrophil antigen-3a (5b) alloantibodies in donor plasma: a report of 2 fatalities. Transfusion 43:641–645

de Alarcon P, Benjamin R, Dugdale M, Kessler C, Shopnick R, Smith P, Abshire T, Hambleton J, Matthew P, Ortiz I, Cohen A, Konkle BA, Streiff M, Lee M, Wages D, Corash L (2005) Fresh frozen plasma prepared with amotosalen HCl (S-59) photochemical pathogen inactivation: transfusion of patients with congenital coagulation factor deficiencies. Transfusion 45:1362–1372

de Jonge J, Groenland TH, Metselaar HJ, IJzermans JN, van Vliet HH, Tilanus HW (2002) Fibrinolysis during liver transplantation is enhanced by using solvent/detergent virus-inactivated plasma (ESDEP). Anesth Analg 94:1127–1131, table of contents

de Valensart N, Rapaille A, Goossenaerts E, Sondag-Thull D, Deneys V (2009) Study of coagulation function in thawed apheresis plasma for photochemical treatment by amotosalen and UVA. Vox Sang 96:213–218

Densmore TL, Goodnough LT, Ali S, Dynis M, Chaplin H (1999) Prevalence of HLA sensitization in female apheresis donors. Transfusion 39:103–106

Domen RE, Hoeltge GA (2003) Allergic transfusion reactions: an evaluation of 273 consecutive reactions. Arch Pathol Lab Med 127:316–320

Donadee C, Raat NJ, Kanias T, Tejero J, Lee JS, Kelley EE, Zhao X, Liu C, Reynolds H, Azarov I, Frizzell S, Meyer EM, Donnenberg AD, Qu L, Triulzi D, Kim-Shapiro DB, Gladwin MT (2011) Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. Circulation 124:465–476

Downes K, Schulman I (2011) Pretransfusion testing, 17th edn. AABB Press, Bethesda

Downes KA, Wilson E, Yomtovian R, Sarode R (2001) Serial measurement of clotting factors in thawed plasma stored for 5 days. Transfusion 41:570

Dumont LJ, Kleinman S, Murphy JR, Lippincott R, Schuyler R, Houghton J, Metzel P (2010) Screening of single-donor apheresis platelets for bacterial contamination: the PASSPORT study results. Transfusion 50:589–599

Dumont LJ, Cancelas JA, Graminske S, Friedman KD, Vassallo RR, Whitley PH, Rugg N, Dumont DF, Herschel L, Siegal AH, Szczepiorkowski ZM, Fender L, Razatos A (2013) In vitro and in vivo quality of leukoreduced apheresis platelets stored in a new platelet additive solution. Transfusion 53:972–980

Dzik WH, Blajchman MA, Fergusson D, Hameed M, Henry B, Kirkpatrick AW, Korogyi T, Logsetty S, Skeate RC, Stanworth S, MacAdams C, Muirhead B (2011) Clinical review: Canadian National Advisory Committee on Blood and Blood Products–Massive transfusion consensus conference 2011: report of the panel. Crit Care 15:242

Eder AF, Chambers LA (2007) Noninfectious complications of blood transfusion. Arch Pathol Lab Med 131:708–718

Eder AF, Sebok MA (2007) Plasma components: FFP, FP24, and thawed plasma. Immunohematology 23:150–157

Eder AF, Herron RM Jr, Strupp A, Dy B, White J, Notari EP, Dodd RY, Benjamin RJ (2010) Effective reduction of transfusion-related acute lung injury risk with male-predominant plasma strategy in the American Red Cross (2006–2008). Transfusion 50:1732–1742

Ely EW, Smith AC, Chiles C, Aquino SL, Harle TS, Evans GW, Haponik EF (2001) Radiologic determination of intravascular volume status using portable, digital chest radiography: a prospective investigation in 100 patients. Crit Care Med 29:1502–1512

FDA. FDA approves octaplas to treat patients with blood clotting disorders. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm336009.htm. Accessed 17 Jan 2013

Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, Song HK, Clough ER, Shore-Lesserson LJ, Goodnough LT, Mazer CD, Shander A, Stafford-Smith M, Waters J, Baker RA, Dickinson TA, FitzGerald DJ, Likosky DS, Shann KG (2011) 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 91:944–982

Flamholz R, Jeon HR, Baron JM, Baron BW (2000) Study of three patients with thrombotic thrombocytopenic purpura exchanged with solvent/detergent-treated plasma: is its decreased protein S activity clinically related to their development of deep venous thromboses? J Clin Apher 15:169–172

Franchini M, Lippi G (2012) Fibrinogen replacement therapy: a critical review of the literature. Blood Transfus 10:23–27

Fuller AJ, Bucklin BA (2010) Blood product replacement for postpartum hemorrhage. Clin Obstet Gynecol 53:196–208

Fung YL, Silliman CC (2009) The role of neutrophils in the pathogenesis of transfusion-related acute lung injury. Transfus Med Rev 23:266–283

Fung MK, Downes KA, Shulman IA (2007) Transfusion of platelets containing ABO-incompatible plasma: a survey of 3156 North American laboratories. Arch Pathol Lab Med 131:909–916

Funk MB, Guenay S, Lohmann A, Henseler O, Heiden M, Hanschmann KM, Keller-Stanislawski B (2012) Benefit of transfusion-related acute lung injury risk-minimization measures–German haemovigilance data (2006–2010). Vox Sang 102:317–323

Gajic O, Gropper MA, Hubmayr RD (2006) Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. Crit Care Med 34:S109–S113

Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, O'Byrne MM, Evenson LK, Malinchoc M, DeGoey SR, Afessa B, Hubmayr RD, Moore SB (2007a) Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Am J Respir Crit Care Med 176:886–891

Gajic O, Yilmaz M, Iscimen R, Kor DJ, Winters JL, Moore SB, Afessa B (2007b) Transfusion from male-only versus female donors in critically ill recipients of high plasma volume components. Crit Care Med 35:1645–1648

Goldberg AD, Kor DJ (2012) State of the art management of transfusion-related acute lung injury (TRALI). Curr Pharm Des 18:3273–3284

Gosselin RC, Marshall C, Dwyre DM, Gresens C, Davis D, Scherer L, Taylor D (2013) Coagulation profile of liquid-state plasma. Transfusion 53:579–590

Heddle N (2007) Febrile nonhemolytic transfusion reactions. In: Transfusion Reactions, 3rd edn. AABB Press, Bethesda

Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ (2007) Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol 3:138–153

Heger A, Romisch J, Svae TE (2006) A biochemical comparison of a pharmaceutically licensed coagulation active plasma (Octaplas) with a universally applicable development product (Uniplas) and single-donor FFPs subjected to methylene-blue dye and white-light treatment. Transfus Apher Sci 35:223–233

Hillyer CD, Josephson CD, Blajchman MA, Vostal JG, Epstein JS, Goodman JL (2003) Bacterial contamination of blood components: risks, strategies, and regulation: joint ASH and AABB

educational session in transfusion medicine. Hematology Am Soc Hematol Educ Program 575–589. PMID 14633800

Hoffman M, Monroe DM 3rd (2001) A cell-based model of hemostasis. Thromb Haemost 85:958–965

Hoffmeister KM, Felbinger TW, Falet H, Denis CV, Bergmeier W, Mayadas TN, von Andrian UH, Wagner DD, Stossel TP, Hartwig JH (2003) The clearance mechanism of chilled blood platelets. Cell 112:87–97

Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH (2013) The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 148:127–136

Hughes DB, Ullery BW, Barie PS (2008) The contemporary approach to the care of Jehovah's witnesses. J Trauma 65:237–247

Iorio A, Basileo M, Marchesini E, Materazzi M, Marchesi M, Esposito A, Palazzesi GP, Pellegrini L, Pasqua BL, Rocchetti L, Silvani CM (2008) The good use of plasma. A critical analysis of five international guidelines. Blood Transfus 6:18–24

Jacobs JF, Baumert JL, Brons PP, Joosten I, Koppelman SJ, van Pampus EC (2011) Anaphylaxis from passive transfer of peanut allergen in a blood product. N Engl J Med 364:1981–1982

