

**QUESTIONS AND ANSWERS ABOUT BLOOD MANAGEMENT  
FOURTH EDITION**

**AMERICAN SOCIETY OF ANESTHESIOLOGISTS  
COMMITTEE ON TRANSFUSION MEDICINE**

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## PREFACE TO THE FOURTH EDITION

An integral part of the practice of anesthesia is the administration of blood and blood components. Anesthesiologists must be knowledgeable about the indications for various blood components, the benefits as well as the risks and adverse effects associated with their use, and aware of approaches for avoiding transfusion therapy if and when appropriate.

The ASA Committee on Blood and Blood Products in 1987 developed and published the first edition of a booklet titled *Questions and Answers About Transfusion Practices* in order to educate and provide a convenient reference on the subject of transfusion medicine. In 1993, this committee, renamed the Committee on Transfusion Medicine, published an updated and expanded second edition of *Questions and Answers About Transfusion Practices*. The third edition of this booklet was published by the 1996-97 Committee on Transfusion Medicine. The 2006-07 ASA Committee on Transfusion Medicine updated the fourth edition of this booklet and changed its title to *Questions and Answers About Blood Management* to reflect the expanding role of new drugs and techniques to manage use of blood and blood components. Blood management has been defined by Society for Advancement of Blood Management (SABM) as “the appropriate use of blood and blood components with a goal of minimizing their use.” The ASA Committee on Transfusion Medicine acknowledges and appreciates the review, input and editing by the College of American Pathologists Transfusion Medicine Resource Committee of this manuscript.

**This document has been developed by the ASA Committee on Transfusion Medicine, but has not been reviewed or approved as a practice parameter or policy statement by the ASA House of Delegates. Variances from the recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. The recommendations are designed to encourage quality patient care and safety in the workplace, but cannot guarantee a specific outcome. They are subject to revision from time to time as warranted by the evolution of technology and practice.**

## **ADMINISTRATIVE**

### **1. What are the functions of a hospital transfusion committee?**

Health care accreditation organizations such as the *Joint Commission on Accreditation of Healthcare Organizations*(now the *joint Commission*), the *College of American Pathologists*, and the *AABB* all require transfusing facilities to have a peer-review program to monitor and address transfusion practices. This monitoring usually occurs under the auspices of an institutional committee known as the “hospital transfusion committee,” “transfusion practices committee,” “blood-usage review committee” or “blood utilization committee.” Blood and blood components are critical in patient care but remain in limited supply, have a finite shelf life and carry numerous risks and significant cost. Monitoring blood usage minimizes inappropriate utilization and creates an environment of blood management. The hospital transfusion committee monitors for blood and blood components ordering practices, patient identification, specimen collection and labeling, infectious and non-infectious adverse events, near-miss events, usage and wastage rates, appropriateness of blood use, blood administration policies, the ability of services to meet patient needs, and compliance with peer-review recommendations.<sup>1</sup> For the committee to be effective, representation and active participation is needed from all of the hospital departments that frequently transfuse as well as nursing administration. The committee may promote patient safety in an institution and bring complex transfusion processes into compliance with regulations.<sup>2</sup> A multidisciplinary committee is preferred as it may facilitate integration, coordination and implementation of processes across multiple clinical services.

Other activities of this committee may include:

- Establishing guidelines, indications, and relevant hospital policies and procedures for the use of blood and blood components and educating hospital staff about them.
- Developing and implementing quality assessment protocols designed to improve patient care and that substantiate that a high level of care is being achieved.

## **2. What is a maximum surgical blood ordering schedules?**

A maximum surgical blood ordering schedule (MSBOS) is a list of the maximum number of RBC units that the blood bank will crossmatch usually preoperatively for a specific procedure, as well as procedures for which a type and screen (T&S) is appropriate. Use of a MSBOS minimizes unnecessary crossmatching to reduce cost and unnecessary utilization of technician time while providing adequate amounts of compatible blood for patients requiring transfusion. MSBOS eliminates the need to determine the number of blood components for each case, reduces last-minute blood orders that don't allow enough time for component preparation, decreases pretransfusion compatibility testing, avoids outdating components, and provides a guide for autologous blood collection. MSBOS should be developed based upon the previous transfusion practices in an individual institution, reviewed periodically to reflect actual usage, and updated when necessary. A close working relationship between anesthesiology, surgery, and the transfusion service facilitates its development and allows for monitoring of effective utilization at an institution.

## **3. What is the C/T ratio?**

The crossmatch/transfusion ratio or "C/T ratio" is the number of RBC units crossmatched divided by the number of RBC units transfused. A C/T ratio of greater than 2 is evidence that an excessive number of RBC units have been crossmatched for that procedure. Crossmatching an excessive number of RBC units that may not be transfused is not an optimal strategy since crossmatching removes red cell units from inventory and increases time and labor of the technical staff who perform the crossmatches and prepare the units for transfusion which results in an increase in cost. While an institution's average C/T ratio may be somewhat useful, however, determination of specialty specific and individual physician C/T ratios may help identify which physicians are ordering type and crossmatch for patients when a type and screen (T&S) might be more appropriate. Individual allowance should be made for the patient undergoing a potentially complex procedure associated with extensive blood loss. A T&S without a crossmatch is acceptable for surgical procedures in which less than 10 percent of the patients require transfusion, but for which there is a potential transfusion requirement.

#### **4. Should recipient informed consent be obtained prior to transfusion?**

Each transfusion of blood and/or blood components carries distinct risks and benefits and thus it is critical to obtain informed consent from the recipient prior to transfusion.<sup>3</sup> The transfusion recipient must be given adequate information to make an informed choice of whether to accept transfusion, to elect an alternative, or to refuse treatment altogether. These choices can be certified on forms that document the process of informed consent. The transfusion recipient should have an opportunity to ask questions and the right to accept or refuse transfusion.<sup>1</sup> The specifications for informed consent are under the purview of a transfusion facility, its relevant medical committees, and legal/risk management advisors. For neonates and children, a parent or other legally authorized adult should act as surrogate for providing transfusion consent. The surrogate's decision to consent to or to refuse transfusion should be acknowledged, and documented in a manner consistent with the facility's policies. Follow-up of transfusion refusal should be consistent with the urgency of the need for transfusion, a facility's policies, the State laws applicable to the patient's age, and other circumstances relevant to the specific patient.

### **DONOR SCREENING AND TESTING**

#### **5. How are blood donors screened to determine their suitability for donation?**

The purpose of blood donor screening and determination of suitability for donation is to simultaneously achieve a safe blood supply and a safe donation process for the donor. The steps of blood donor screening include a *donor history*, a *physical examination* and then if the donor meets criteria, testing of the donor blood specimen for specific infectious agents.

*Donor History:* Before each donation, potential blood donors are asked questions about their medical history and whether or not they are involved in high risk behavior with respect to transmissible infectious diseases to determine if the donation process will be safe for the donor and if the donated blood will be safe for the recipient. Historically, blood centers were responsible for developing their

own questionnaires. In June 2004 the Uniform Donor History Questionnaire (UDHQ) was accepted by the Food and Drug Administration for screening blood donors. Developed by an inter-organizational task force, the UDHQ standardized and streamlined the donor screening process to make it more effective in capturing relevant donor information. The risk history questions address exposure risks for or symptoms of transfusion-transmitted diseases (i.e. hepatitis, human immunodeficiency virus [HIV], malaria, Chagas disease, babesiosis, and Creutzfeldt-Jakob disease). Donor screening questions can be classified into several broad categories: Travel into areas endemic for malaria, Chagas disease or certain HIV subtypes; activities or history of events that may increase the risk of acquiring parenterally transmitted infections, i.e., high-risk sexual activities, recent non-sterile skin piercing, blood transfusion or tissue transplant; signs, symptoms or history of infectious diseases; medication taken (prescription or over-the-counter); and general health questions to ensure a safe donation for the donor.

*Donor Physical Examination:* Vital signs and a hemoglobin/hematocrit level are obtained on the day of donation to assure hemodynamic stability and safety of donation for the donor.

