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...
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 (PrPSc). 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).
10 Split Blood Products

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

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

Table 10.1: ABO compatibility of blood components

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.
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...
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).

### 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).

### 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 to 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 $5.5 \times 10^{10}$ platelets per unit, with a typical adult dose formed by pooling 4–6 concentrates (AABB 2013a). Apheresis platelets contain over $3 \times 10^{11}$ 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 × 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 × 10^9/L (British Committee for Standards in Haematology 2012). The transfusion of one unit of platelets typically increases platelet count by 20−40 × 10^9/L.

The majority (86 %) of platelets are given to patients with hemato logic 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 >100×10^9/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
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 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).
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

| 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)
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.

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