Josephson CD, Castillejo MI, Grima K, Hillyer CD (2010) ABO-mismatched platelet transfusions: strategies to mitigate patient exposure to naturally occurring hemolytic antibodies. Transfus Apher Sci 42:83–88

Jutzi M, Levy G, Taleghani BM (2008) Swiss haemovigilance data and implementation of measures for the prevention of transfusion associated acute lung injury (TRALI). Transfus Med Hemother 35:98–101

Kakaiya RM, Triulzi DJ, Wright DJ, Steele WR, Kleinman SH, Busch MP, Norris PJ, Hillyer CD, Gottschall JL, Rios JA, Carey P, Glynn SA (2010) Prevalence of HLA antibodies in remotely transfused or alloexposed volunteer blood donors. Transfusion 50:1328–1334

Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, Kitchen S, Makris M (2011) Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 154:311–324

Kelher MR, Masuno T, Moore EE, Damle S, Meng X, Song Y, Liang X, Niedzinski J, Geier SS, Khan SY, Gamboni-Robertson F, Silliman CC (2009) Plasma from stored packed red blood cells and MHC class I antibodies causes acute lung injury in a 2-event in vivo rat model. Blood 113:2079–2087

Keller-Stanislawski B, Reil A, Gunay S, Funk MB (2010) Frequency and severity of transfusion-related acute lung injury–German haemovigilance data (2006–2007). Vox Sang 98: 70–77

Kerkhoffs JL, van Putten WL, Novotny VM, Te Boekhorst PA, Schipperus MR, Zwaginga JJ, van Pampus LC, de Greef GE, Luten M, Huijgens PC, Brand A, van Rhenen DJ (2010) Clinical effectiveness of leucoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. Br J Haematol 150:209–217

Khuri SF, Healey N, MacGregor H, Barnard MR, Szymanski IO, Birjiniuk V, Michelson AD, Gagnon DR, Valeri CR (1999) Comparison of the effects of transfusions of cryopreserved and liquid-preserved platelets on hemostasis and blood loss after cardiopulmonary bypass. J Thorac Cardiovasc Surg 117:172–183; discussion 83–84

Klein H, Anstee D (2006) Mollison's blood transfusion, 11th edn. Blackwell Publishing, Malden/Oxford

Kleinman S, Chan P, Robillard P (2003) Risks associated with transfusion of cellular blood components in Canada. Transfus Med Rev 17:120–162

Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, Meade M, Morrison D, Pinsent T, Robillard P, Slinger P (2004) Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 44:1774–1789

Kleinman S, Dumont LJ, Tomasulo P, Bianco C, Katz L, Benjamin RJ, Gajic O, Brecher ME (2009) The impact of discontinuation of 7-day storage of apheresis platelets (PASSPORT) on

recipient safety: an illustration of the need for proper risk assessments. Transfusion 49:903–912

Kleinman S, Grossman B, Kopko P (2010) A national survey of transfusion-related acute lung injury risk reduction policies for platelets and plasma in the United States. Transfusion 50:1312–1321

Kopko PM, Popovsky MA, MacKenzie MR, Paglieroni TG, Muto KN, Holland PV (2001) HLA class II antibodies in transfusion-related acute lung injury. Transfusion 41:1244–1248

Kopko PM, Paglieroni TG, Popovsky MA, Muto KN, MacKenzie MR, Holland PV (2003) TRALI: correlation of antigen-antibody and monocyte activation in donor-recipient pairs. Transfusion 43:177–184

Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Gorlinger K, Haas T, Imberger G, Jacob M, Lance M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelso AJ, Wouters P, Wyffels P (2013) Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 30:270–382

Li G, Daniels CE, Kojicic M, Krpata T, Wilson GA, Winters JL, Moore SB, Gajic O (2009) The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic) in the differentiation between transfusion-related acute lung injury and transfusion-related circulatory overload in the critically ill. Transfusion 49:13–20