## **6. What tests are performed on donor blood?**

Each blood donation is tested for ABO Group, Rh type, the presence of unexpected non-ABO red cell antibodies, and infectious disease markers. The presence or absence of the D antigen determines whether a patient is Rh-positive or Rh-negative. An antibody screen is performed to detect any unexpected non-ABO red cell antibodies; if the antibody screen is positive the specificity of the antibody is then identified. Donor units are not routinely phenotyped for red cell antigens other than A, B and D; however, if red cells are being crossmatched for a recipient with a specific unexpected red cell alloantibody other than anti-D, the donor red cells are then phenotyped to assure that the RBC unit selected for crossmatching for transfusion is negative for the antigen against which the antibody is directed.

The FDA mandates that donated blood be tested to minimize infectivity for hepatitis B and C viruses, human immunodeficiency virus [HIV], HIV-1 and HIV-2, human T-cell lymphotropic virus (HTLV)-I/II and syphilis. The tests routinely performed for specific infectious diseases are listed in Table I:

**Table I**  
**Transmissible Disease Testing of Donor Blood**

Infectious agent	Tests
Syphilis	serologic
Hepatitis B virus	Hepatitis B surface antigen (HBsAg) Antibodies to hepatitis B core antigen (Anti-HBc)
Hepatitis C virus	HCV nucleic acid amplification test Antibodies to hepatitis C (anti-HCV)
HIV-1 HIV-2	HIV-1 nucleic acid amplification test Anti-HIV-1 and Anti-HIV2
HTLV-I HTLV-II	Antibodies to human T-cell lymphotropic virus I/II (anti-HTLV I/II)
West Nile Virus	West Nile Virus nucleic acid amplification test
Chagas	Antibodies to <i>T. cruzi</i>

Improved testing methodology and the use of nucleic acid amplification testing has improved the sensitivity and often specificity of these assays and has significantly decreased the window period (the period between infection and its detection by tests). If the test result from a donated unit of blood is abnormal for any of these disease markers, the unit is discarded and the donor is notified.

**Other tests of blood**

For a selected group of recipients who are susceptible to significant morbidity from cytomegalovirus (CMV) infection, cellular blood components (red cells and platelets) may be tested for CMV serology to reduce transmission of CMV; however leukocyte-reduction also reduces CMV risk and thus leukocyte reduced cellular components are considered to be CMV-reduced risk. For transfusion and red cell exchange in certain neonatal populations, donor blood may be screened for the presence of the HgbS to optimize oxygen delivery. Because of the risk for bacterial growth due to room temperature storage conditions, platelet components are also tested using several different methods of bacterial detection by blood collecting agencies and transfusion services.

## **SPECIAL TYPES OF BLOOD DONATIONS**

### **7. What are the advantages and disadvantages of designated or “directed” donations?**

Fear of transfusion-transmitted diseases may lead a patient to request “designated donors,” i.e., donors known to a patient and selected for donation with the stipulation that their blood be reserved for a specific patient’s use. Arguments against the concept of designated donors include:

- An additional, significant clerical burden with concomitant increased opportunity for clerical errors.
- Coordination of the timing of donation prior to the time of surgery may cause some difficulty.
- The possibility of coercion of the blood donor may induce the donor to withhold information that would ordinarily make them ineligible to donate.
- Loss of donor confidentiality and legal protection since donor identity is known to the recipients.

The concept that individuals known by the transfusion recipient may provide safer blood than units collected from the volunteer donors is not valid. Because of the potential increased risk for alloimmunization of an Rh negative female who receives a blood transfusion from an Rh positive male sexual partner and subsequent hemolytic disease of the newborn, blood transfusions from a male donor to a female sexual partner are not recommended. Cellular blood components from blood relatives carry an increased risk of causing transfusion associated graft-versus-host disease (TA-GVHD), even in

an immunocompetent recipient, and should be irradiated to prevent TA-GVHD.<sup>4</sup> While an objective advantage to designated donations is not apparent and such donations in some instances may even cause harm, they may alleviate some fear in patients.

#### **8. What is a limited (minimal) donor exposure program?**

Limited donor exposure transfusion is based on the assumption that decreasing the number of donor exposures will result in a concurrent decrease in transfusion-related infections or complications.<sup>5</sup> This is most often used in the pediatric and neonatal patient populations. A donor, often a parent, may donate multiple units of blood over a period of time designated for a particular patient. Transfusion services may assign a particular RBC unit to a pediatric patient and take aliquots from the RBC unit for the shelf-life of the unit. The short shelf life of platelets limits the applicability of this practice for this component though some hospitals elect to assign single donor apheresis platelet units to neonates. The same donor may also donate apheresis platelets a few days before the recipient's surgery date.

### **BLOOD COLLECTION**

#### **9. How does the preparation of whole blood, blood components, and apheresis components differ?**

A blood donor may donate whole blood or donate a specific component of blood using apheresis technology (e.g. apheresis or single donor platelets). At the time of whole blood donation, blood is collected into a sterile plastic bag containing an anticoagulant-preservative. Integral tubing connected with satellite bags allows for the separation of whole blood into various components using differential speed centrifugation techniques (Figure 1.) One whole blood donation may be separated into 1 unit of plasma, 1 unit of RBC, and 1 unit of whole blood-derived ("random donor") platelets. Each of these components are then stored under optimal conditions. Processing whole blood into its components permits transfusion therapy directed at replacement of a particular constituent of blood (i.e. plasma proteins, red cells, or platelets), permits several patients to benefit from one blood donation, and avoids the administration of unnecessary blood components.

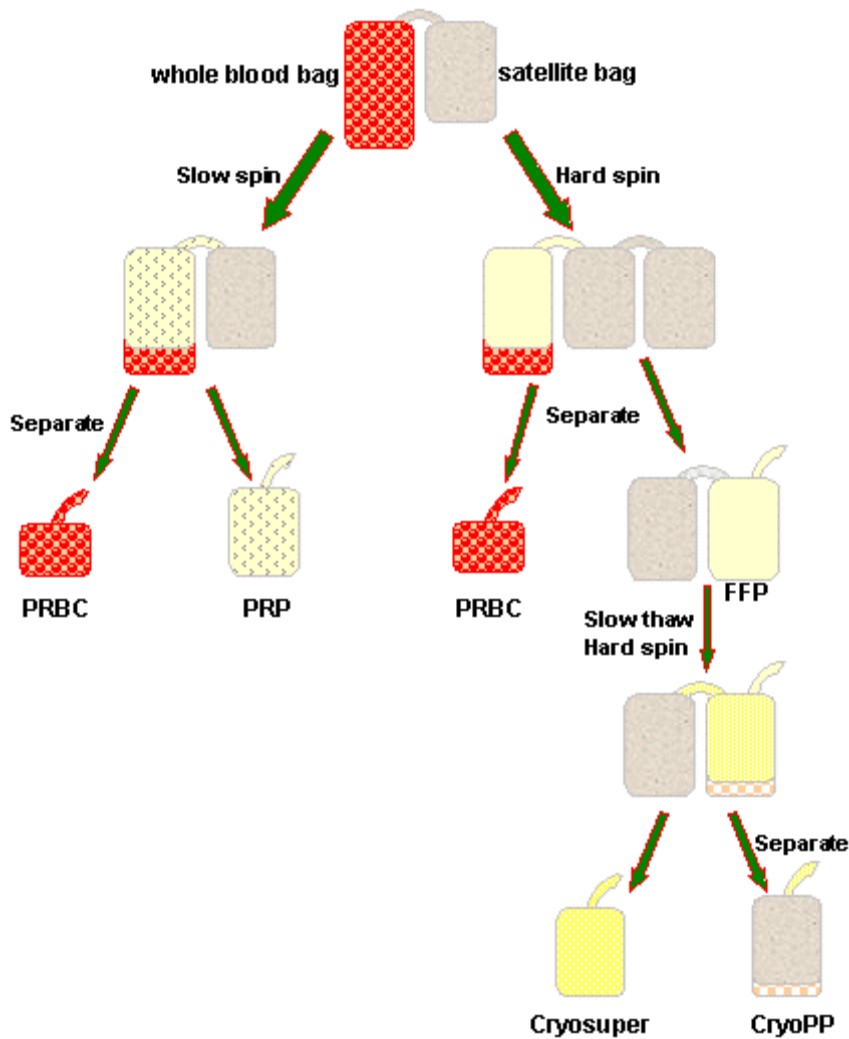


Figure 1. PRBC = Packed red blood cells; PRP = Platelet-rich plasma; FFP = Fresh frozen plasma; Cryosuper = Cryosupernatant; CryoPP = Cryoprecipitate. (Figure from <http://diaglab.vet.cornell.edu/clinpath/modules/coags/compprod.htm> date last accessed November 11, 2007)<sup>6</sup> Please note that platelet rich plasma (PRP) is centrifuged and made into one random donor platelet unit (RDP) and one unit of platelet poor plasma.