Li G, Kojicic M, Reriani MK, Fernandez Perez ER, Thakur L, Kashyap R, Van Buskirk CM, Gajic O (2010) Long-term survival and quality of life after transfusion-associated pulmonary edema in critically ill medical patients. Chest 137:783–789

Li G, Rachmale S, Kojicic M, Shahjehan K, Malinchoc M, Kor DJ, Gajic O (2011) Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion 51:338–343

Lucas G, Win N, Calvert A, Green A, Griffin E, Bendukidze N, Hopkins M, Browne T, Poles A, Chapman C, Massey E (2012) Reducing the incidence of TRALI in the UK: the results of screening for donor leucocyte antibodies and the development of national guidelines. Vox Sang 103:10–17

Marques MB, Tuncer HH, Divers SG, Baker AC, Harrison DK (2005) Acute transient leukopenia as a sign of TRALI. Am J Hematol 80:90–91

McCullough J, Steeper TA, Connelly DP, Jackson B, Huntington S, Scott EP (1988) Platelet utilization in a university hospital. JAMA 259:2414–2418

McCullough J, Vesole DH, Benjamin RJ, Slichter SJ, Pineda A, Snyder E, Stadtmauer EA, Lopez-Plaza I, Coutre S, Strauss RG, Goodnough LT, Fridey JL, Raife T, Cable R, Murphy S, Howard FT, Davis K, Lin JS, Metzel P, Corash L, Koutsoukos A, Lin L, Buchholz DH, Conlan MG (2004) Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. Blood 104:1534–1541

Meng ZH, Wolberg AS, Monroe DM 3rd, Hoffman M (2003) The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma 55:886–891

Middelburg RA, Van Stein D, Zupanska B, Uhrynowska M, Gajic O, Muniz-Diaz E, Galvez NN, Silliman CC, Krusius T, Wallis JP, Vandenbroucke JP, Briet E, Van Der Bom JG (2010) Female donors and transfusion-related acute lung injury: a case-referent study from the International TRALI Unisex Research Group. Transfusion 50:2447–2454

Mintz PD, Bass NM, Petz LD, Steadman R, Streiff M, McCullough J, Burks S, Wages D, Van Doren S, Corash L (2006a) Photochemically treated fresh frozen plasma for transfusion of patients with acquired coagulopathy of liver disease. Blood 107:3753–3760

Mintz PD, Neff A, MacKenzie M, Goodnough LT, Hillyer C, Kessler C, McCrae K, Menitove JE, Skikne BS, Damon L, Lopez-Plaza I, Rouault C, Crookston KP, Benjamin RJ, George J, Lin JS, Corash L, Conlan MG (2006b) A randomized, controlled Phase III trial of therapeutic plasma exchange with fresh-frozen plasma (FFP) prepared with amotosalen and ultraviolet A light compared to untreated FFP in thrombotic thrombocytopenic purpura. Transfusion 46:1693–1704

Moffatt SE (2013) Hypothermia in trauma. Emerg Med J 30:989–996

Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, Greenberg SM, Huang JN, MacDonald RL, Messe SR, Mitchell PH, Selim M, Tamargo RJ (2010) Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 41:2108–2129

Murad MH, Stubbs JR, Gandhi MJ, Wang AT, Paul A, Erwin PJ, Montori VM, Roback JD (2010) The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion 50:1370–1383

Nascimento B, Rizoli S, Rubenfeld G, Fukushima R, Ahmed N, Nathens A, Lin Y, Callum J (2011) Cryoprecipitate transfusion: assessing appropriateness and dosing in trauma. Transfus Med 21:394–401

O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM (2004) Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 126:11–28

Ozier Y, Muller JY, Mertes PM, Renaudier P, Aguilon P, Canivet N, Fabrigli P, Rebibo D, Tazerout M, Trophilme C, Willaert B, Caldani C (2011) Transfusion-related acute lung injury: reports to the French Hemovigilance Network 2007 through 2008. Transfusion 51:2102–2110

Palavecino EL, Yomtovian RA, Jacobs MR (2010) Bacterial contamination of platelets. Transfus Apher Sci 42:71–82

Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A (2008) Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. BMJ 336:1006–1009

Pidcoke HF, McFaul SJ, Ramasubramanian AK, Parida BK, Mora AG, Fedyk CG, Valdez-Delgado KK, Montgomery RK, Reddoch KM, Rodriguez AC, Aden JK, Jones JA, Bryant RS, Scherer MR, Reddy HL, Goodrich RP, Cap AP (2013) Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. Transfusion 53(Suppl 1):137S–149S

Platelet transfusion therapy. National Institutes of Health Consensus Conference (1987) Transfus Med Rev 1:195–200.

Pock K, Heger A, Janisch S, Svae TE, Romisch J (2007) Thrombin generation capacity is impaired in methylene-blue treated plasma compared to normal levels in single-donor fresh-frozen plasma, a licensed solvent/detergent-treated plasma (Octaplas) and a development product (Uniplas). Transfus Apher Sci 37:223–231

Popovsky MA (2004) Transfusion and the lung: circulatory overload and acute lung injury. Vox Sang 87(Suppl 2):62–65

Popovsky MA (2009) Transfusion-associated circulatory overload: the plot thickens. Transfusion 49:2–4

Popovsky MA (2010) The Emily Cooley Lecture 2009 To breathe or not to breathe-that is the question. Transfusion 50:2057–2062

Popovsky MA, Moore SB (1985) Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 25:573–577

Popovsky MA, Audet AM, Andrzejewski C Jr (1996) Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. Immunohematology 12:87–89

Powers A, Stowell CP, Dzik WH, Saidman SL, Lee H, Makar RS (2008) Testing only donors with a prior history of pregnancy or transfusion is a logical and cost-effective transfusion-related acute lung injury prevention strategy. Transfusion 48:2549–2558

Rao AK, Murphy S (1982) Secretion defect in platelets stored at 4 degrees C. Thromb Haemost 47:221–225

Rebulla P, Finazzi G, Marangoni F, Avvisati G, Gugliotta L, Tognoni G, Barbui T, Mandelli F, Sirchia G (1997) The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. N Engl J Med 337:1870–1875

Reesink HW, Lee J, Keller A, Dennington P, Pink J, Holdsworth R, Schennach H, Goldman M, Petraszko T, Sun J, Meng Y, Qian K, Rehacek V, Turek P, Krusius T, Juvonen E, Tiberghien P, Legrand D, Semana G, Muller JY, Bux J, Reil A, Lin CK, Daly H, McSweeney E, Porretti L,

Greppi N, Rebulla P, Okazaki H, Sanchez-Guerrero SA, Baptista-Gonzalez HA, Martinez-Murillo C, Guerra-Marquez A, Rodriguez-Moyado H, Middelburg RA, Wiersum-Osselton JC, Brand A, van Tilburg C, Dinesh D, Dagger J, Dunn P, Brojer E, Letowska M, Maslanka K, Lachert E, Uhrynowska M, Zhiburt E, Palfi M, Berlin G, Frey BM, Puig Rovira L, Muniz-Diaz E, Castro E, Chapman C, Green A, Massey E, Win N, Williamson L, Silliman CC, Chaffin DJ, Ambruso DR, Blumberg N, Tomasulo P, Land KJ, Norris PJ, Illoh OC, Davey RJ, Benjamin RJ, Eder AF, McLaughlin L, Kleinman S, Panzer S (2012) Measures to prevent transfusion-related acute lung injury (TRALI). Vox Sang 103:231–259

Reil A, Keller-Stanislawski B, Gunay S, Bux J (2008) Specificities of leucocyte alloantibodies in transfusion-related acute lung injury and results of leucocyte antibody screening of blood donors. Vox Sang 95:313–317

Rice TW, Ware LB, Haponik EF, Chiles C, Wheeler AP, Bernard GR, Steingrub JS, Hite RD, Matthay MA, Wright P, Ely EW (2011) Vascular pedicle width in acute lung injury: correlation with intravascular pressures and ability to discriminate fluid status. Crit Care 15:R86

Riedler GF, Haycox AR, Duggan AK, Dakin HA (2003) Cost-effectiveness of solvent/detergent-treated fresh-frozen plasma. Vox Sang 85:88–95

Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, Fung M, Hamilton M, Hess JR, Luban N, Perkins JG, Sachais BS, Shander A, Silverman T, Snyder E, Tormey C, Waters J, Djulbegovic B (2010) Evidence-based practice guidelines for plasma transfusion. Transfusion 50:1227–1239

Roubinian N, Toy P, Looney M, Hubmayr R, Gropper M, Koenigsberg M et al (2012) Role of fluid balance and number of blood transfusions in distinguishing TACO and TRALI. AABB Annual Meeting Abstract S93-040B

Sachs UJ, Kauschat D, Bein G (2005) White blood cell-reactive antibodies are undetectable in solvent/detergent plasma. Transfusion 45:1628–1631

Shaz BH, Hillyer CD (2010) Is there transfusion-related acute renal injury? Anesthesiology 113:1012–1013

Sidhu RS, Le T, Brimhall B, Thompson H (2006) Study of coagulation factor activities in apheresed thawed fresh frozen plasma at 1–6 degrees C for five days. J Clin Apher 21:224–226

Sihler KC, Napolitano LM (2010) Complications of massive transfusion. Chest 137:209–220

Silliman CC (2006) The two-event model of transfusion-related acute lung injury. Crit Care Med 34:S124–S131

Sinnott P, Bodger S, Gupta A, Brophy M (2004) Presence of HLA antibodies in single-donor-derived fresh frozen plasma compared with pooled, solvent detergent-treated plasma (Octaplas). Eur J Immunogenet 31:271–274

Skeate RC, Eastlund T (2007) Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. Curr Opin Hematol 14:682–687

Slichter SJ (2007) Platelet transfusion therapy. Hematol Oncol Clin North Am 21:697–729, vii

Slichter SJ, Harker LA (1978) Thrombocytopenia: mechanisms and management of defects in platelet production. Clin Haematol 7:523–539

Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, Gernsheimer TB, Ness PM, Brecher ME, Josephson CD, Konkle BA, Woodson RD, Ortel TL, Hillyer CD, Skerrett DL, McCrae KR, Sloan SR, Uhl L, George JN, Aquino VM, Manno CS, McFarland JG, Hess JR, Leissinger C, Granger S (2010) Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 362:600–613

Sniecinski RM, Chen EP, Levy JH, Szlam F, Tanaka KA (2007) Coagulopathy after cardiopulmonary bypass in Jehovah's Witness patients: management of two cases using fractionated components and factor VIIa. Anesth Analg 104:763–765

Spector I, Corn M, Ticktin HE (1966) Effect of plasma transfusions on the prothrombin time and clotting factors in liver disease. N Engl J Med 275:1032–1037

Stafford-Smith M, Lockhart E, Bandarenko N, Welsby I (2010) Many, but not all, outcome studies support exclusion of female plasma from the blood supply. Expert Rev Hematol 3:551–558

Stanworth SJ (2007) The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. Hematology Am Soc Hematol Educ Program 179–186. PMID 18024627

Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, Dodd RY (2009) Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion 49(Suppl 2):1S–29S

Su L, Kamel H (2007) How do we investigate and manage donors associated with a suspected case of transfusion-related acute lung injury. Transfusion 47:1118–1124

Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH (2010) Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher 25:83–177

Theusinger OM, Baulig W, Seifert B, Emmert MY, Spahn DR, Asmis LM (2011) Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth 106:505–511

Tobian AA, Sokoll LJ, Tisch DJ, Ness PM, Shan H (2008) N-terminal pro-brain natriuretic peptide is a useful diagnostic marker for transfusion-associated circulatory overload. Transfusion 48:1143–1150

Toy P, Gajic O, Bacchetti P, Looney MR, Gropper MA, Hubmayr R, Lowell CA, Norris PJ, Murphy EL, Weiskopf RB, Wilson G, Koenigsberg M, Lee D, Schuller R, Wu P, Grimes B, Gandhi MJ, Winters JL, Mair D, Hirschler N, Sanchez Rosen R, Matthay MA (2012) Transfusion-related acute lung injury: incidence and risk factors. Blood 119:1757–1767