Apheresis technology is used to collect red cells, platelets, or plasma from a donor and then returns the remaining constituents to the blood donor; an apheresis donation may take up to 90 minutes based on the technology used. See section 20 on Platelets.

## **TRANSFUSION RECIPIENT PRETRANSFUSION COMPATIBILITY TESTING**

### **10. Why would the blood bank reject a patient specimen collected for pre-transfusion compatibility testing?**

Strict adherence to the specimen labeling requirements may significantly decrease erroneous blood grouping and consequently decrease the likelihood of transfusing potentially life-threatening ABO incompatible blood components. One study found that specimens that failed to meet specimen acceptability criteria were 40 times more likely to have a blood grouping discrepancy.<sup>7</sup> The phlebotomist must label each blood specimen tube with two independent patient identifiers and the date of collection in the presence of the patient. There must be a mechanism to identify the phlebotomist. Each institution should have policies and procedures that define specimen identifying information and how to manage mislabeled specimens. When a pre-transfusion specimen is received in the laboratory, laboratory personnel must confirm that the information on the specimen label and on the pre-transfusion testing request is identical. If there is any doubt about the identity of the patient or the labeling of the specimen, a new specimen must be obtained.

### **11. What is the difference between a type, a screen and a crossmatch?**

Pretransfusion compatibility testing is performed to prevent transfusion of incompatible blood that may result in a hemolytic transfusion reaction.<sup>8</sup> (See Table II) A type and screen (T&S) consists of a group of tests performed on a patient's blood specimen as part of pretransfusion testing and includes typing the patient's red cells for ABO and Rh blood groups and screening the patient's plasma or serum for the presence of unexpected non-ABO antibodies. The ABO group is determined by typing the patient's red cells using anti-A and anti-B reagents (forward type) and by testing the patient's serum against A and B reagent cells (reverse type). The patient's RBCs are also tested with Anti-D for the presence (Rh positive) or absence (Rh negative) of the D antigen. The patient's serum or plasma is screened for the presence of unexpected antibodies by incubating it with two selected reagent red cell panels (screening cells) that contain all of the critical non-ABO antigens using an antihuman globulin

(AHG) technique (indirect antiglobulin test or Coombs test). The screening cells are Group O and are selected in such a way that all common non-ABO red cell antigens capable of inducing clinically significant red cell antibodies are represented on at least one screening cell. Two, three or four screening cells may be used. A clinically significant red cell antibody is one that may result in hemolysis and/or hemolytic disease of the newborn. If an antibody is detected in the patient's serum or plasma, the antibody screen is considered positive. ABO group, Rh type and antibody detection screening take approximately 45 minutes to perform. If the antibody screen is negative and the patient has no past history of unexpected antibodies, the patient may receive RBC that are tested for ABO compatibility by performing an immediate spin crossmatch or an electronic/computer crossmatch. ABO- and Rh-compatible blood is selected from the inventory and issued within five to 10 minutes following immediate spin crossmatch or computer/electronic crossmatch. If the antibody screen is positive, the unexpected antibody or antibodies must first be identified before antigen negative-compatible RBC units can be found and then crossmatched all of which usually takes several hours.

In a serologic crossmatch, the patient's serum is incubated with an aliquot of red cells from a specific donor unit to verify in vitro compatibility. A crossmatch is performed with a short incubation time at room temperature (immediate spin) intended solely to verify ABO compatibility or with a long incubation time at 37 C degrees (AHG crossmatch) intended to verify compatibility for clinically significant non-ABO red cell antigens. The immediate spin crossmatch takes five to 10 minutes, while the AHG crossmatch takes at least 45 minutes. The electronic/computer crossmatch may be performed instead of an immediate spin crossmatch and uses a computer system to select a RBC unit based on a series of validated computer algorithms. Serologic testing of the donor RBC unit with patient specimen is NOT performed in this scenario.

A crossmatch is only performed if a valid (less than 72 hours old) T&S specimen is available and should be ordered only if the likelihood of transfusing red cells to the patient is high. An AHG

crossmatch is only required for patients with a current or past history of clinically significant unexpected antibodies in their serum/plasma.

**Table II: Pretransfusion Compatibility Tests**

Order	Tests Performed	Time to Perform
Draw and Hold	NONE	Not applicable
Type & Screen (T&S)	ABO and Rh Antibody Detection Screen	~45 minutes
Type and Crossmatch (T&C) (with negative antibody screen)	ABO and Rh Antibody Detection Screen Immediate spin or electronic crossmatch	~60 minutes
Type and Crossmatch (With positive antibody screen)	ABO and Rh Antibody Detection Screen Antibody identification Selection of antigen negative RBCs AHG crossmatch	Up to hours and may be longer based on complexity of antibody identification and acquisition of antigen negative blood if needed

## ADMINISTRATION OF BLOOD AND COMPONENTS

### 12. What are the advantages and disadvantages of component therapy?

The primary advantage of component therapy is that specific portions of the blood that patients require can be administered, allowing several patients to benefit from one donation. Administration of unnecessary or unwanted components is also avoided. In addition, the storage requirements of components differ, and separation permits each to be stored under optimal conditions to enhance component efficacy.

The primary disadvantage of component therapy is encountered in treating patients with massive blood loss requiring massive transfusion since these patients would benefit from whole blood with respect to not only restoration of oxygen carrying capacity but also restoration of hemostatic function (i.e. via fresh platelets and plasma within whole blood). Multiple components are more expensive and more difficult to transfuse than whole blood. In addition, exposure to the infectious complications of transfusion can be increased as the number of donor exposures increases.

### **13. What data must be verified prior to initiating transfusion of a blood component?**

Accurate identification and linking of the transfusion component and the intended recipient may be the single most important step in ensuring transfusion safety, as clerical or management system errors are the most frequent cause of ABO-incompatible transfusions.<sup>9</sup> In the practice of anesthesiology, the anesthesiologist typically represents the final point in the transfusion process where patient or blood component identification errors can be detected and thus, he or she plays a critical role in patient safety with respect to transfusion. The anesthesiologist is typically responsible for verifying specific information prior to initiating transfusion of a blood component. The **patient's name and hospital identification number** on the patient's identification band must be identical with the name and hospital identification number on the form attached to the unit to be transfused. For anesthetized patients, the name and hospital identification number on the form attached to the unit of blood to be transfused must be verified with the patient's name and hospital identification number on the patient's identification/anesthesia record. The patient should be asked his or her name preoperatively. Attached to the unit to be transfused is the **unit identification number**. The anesthesiologist and another individual (e.g. circulating nurse) **must** verify and confirm that the number on the unit matches the label attached to the unit. The **ABO and Rh type** on the label attached to the unit must agree with the blood type recorded on the unit to be transfused. The patient's ABO/Rh type and the ABO/Rh type of the component may not be identical, but the information on the unit and on the unit's label must be identical. The expiration date of the donor unit should be verified as acceptable before infusion. In emergency situations, a temporary identification designation and/or number are assigned to patients whose identifications are unknown. Finally, the unit should also be inspected for discoloration and large clots or bubbles, which may indicate that bacterial contamination has occurred.

## **RED BLOOD CELLS**

### **14. What red cell components are available?**

Whole blood units contain approximately 450-500 mL donated blood plus approximately 70 mL of a citrate-based anticoagulant-preservative solution, which is utilized to maintain the viability of red blood cells. One unit of whole blood collected and stored with citrate-phosphate-dextrose-adenine (CPDA-1) solution has a 35-day shelf life and a hematocrit of approximately 35 percent. Whole blood is indicated for acute, massive blood loss, although red blood cells and crystalloid solution can be used as effectively. However, few blood centers or hospitals maintain an inventory of CPDA-1 Whole Blood.

Some have studied the use of **fresh whole blood** as an alternative to using red blood cells, platelets and FFP in cardiac surgery. It was thought that autologous or allogeneic blood transfused within 12 hours of collection might reduce blood loss and the need for platelets and FFP. Although one study showed less postoperative blood loss in infants,<sup>10</sup> most concluded that the logistic problems of obtaining fresh blood from a prescreened donor outweighed any advantages.<sup>11</sup> Nonetheless, its indication for massive transfusion particularly in combat and in disasters is still under investigation, with studies showing benefits (and even superiority) over component therapy.<sup>12</sup>

**“Red Blood Cells”** is the preferred term for what is frequently called “packed red blood cells.” One unit of whole blood is separated into red blood cells and platelet-rich plasma by centrifugation (Figure 1). Similar to whole blood, a unit of Red Blood Cells collected in CPDA-1 anticoagulant-preservative solution has a hematocrit of approximately 70 percent and a shelf life of 35 days. Alternatively, 100 mL of an additive solution such as Adsol® (AS-1), Nutricel® (AS-3), or Optisol® (AS-5) can be added to Red Blood Cells with CP2D or CPDA-1 to prolong shelf life to 42 days and decrease viscosity, reducing the hematocrit to approximately 60 percent. Most RBCS in the USA transfused in USA are Adsol® units. Red Blood Cells are only indicated for raising the oxygen-carrying capacity, although they also provide volume when given to patients acutely hemorrhaging.

**Glycerolized Red Blood Cells** are stored frozen at -65°C or lower for up to 10 years. Glycerol is used to protect the red cells during freezing and thawing and is removed by washing before transfusion.

Conventional washing process requires “entry” of the unit and thus the deglycerolized red cells are available for only 24 hours at 1° to 6°C after thawing. Development of an automated closed cell processing system in conjunction with using nutrient- additive solutions such as AS-3 have extended the post-wash storability of the blood to 14 days following thawing.<sup>13,14</sup> This approach is indicated for prolonged storage of rare red cells for patients with antibodies to red cells with rare red cell antigen phenotypes, storage of group O Red Blood Cells to treat patients during times of shortage (i.e., increases in local demand due to a large-scale catastrophe) and, occasionally, for autologous donors unable to tolerate serial phlebotomy during the immediate 42-day preoperative period. Despite thorough washing, small amounts of free hemoglobin may be visualized as a pink-tinged supernatant; however, the unit should be returned to the blood bank (as should any red blood cell unit) if the supernatant appears dark red and/or cloudy.

**Leukocyte-Reduced Red Blood Cells** are primarily indicated for patients with a history of multiple febrile nonhemolytic transfusion reactions, for select patients who are frequent transfusion candidates and thus at risk for alloimmunization to leukocyte antigens, and for prevention of cytomegalovirus infection in high-risk patients who are immunocompromised (targeted populations).<sup>15</sup> For the same reasons (i.e. reducing the risk of cytomegalovirus transmission, febrile nonhemolytic reactions and alloimmunization), Leukocyte-Reduced Red Blood Cells are increasingly being used in general population of transfused patients and universal leukocyte reduction is now mandated in Canada and many European countries as well.<sup>16</sup> The same practice has been implemented in the US since 2005 on a voluntary basis.<sup>16</sup> In spite of being a safe procedure, the beneficial effects of leuko-reduction on infection and mortality in non-targeted populations remain controversial.<sup>17</sup> However, certain patient populations at high risk (e.g. trauma, cardiac surgery) with systemic endothelial activation/dysfunction related to the systemic inflammatory response) may benefit from leukoreduced units to attenuate target organ injury/ mortality as related to one of several potential mechanisms (e.g. platelet-leukocyte complexes, cytokines or white cell mediators like elastase). This is supported by four randomized,

controlled trials involving nearly 2500 patients, which revealed a 50-70% reduction in mortality in patients who were randomly assigned to receive leukocyte reduced PRBC units.<sup>18-20</sup>

Third-generation adsorption filters enable the removal of 99.9 percent of donor leukocytes and are more effective than the cell washing and centrifugation techniques used previously. Nonetheless, leuko-reduction filters have been linked to certain adverse reactions including, on rare occasions, unexpected hypotension (i.e., secondary to charged filter induced generation of bradykinin and potential accumulation due to reduced clearance in patients receiving acetylcholinesterase inhibitors), activation of complement and coagulation and hemolysis.<sup>16,17</sup> Specific leukoreduction filters are made for either red blood cells or platelet transfusion.

**Washed Red Blood Cells** are prepared by centrifugation with saline to remove almost all plasma and cytokines. They are indicated only for patients who have had severe allergic reactions associated with transfusion or immunoglobulin A (IgA) deficiency. Washed red blood cells have transfusion hazards similar to those associated with Red Blood Cells (including risk of transmitting hepatitis and other infectious diseases) and they must be given through a standard blood filter, and can be stored no longer than 24 hours because of the risk of bacterial contamination following washing in an open system.<sup>21</sup> As in the case of frozen Red Blood Cells, development of automated closed wash systems is expected to prolong the storage time beyond 24 hours.<sup>22</sup> Washing of red cells may be used to remove excess potassium from older units.

**Irradiated Whole Blood or Red Blood Cells** are blood components that have been exposed to a standard dose of ionizing (gamma) radiation to render viable lymphocytes incapable of engraftment in premature newborns, highly immunocompromised patients (e.g., bone marrow or solid organ transplant) and blood relatives of directed donations to reduce the possibility of transfusion-related graft-versus-host disease, a lethal complication.<sup>23</sup> Increased membrane permeability has been noted after

irradiation, with the irradiated red cells leaking potassium at an accelerated rate.<sup>24</sup> Mild functional impairment manifested by significant leakage of potassium and accumulation of plasma hemoglobin has been demonstrated subsequent to gamma irradiation.<sup>25</sup> This issue can become especially problematic if blood is stored for extended periods of time following irradiation resulting in rare but serious incidences of hyperkalemic cardiac arrhythmia or serious conduction abnormality (e.g. AV block, asystole).<sup>23</sup> Washing the red cell component can be used to remove excess potassium. Irradiated Red Blood Cells have a reduced storage period (not to exceed 28 days after irradiation) in order to limit the deleterious effects this treatment can have.

### **15. How can the necessary volume for a red cell transfusion be estimated?**

Red Blood Cells are indicated in symptomatic, anemic patients to restore oxygen-carrying capacity. Hypovolemia due to either mild hemorrhage or dehydration without a significant reduction in red cell mass should be managed with crystalloid or colloid solutions. Red cells may be used as a replacement solution in the setting of severe bleeding (e.g. > 1-2 liters/hour) in an attempt to manage ongoing hypovolemia/anemia. Transfusion volume required for individual patients can be estimated using the patient's hematocrit, blood volume and state of hydration. Identification of predictors of transfusion requirement as a means to justify the number of units to cross-match for a particular patient is under active investigation with numerous studies published. It should be emphasized that in many cases, transfusion rates and/or amounts can be effectively reduced by employing blood conservation techniques.<sup>26,27</sup>

One unit of red blood cells will increase the hematocrit by approximately 3 percent and the hemoglobin by about 1g/dL in the average adult.<sup>28</sup> Ten mL/kg of Red Blood Cells will raise hematocrit by 10 percent. The increase in the recipient's hematocrit will vary depending upon many factors, which include the donor's hematocrit, the recipient's fluid status and size, the anticoagulant-preservative solution utilized, the rate of active bleeding and the duration of storage of the unit transfused.