Triulzi DJ, Kleinman S, Kakaiya RM, Busch MP, Norris PJ, Steele WR, Glynn SA, Hillyer CD, Carey P, Gottschall JL, Murphy EL, Rios JA, Ness PM, Wright DJ, Carrick D, Schreiber GB (2009) The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. Transfusion 49:1825–1835

Vamvakas E (2007) Allergic and anaphylactic reactions. In: Transfusion reactions, 3rd edn. AABB Press, Bethesda

Vamvakas EC, Blajchman MA (2010) Blood still kills: six strategies to further reduce allogeneic blood transfusion-related mortality. Transfus Med Rev 24:77–124

van der Meer PF, Kerkhoffs JL, Curvers J, Scharenberg J, de Korte D, Brand A, de Wildt-Eggen J (2010) In vitro comparison of platelet storage in plasma and in four platelet additive solutions, and the effect of pathogen reduction: a proposal for an in vitro rating system. Vox Sang 98:517–524

van Stein D, Beckers EA, Sintnicolaas K, Porcelijn L, Danovic F, Wollersheim JA, Brand A, van Rhenen DJ (2010) Transfusion-related acute lung injury reports in the Netherlands: an observational study. Transfusion 50:213–220

Vasconcelos E, Figueiredo AC, Seghatchian J (2003) Quality of platelet concentrates derived by platelet rich plasma, buffy coat and Apheresis. Transfus Apher Sci 29:13–16

Vilahur G, Choi BG, Zafar MU, Viles-Gonzalez JF, Vorchheimer DA, Fuster V, Badimon JJ (2007) Normalization of platelet reactivity in clopidogrel-treated subjects. J Thromb Haemost 5:82–90

Viuff D, Lauritzen B, Pusateri AE, Andersen S, Rojkjaer R, Johansson PI (2008) Effect of haemodilution, acidosis, and hypothermia on the activity of recombinant factor VIIa (NovoSeven). Br J Anaesth 101:324–331

Vlaar AP, Binnekade JM, Prins D, van Stein D, Hofstra JJ, Schultz MJ, Juffermans NP (2010) Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case-control study. Crit Care Med 38:771–778

Walker RH (1987) Special report: transfusion risks. Am J Clin Pathol 88:374–378

Wallis JP (2003) Transfusion-related acute lung injury (TRALI)–under-diagnosed and under-reported. Br J Anaesth 90:573–576

Wallis JP (2007) Transfusion-related acute lung injury (TRALI): presentation, epidemiology and treatment. Intensive Care Med 33(Suppl 1):S12–S16

Wehrli G, Taylor NE, Haines AL, Brady TW, Mintz PD (2009) Instituting a thawed plasma procedure: it just makes sense and saves cents. Transfusion 49:2625–2630

Welsby IJ, Troughton M, Phillips-Bute B, Ramsey R, Campbell ML, Bandarenko N, Mathew JP, Stafford-Smith M (2010) The relationship of plasma transfusion from female and male donors with outcome after cardiac surgery. J Thorac Cardiovasc Surg 140:1353–1360

Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, de Boisblanc B, Connors AF Jr, Hite RD, Harabin AL (2006) Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 354:2213–2224

Wikkelso A, Lunde J, Johansen M, Stensballe J, Wetterslev J, Moller AM, Afshari A (2013) Fibrinogen concentrate in bleeding patients. Cochrane Database Syst Rev 8, CD008864

Yazer MH, Cortese-Hassett A, Triulzi DJ (2008) Coagulation factor levels in plasma frozen within 24 hours of phlebotomy over 5 days of storage at 1 to 6 degrees C. Transfusion 48:2525–2530

Yazer MH, Triulzi DJ, Hassett AC, Kiss JE (2010) Cryoprecipitate prepared from plasma frozen within 24 hours after phlebotomy contains acceptable levels of fibrinogen and VIIIC. Transfusion 50:1014–1018

Zhou L, Giacherio D, Cooling L, Davenport RD (2005) Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. Transfusion 45:1056–1063