## 16. Is there a safe level of anemia for surgical patients?

In recent years, it has been recognized that little stress is placed on the human body by acutely reducing the volume of circulating red blood cells by as much as 15 percent to 30 percent, provided that intravascular volume is maintained and that the starting hematocrit is normal.<sup>29</sup> Acute isovolemic reduction of hemoglobin to as low as 5 g/dL may be well tolerated in healthy resting adults without impairment in systemic oxygen delivery.<sup>30</sup> However, the associated increase in heart rate might pose a problem in context of ischemic heart in severe anemia or with substantial cardiac dysfunction (i.e., cardiomyopathy).<sup>31</sup> Nonetheless, in most of the cases, various hemodynamic and non-hemodynamic mechanisms compensate for anemia without increasing oxygen demand in heart.<sup>32</sup> Although losses of up to 40 percent of blood volume in young healthy patients can be treated adequately with crystalloid and are generally well-tolerated, a loss of greater than 40 percent of total blood volume may be life-threatening.<sup>33</sup> There is no single minimum acceptable hemoglobin for all patients. Chronic anemia is better tolerated than acute anemia. The key to the tolerance of anemia is the maintenance of normovolemia and compensatory mechanisms that increase cardiac output and improve oxygen transport by elevating 2,3-diphosphoglycerate levels as well as the patient's cardiovascular reserve.<sup>34</sup> As mentioned earlier, patients with cardiac disease or atherosclerotic flow-restricting lesions have limited adaptability to anemia, and are especially susceptible to detrimental effects of tachycardia. Indeed, many factors should be considered in the transfusion decision, including the patient's current intravascular volume, the duration and extent of anemia, and the presence of pathology that affects cardiopulmonary function and circulation. Suggested guidelines for transfusion must balance the risks of transfusion, including possible infectious disease transmission, TRALI, bacterial sepsis, target organ injury versus the need for oxygen-carrying capacity in recovery from trauma, surgery or illness. In the "ASA practice guidelines for perioperative blood transfusion and adjuvant therapies,"<sup>33</sup> the task force noted in its recommendations that transfusion of "red blood cells should usually be administered when the hemoglobin concentration is low (e.g., less than 6 g/dL in a young, healthy patient), especially when the anemia is acute. Red blood cells are usually unnecessary when the hemoglobin concentration is

more than 10 g/dL. These conclusions may be altered in the presence of anticipated blood loss or active critical (i.e., myocardium, central nervous system or renal) or target organ ischemia. The determination of whether intermediate hemoglobin concentrations (i.e., 6-10 g/dL) justify or require RBC transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.”<sup>33</sup>

Studies in critically ill (i.e., within an intensive care unit setting) anemic patients without coronary artery disease have shown restrictive transfusion triggers as low as 7 mg/dL to be safe,<sup>35,36</sup> and more studies in this field are underway. **By all accounts, hemoglobin triggers for transfusion are not to be taken as absolute indications and cardiac patients should be transfused if signs or symptoms of inadequate myocardial oxygenation are present.**<sup>37</sup> The same rule applies to other anemic patients. Currently, red cell transfusion should be considered in:

- anemic patients with relative hypotension/tachycardia,
- new ST-segment depression more than 0.1 mV or new ST-segment elevation more than 0.2 mV, new wall motion abnormality,
- mixed venous oxygen partial pressure less than 25 mmHg,
- Oxygen extraction rate more than 50%,
- mixed venous oxygen saturation less than 50% and more than 10% decrease in oxygen consumption.

Available evidence supports transfusion in absence of physiologic signs with hemoglobin levels below 6 mg/dL in general patient population, below 7 mg/dL in patients above 80 years old or in febrile/hypermetabolic patients, and below 8 mg/dL in patients with coronary artery disease or CHF.<sup>37</sup>

#### **17. How should emergency transfusion needs be met before crossmatched blood is available?**

While waiting for crossmatched blood to be available, emergency transfusion needs can be met in various ways, depending on the clinical status of the patient and the equipment available. Most patients can tolerate an acute decrease in hemoglobin and oxygen-carrying capacity providing circulating volume is maintained. Crystalloid or colloid solutions may be infused to increase intravascular volume and stabilize the vital signs, although overzealous administration of crystalloid to normalize blood pressure may be disadvantageous in certain patient subsets (e.g., penetrating torso injuries).<sup>38</sup> In fact, studies have shown that attempting to achieve normal blood pressure in the setting of active bleeding through extensive fluid therapy is associated with disruption of hemostatic mechanisms, dilution of clotting factors, increased blood loss and decreased survival. Therefore, maintaining blood pressure below normal (systolic 80 mmHg; mean 50-60 mmHg) and heart rate under 120 while closely monitoring indicators of organ ischemia are the suggested goals for early resuscitation.<sup>39</sup> If the patient has cardiac disease, pulmonary disease or cerebrovascular disease, and acute anemia will pose increased risk, or if the patient is in extremis, then either type-specific or type O Rh-negative red cells can be administered while waiting for a crossmatch to be performed. Type O Rh-positive Red Blood Cells for males or postmenopausal females can be transfused in this setting as well. Administration of Group O uncrossmatched blood is safe provided that the patient is not already alloimmunized to any non-ABO red cell antigens.

Administration of a substantial number Group O Rh-negative blood may potentially lead to hemolysis if multiple units of Group O Whole Blood (containing anti-A and anti-B antibodies) have been transfused to patients with Group A or B blood. The patient can be switched back to his or her inherent type-specific blood after subsequent testing by the blood bank indicates it is safe to do so.

Development of artificial oxygen-carrying agents (so called Blood substitutes) that can be easily stored and readily given to patients with no crossmatching is expected to revolutionize resuscitation in emergency setting. These products are not currently approved for use by the FDA and are discussed in Sections 43 and 44.

## **18. Which intravenous solutions are compatible with red blood cells?**

When additive solutions such as Adsol® are used, no dilution of Red Blood Cells is necessary to assure rapid infusion.<sup>40</sup> For red cells stored in other preservatives in which the hematocrit may be as high as 70 percent to 80 percent, 60 to 100 mL of 0.9-percent saline can be added to Red Blood Cells to facilitate rapid infusion and minimize hemolysis.

Calcium-containing solutions must not be added to blood, particularly at slow infusion rates, because small clots may form due to the presence of calcium in excess of the chelating ability of the citrate anticoagulant.<sup>41</sup> Hypotonic solutions such as 5-percent dextrose in water should not be used to dilute red cells since clumping of the cells or hemolysis may occur.

Although isosmolar calcium-free electrolyte solutions can be used as diluents,<sup>42</sup> the safest practice is to use normal saline, as the exact content of commercially available electrolyte solutions may not be readily recognized.

## **19. What filters are used to administer blood components?**

Although an anticoagulant is added to blood when it is collected, small clots are occasionally present in donor units, requiring filtration at the time of infusion. Standard blood administration sets usually have a clot screening filter with a pore size of 170-200  $\mu\text{m}$ . These filters permit rapid transfusion and should be used for administration of red cell components, platelet and granulocyte concentrates, FFP and cryoprecipitate.

During storage, microaggregates consisting of platelets, leukocytes and fibrin form in red blood cell products. These microaggregates can pass through 170  $\mu\text{m}$  filters and lodge in the pulmonary circulation. Therefore, use of microaggregate (20 to 40  $\mu\text{m}$ ) filters has become increasingly popular in the US,<sup>43</sup> although this practice has not been proven to reduce the incidence of respiratory distress

syndrome in patients receiving multiple transfusions.<sup>44</sup> The usefulness of microaggregate filters is still debated and there is no firm indication for their use during routine transfusions, even when large volumes of blood are administered (massive transfusion). However, they are used during cardiopulmonary bypass (arterial inflow cannulae) to prevent entrance of microaggregates into the systemic circulation.

Third-generation adhesion/adsorption leukocyte reduction filters, which remove greater than 99.9 percent of the leukocytes, may be useful in reducing nonhemolytic febrile reactions (secondary to host antibodies against donor leukocytes), cytomegalovirus transmission, human leukocyte antigen (HLA) alloimmunization and platelet refractoriness. Leukoreduction filtration, if performed, usually is conducted by the blood center shortly after collection. These filters are expensive and their exact role remains to be identified. Moreover, they have been linked to certain side effects as mentioned earlier.<sup>16,17</sup>

## **PLATELETS**

### **20. How are platelets prepared and administered?**

Random-donor platelets can be prepared from whole blood stored at 22°C within eight hours of collection.<sup>45</sup> After the collection of approximately 500 mL of whole blood into collection bags containing citrate-based anticoagulant-preservative solution, the blood is centrifuged. Following centrifugation, the platelet-rich plasma (PRP) is separated into an attached empty satellite bag. (Figure1) This PRP is centrifuged again and separated into one unit of platelet concentrate and one unit of plasma. Each unit of platelets contains approximately  $5 \times 10^{10}$  platelets in 50 to 70 mL of plasma. Any where from 5 to 10 units of platelets may be pooled together in a single component bag.

Alternatively, platelets can be isolated from the buffy coat layer, following centrifugation of whole blood in specific bags that removes RBC and plasma through tubings in the bottom and top of the bag. The platelet-enriched buffy coat is further processed (through centrifugation and/or leuko-reduction

filters) to eliminate WBCs and remaining RBCs. This method is currently employed primarily in Europe and Canada and it permits storage of whole blood at 22°C for up to 24 hours prior to platelet removal and provides some logistic and other potential advantages.<sup>45</sup>

In another increasingly utilized method, apheresis platelets (Single Donor) are obtained by performing apheresis on volunteer donors. During this procedure, large volumes of donor blood are processed into an extracorporeal circuit and centrifuged to separate the components. The red blood cells and a certain percentage of the plasma are returned to the donor. A single donor donates the equivalent of  $3-5 \times 10^{11}$  or four to six units of platelets suspended in a volume of 200 to 400 mL of plasma. Apheresis-derived platelets minimize the number of donor exposures for the transfusion recipient and have become the primary source of platelets in the US.<sup>45</sup>

Platelets should be stored at room temperature (20° to 24°C) for up to five days with continuous gentle agitation to prevent platelet aggregation. All platelet products should be tested for bacterial contamination prior to transfusion. The administration of ABO-specific platelets is not strictly (i.e., usually limited to 300-500 mL of out-of-group plasma) required because platelet concentrates contain few red blood cells. However, administration of non-ABO specific platelets may be of concern with transfusion of pediatric patients with a small blood volume because of anti-A and/or anti-B in the plasma. The administration of out-of-group pooled platelet components leads to transfusion of plasma containing anti-A and/or anti-B, resulting in passive alloimmunization and may cause a weakly positive direct antiglobulin test due to anti-A and or anti-B from the plasma. Platelets can be infused through a platelet or standard component administration set with a 170-micron filter. Microaggregate filters (20-micron to 40-micron) should not be used because they will remove most of the platelets.

## **21. What are the indications for platelet therapy?**

The majority of platelet units are given prophylactically to prevent or to manage active bleeding in surgical and non-surgical contexts. Platelets should be administered to correct a deficiency in either

platelet number (thrombocytopenia) or platelet function (thrombocytopathy or qualitative platelet disorders). One unit of apheresis platelets or a pool of 4 to 6 whole blood-platelets (derived from 4 to 6 units, “six-pack”) increases the platelet count by approximately  $30\text{-}50 \times 10^9/\text{L}$  in the average adult. For pediatric patients a dose of 10 ml/kg or one unit of platelets/10 kg will generally increase the platelet count to adequate levels.<sup>46</sup> Surgical and obstetrical patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than  $50 \times 10^9/\text{L}$  and rarely require therapy if it is greater than  $100 \times 10^9/\text{L}$ .<sup>33</sup> In patients undergoing CPB, platelet transfusion should be reserved for those patients with excessive post-operative bleeding with no identifiable surgical source.<sup>47</sup> Factors to consider for the transfusion of platelets for counts between  $50\text{-}100 \times 10^9/\text{L}$  are the type of surgery, extent of actual blood loss or microvascular bleeding, presence of potent antiplatelet medications (e.g. clopidogrel, IIb/IIIa antagonists etc) and disorders like uremia known to affect platelet function and coagulation. Operation at critical sites (e.g. neuro or ophthalmic surgery) usually entails increasing the platelet to around levels  $100 \times 10^9/\text{L}$  in order to ensure adequate hemostasis with platelet counts above  $50 \times 10^9/\text{L}$ .<sup>47</sup> Operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than  $50 \times 10^9/\text{L}$ .<sup>33</sup> It should be remembered, however, that the platelet count does not provide an assessment of platelet function and platelet transfusion may be indicated, even above  $100 \times 10^9/\text{L}$  count, if platelet dysfunction is suspected when microvascular bleeding is unresponsive to other therapies<sup>33</sup> and/or there is a recent history of taking aspirin or other more potent or longer half-life platelet-inhibiting drugs (e.g. clopidogrel). Potent agents such as glycoprotein IIb/IIIb antagonists may require 2 or more apheresis platelet units to achieve normal hemostasis while effects of some other agents (e.g., clopidogrel) have not consistently been shown to be reversed with platelets.<sup>48</sup> Various herbal compounds have been shown to interfere with platelet function.<sup>49</sup> Qualitative coagulation tests, such as bleeding time have been shown to have poor reproducibility and limited value whereas newer platelet function tests such as thromboelastograph testing may identify causes of platelet dysfunction.<sup>50,51</sup> While many studies have shown that general prophylactic platelet transfusion trigger of  $10 \times 10^9/\text{L}$  in non-surgical patients (e.g. in bone marrow transplanted or leukemic patients with thrombocytopenia) is safe and associated with less platelet use,

compliance with this restrictive trigger remains somewhat low.<sup>52</sup> If these patients are unstable, bleeding or undergoing invasive procedures, the prophylactic platelet transfusion trigger in these patients may be substantially higher.<sup>53</sup> The prophylactic administration of platelets is not recommended in patients with chronic thrombocytopenia caused by increased platelet destruction (e.g., idiopathic thrombocytopenic purpura and may in fact be ineffective (i.e., as related to platelet refractoriness) in a substantial percentage of these patients).<sup>21,33</sup>

## **FRESH FROZEN PLASMA**

### **22. How is fresh frozen plasma prepared and administered?**

After removal of red blood cells from the whole blood, the remaining platelet-rich plasma is further centrifuged to separate the platelets from the plasma. The remaining plasma contains all the blood coagulation factors, fibrinogen and other plasma proteins in a volume of 170 to 250 mL.<sup>54</sup> The plasma is then frozen within eight hours of phlebotomy to prevent complete inactivation of temperature-sensitive (“labile”) coagulation factors V and VIII. At temperatures colder than -18°C, FFP can be stored for up to one year with minimal loss of coagulant activity. Prior to the administration of FFP, the plasma must be thawed in a waterbath at 37°C, which takes approximately 30 minutes. After thawing, the units of FFP are stored at 1° to 6°C and are generally transfused within 24 hours. FFP should be administered through a component administration set with a 170-micron filter. FFP which has been thawed but not used within 24 hours can be relabeled as “Thawed Plasma” (TP) and stored at 1-6 °C for an additional 4 days. Thawed plasma maintains normal levels of all factors except factor V which falls to 80% of normal and factor VIII which falls to 60% of normal. Since these levels are above the in-vivo threshold for normal hemostatic function for these factors and FVIII is an acute phase reactant, TP can be used as a substitute for FFP.<sup>55</sup>

### **23. What are the indications for fresh frozen plasma?**

FFP is generally used for the treatment of microvascular bleeding due to congenital and acquired coagulopathies resulting in a prolongation of either the activated partial thromboplastin time (aPTT) or

prothrombin time (PT) greater than 1.5 times normal,<sup>33,56</sup> or a coagulation factor assay of less than 25 percent.<sup>54</sup> To control for differences in reagent sensitivity used to perform the PT, the international normalized ratio (INR) was developed. The INR is calculated by the following equation  $INR = [PT \text{ patient}/PT \text{ geometric mean control}]^{ISI}$ ; the ISI or International Sensitivity Index value is designated for each reagent/instrument combination using established standard reagents. Evidence-based data supporting administration of FFP in patients with INR values <2 are lacking.<sup>57</sup> In emergent situations, FFP may be used to reverse the effect of warfarin prior to surgery or during active bleeding episodes. However, if time permits, oral or parenteral vitamin K will produce the same effect in six to 12 hours without exposing patients to the risks associated with allogeneic blood components. FFP should not be transfused prophylactically during massive hemorrhage, be used as a volume expander or be used as a source of nutrition. In the patient who has been transfused with more than 1-2 blood volumes and PT and PTT cannot be obtained in a timely fashion, FFP may be administered after administration of platelets to correct microvascular bleeding believed to be due to coagulation deficiency.<sup>33</sup> When FFP is indicated, it should be administered in a dose calculated to achieve a minimum of 30 percent of plasma factor concentration. Ten to 15 mL/kg of FFP will generally result in a rise of most coagulation proteins by 25-30% (or increases in 0.25 to 0.3 U/mL), although a dose of 5 to 8 mL/kg may be adequate to urgently reverse warfarin anticoagulation. This varies based on the initial levels of the vitamin K dependent coagulation factors.<sup>33</sup>

## **CRYOPRECIPITATE**

### **24. How is cryoprecipitate prepared and administered?**

Cryoprecipitated antihemophilic factor, or cryoprecipitate, is prepared from a unit of FFP. It is the cold-insoluble white precipitate that forms when a bag of FFP is thawed at 1° to 6°C. This cold-insoluble material is removed following centrifugation and immediately refrozen at -18°C, and it can be stored at this temperature for up to one year.<sup>58</sup> Each unit of cryoprecipitate contains 80 to 150 units of Factor VIII, 150 to 250 mg of fibrinogen, von Willebrand factor, Factor XIII, and fibronectin in a volume of 5 to 15 mL.<sup>58</sup> Cryoprecipitate must be transfused within four to six hours of thawing if

given to replenish factor VIII levels and should be infused through a 170 to 260 micron component filter.<sup>59</sup>

## **25. What are the indications for cryoprecipitate?**

Today cryoprecipitate is used primarily to augment fibrinogen levels depleted because of massive hemorrhage or disseminated intravascular coagulopathy (DIC). Rarely, it is used for the treatment of congenital or acquired Factor XIII deficiency. Cryoprecipitate can also be administered prophylactically for nonbleeding perioperative or peripartum patients with congenital fibrinogen deficiencies or von Willebrand's disease (deficient or abnormal von Willebrand molecule) unresponsive to desmopressin, a 1-desamino-8-d-arginine vasopressin (DDAVP).<sup>33</sup> Although cryoprecipitate was originally used to for patients with hemophilia A and von Willebrand's disease, select intermediate purity Factor VIII concentrates are standard therapy for von Willebrand's disease and recombinant or highly purified Factor VIII concentrate for hemophilia A because of its greater efficacy and safety profile. The intermediate purity concentrate contains significant therapeutic quantities of the von Willebrand's component of Factor VIII, whereas the high purity preparations contain primarily the hemophilia A component of Factor VIII.

For fibrinogen replacement therapy, one unit of cryoprecipitate per 10 kg body weight increases plasma fibrinogen by approximately 50-70 mg/dL in the absence of continued consumption or massive bleeding.<sup>60</sup> The minimum hemostatic level of fibrinogen is less than or equal to 70-100 mg/dL. Because cryoprecipitate does not contain Factor V, it should not be the sole replacement therapy for disseminated intravascular coagulopathy (DIC), which is almost always associated with a variety of factor deficiencies and thrombocytopenia.<sup>21</sup> Hence, fresh frozen plasma also needs to be administered along with platelet concentrates in those settings where a coagulopathy secondary to DIC is likely occurring.

## **ADDITIONAL PLASMA DERIVATIVES**

## 26. What other plasma derivatives are available?

A number of plasma derivatives are available to treat coagulation deficiencies. Factor VIII concentrates are available to treat Factor VIII deficiency (hemophilia A). Although administration of concentrated Factor VIII concentrates was initially associated with a relatively high incidence of infectious disease transmission,<sup>61</sup> advances in purification techniques and screening tests have dramatically reduced the risk of disease transmission. The development of recombinant factor VIII in many instances has replaced human-based blood derivatives for the treatment of Factor VIII deficiency. Recombinant Factor VIII has the major advantage of not carrying the risk of transmitting viral diseases. Mild Factor VIII deficiency and Type 1 (80% of von Willebrand's disease) von Willebrand's disease (vWd) may be partially corrected with DDAVP. Administration of DDAVP is typically associated with a significant increase in both circulating factor VIII and von Willebrand's factor (vWf).<sup>62</sup>

In addition to Factor VIII concentrates, other specific plasma derivatives available for management of disorders of coagulation include Factor IX complex (prothrombin complex), Factor IX concentrate, Fibrogammin P (Factor XIIIa) and antithrombin III (ATIII) concentrate. Factor IX complex contains clinically significant quantities of Factors II, VII and X in addition to Factor IX. Hence, besides being originally used for the management of Factor IX deficiency (hemophilia B, or Christmas disease), Factor IX complex also has been employed to treat isolated deficiencies of the other vitamin K-dependent factors and to correct of warfarin-induced hemorrhage. However, this product activate the hemostatic system, leading to thrombosis and DIC, particularly in liver disease associated with associated ATIII deficiency or in patients on either extracorporeal membrane oxygenation or ventricular assist devices with ongoing activation or DIC.<sup>63</sup> In contrast, Factor IX concentrates contain negligible amounts of Factors II, VII and X and consequently are much less thrombogenic; therefore, they are preferred for the correction of an isolated Factor IX deficiency.<sup>21</sup> Recombinant Factor IX is currently available and has the advantage of no infectious risk with transfusion.

ATIII deficiency is usually congenital in origin but also can be acquired (i.e., in the setting of prolonged exposure to unfractionated heparin). Because ATIII is the major plasma inhibitor of thrombin, patients with ATIII deficiency are highly prone to thromboembolism. ATIII also has an important role as an inhibitor of the activated serum protease factors II, IX, X, XI and XII. Because the anticoagulant effect of heparin is predominately due to its ability to greatly increase the inhibitory activity of ATIII, patients with moderate to marked ATIII deficiency may require ATIII replacement therapy if they display evidence of heparin resistance. This is critically important for major cardiovascular procedures and surgeries involving cardiopulmonary bypass. Normal ATIII levels can be achieved by administering either human or recombinant preparation of ATIII concentrate. Prophylactic treatment with ATIII concentrate also is recommended for patients with a hereditary deficiency of ATIII (plasma level of 50 percent or less compared to normal) who have a history of thromboembolism or are undergoing surgical or obstetrical procedures associated with a high incidence of thromboembolism.<sup>64</sup> Recombinant, transgenic ATIII is not currently available.

## **ADVERSE EFFECTS OF TRANSFUSION**

### **27. What is the risk of infectious disease transmission after transfusion?**

Currently in the US, blood safety relies upon a system of voluntary donation with a detailed donor history and a variety of serologic and nucleic acid testing techniques for HIV 1/2, human T-cell lymphotropic virus (HTLV) I/II, hepatitis C virus (HCV), hepatitis B virus (HBV), West Nile virus, and *Treponema pallidum*.<sup>65</sup> These methods have led to a remarkable decrease in the incidence of transfusion-transmitted viral infections and the blood supply seems to be safe. However, there always exists the possibility that there may be a currently unidentified pathogen within our blood supply. In fact, transfusion-transmitted bacterial infections and sepsis (especially with platelet transfusions) now overshadow viral infections as the most frequent infectious complications of transfusion.<sup>66</sup> Use of the new nucleic acid testing technology has decreased the window period to 11 days for HIV and 8-10 days for hepatitis C.<sup>67</sup> Yet, blood donation by seronegative individuals may occur during the infectious

window period when they are undergoing seroconversion and infection cannot be detected by available laboratory tests. Newly emerging infective agents such as prions are other potential threats to blood safety. New pathogen reduction /elimination technologies are under investigation to minimize the residual risk of known and newly emerging infections.<sup>65</sup>

In many cases, blood is not the source of an infection that occurs following transfusion. Definitive evidence of transmission by transfusion requires documentation of seroconversion or new infection in the recipient and isolation of an agent with genomic identity from both the recipient and implicated donor. Presumptive evidence of transmission via transfusion includes recipient seroconversion within an appropriate interval after transfusion and/or identification of appropriate markers of infection in an implicated donor on follow-up investigation. The diagnosis of transfusion-transmitted HIV infection is most frequently made as a result of look-back procedures initiated by blood centers. Look-back protocols involve the process whereby blood collection facilities attempt to identify prior recipients of blood donated by individuals who subsequently test positive for HIV. Similar approach has been employed to track down those who may have been infected by other agents (e.g. HCV) through blood transfusions.<sup>68</sup>

### Bacterial Infection

There has been little improvement in reducing the risk of bacterial contamination since the introduction of closed collection systems. Current risk estimates of bacterial infection are 1 per 2000 to 8000 platelet units and 1 per 28,000 to 143,000 red cells units.<sup>69</sup> Transfusion-associated sepsis is the most frequent cause of death from transfusion-transmitted infections and the second most common cause of transfusion related death (20-30 deaths/ million units transfused) as reported to the FDA,<sup>70</sup> representing 17-22% of all reported fatalities (1 per 50,000-500,000 units platelets and 1 per 8,000,000 red cell units.)<sup>66</sup> The most common bacteria implicated in sepsis from red blood cells are *Yersinia enterocolitica* (46%), *Pseudomonas* spp. (25%) and *Serratia* spp. (11%). The common organisms identified in platelet units implicated in transfusion-associated sepsis include *Staphylococcus* spp.

(42%), *Streptococcus* spp. (12%), *Escherichia coli* (9%), *Bacillus* spp. (9%), *Salmonella* spp. (9%), *Serratia* spp. (8%) and *Enterobacter* spp. (7.0%). The major sources of bacterial contamination are related to blood collection sites (i.e., skin at venipuncture collection site), asymptomatic or low-grade bacteremia in donor, disposables, and the environment.<sup>66</sup> With the implementation of culturing of platelet units, the risk of reported (i.e., recognized) post-transfusion sepsis has declined to 1/75,000 and the risk of fatality reduced to 1/600,000. Note, however, that most whole blood-derived platelet units are not cultured but are tested using less-sensitive surrogate techniques at the time of this writing.<sup>71</sup>

### *Hepatitis*

Posttransfusion hepatitis may be evident clinically, but the majority of cases are subclinical. Introduction of testing for HCV in 1990 and subsequent implementation of an improved test have decreased the incidence of HCV. Current estimates are around 1 in 1,600,000 to 3,100,000 component units.<sup>67,69</sup> It is estimated that up to 90 percent of infections become chronic, but clinical liver disease develops in only 10 percent to 20 percent. The incidence of transfusion-associated HBV, for which testing has been employed for many years, is estimated to be 1 in 31,000 to 220,000.<sup>67,69</sup> Hepatitis A, for which there is no carrier state, is rarely seen in association with transfusion. With transmission being probable only during the brief period of asymptomatic viremia lasting a few weeks, the reported risk estimate is extremely low (perhaps in the order of 1 per 10,000,000 units.)<sup>69</sup> At this time, no causal relationship between the newly discovered hepatitis G virus (also called GBV-C) and hepatitis has been established. Current opinion is that the majority of cases of non-A, non-B, non-C hepatitis are due to an as yet undiscovered hepatitis agent or agents or to nonviral causes.<sup>72</sup>

### *Human Immunodeficiency Virus, Types I and II*

Testing for antibody to HIV-I and HIV-2 was implemented in 1985 and 1992 respectively. The most recent estimates of HIV infection are 1 in 1,478,000 to 4,700,000 units.<sup>69,73</sup>

### *Human T-lymphotropic Virus, Types I and II*

The transmission of HTLV-I/II by transfusion is limited to cellular blood components and data suggest that presence of viable lymphocytes is necessary of HTLV transmission.<sup>73</sup> The estimated transfusion risk is 1 in 1,900,000 units.<sup>73</sup> Two diseases are associated with HTLV-I infection albeit infrequently: 1) a chronic degenerative neurologic disease, HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP) characterized by progressive lower extremity weakness, spasticity, sensory deficits and urinary incontinence; and 2) adult T-cell leukemia/lymphoma. The lifetime risk of developing overt neurologic or neoplastic disease is thought to be less than 4 percent.<sup>74</sup> The consequences of HTLV-II infection are less clear but also may include HAM/TSP.

### *Cytomegalovirus*

CMV can be transmitted by transfusion, but clinical disease in immunocompetent patients is rare. Infection can lead to life-threatening multisystem disease in immunocompromised patients such as low-birth-weight infants and bone marrow or solid organ transplant recipients. Use of leukocyte-reduced or CMV-seronegative cellular blood components is recommended to prevent infection in patients at risk for CMV disease.<sup>73</sup>

### *West Nile Virus*

Recently, cases of transfusion-transmitted West Nile virus have been confirmed in the US.<sup>75</sup> Following these reports, nucleic acid testing for West Nile virus was widely implemented in the US in 2003, which resulted in identification and removal of around 1000 potentially infected donations in the same year.<sup>76</sup> Transmission may still occur, however.

### *Other Infectious Agents*

Transmission of parasitic diseases (malaria, babesiosis, toxoplasmosis and Chagas' disease) is extremely rare in the United States. Transmission of syphilis is also rare because *Treponema pallidum* is a fragile organism that does not survive prolonged storage at 4°C. Although theoretically possible, there has been no reported case of transfusion-transmitted Lyme disease. Other potentially

transmissible diseases include Epstein-Barr virus, leishmaniasis, Lyme disease, brucellosis and several human herpes viruses. Few cases of clinical disease (anemia) have been associated with parvovirus B-19 transmission by blood component transfusion.<sup>73</sup> Rare case reports of variant Creutzfeldt-Jakob disease (vCJD) following receiving blood of persons who later developed vCJD put forward prions as another potential risk.<sup>77</sup> No cases of vCJD have been identified in the US except among individuals whose travel or immigration would have excluded them from donating in this country. A number of other agents have been shown to be transmitted by transfusion, but have not been documented to cause clinical disease so far. These agents include TTV, SENV and GBV-C mentioned earlier.<sup>73</sup>

## **28. What are the manifestations of hemolytic transfusion reactions?**

Hemolytic transfusion reactions (HTRs) involve lysis of red blood cells. The hemolysis can occur intravascularly or extravascularly and can be caused by immunologic incompatibility between the donor and recipient or result from nonimmune mechanisms.

### *Immune Reactions*

Most serious HTRs are caused by transfusion of ABO-incompatible red blood cells. The incidence of fatal HTRs is 1 in 300,000 to 1 in 700,000 RBC transfusions,<sup>78</sup> but the incidence of ABO-incompatible RBC transfusions is reported to be approximately 1 in 14,000 to 33,000 units.<sup>79</sup> Risk of acute HTR is estimated at 1 in 11,000 to as low as 1 in 1,000,000 units.<sup>69,73,79</sup> Signs and symptoms of HTRs are usually evident during the transfusion and may occur following administration of as little as 10 to 20 mL of incompatible blood. Acute HTRs usually are caused by clerical or system errors resulting in patients receiving the wrong red blood cells. The severity of a reaction is generally proportional to the amount of incompatible blood infused, the type of incompatibility and the length of time before treatment is initiated. Signs and symptoms include chills, fever, chest and flank pain, and nausea. Patients often voice concerns that something is wrong with the transfusion. In the anesthetized patient, the only signs may be hemoglobinuria, a bleeding diathesis and unexplained hypotension.

When an acute HTR is suspected, the transfusion must be stopped and the transfusion service notified immediately so that a transfusion reaction investigation may be performed including rechecking the crossmatched units. Treatment is directed toward the most serious sequelae — acute renal failure and coagulopathy. Urine output should be maintained at a minimum of 1 to 2 mL/kg/hour with IV fluids while alkalization of the urine should also be considered. Furosemide may be administered and low-dose dopamine may enhance renal cortical blood flow and be beneficial in treating hypotension. Laboratory evaluation includes the direct antigen test, urine and plasma hemoglobin determinations, other tests verifying hemolysis (elevations in LDH, bilirubin, and/or undetectable haptoglobin) and baseline coagulation studies (platelet count, prothrombin time, activated partial thromboplastin time and fibrinogen level).

Immune extravascular reactions, often referred to as delayed reactions, occur following transfusion of red blood cells containing an antigen other than ABO to a patient with an undetected alloantibody. Estimated risk of delayed HTR is much higher than acute HTR at about 1 in 1000 to 9000 units.<sup>69,73,79</sup> The transfused red blood cells may survive initially, but may hemolyze within days to weeks. These reactions represent an anamnestic response of an antibody undetected by pretransfusion compatibility testing and therefore are not preventable. They may only become apparent because of a decreasing hemoglobin level, an unexplained lack of therapeutic benefit from a red blood cell transfusion or with detection of a new antibody when an antibody screen is repeated. Laboratory findings may include a positive direct antiglobulin (Coombs) test and an unexplained rise in bilirubin. No treatment is generally indicated, although antigen negative blood will be identified for the patient who may subsequently require additional Red Blood Cell transfusion.

### *Nonimmune Reactions*

Nonimmune hemolysis is generally preventable with strict adherence to proper handling and administration of blood components. Exposure to hypotonic or hypertonic solutions (e.g., 5-percent or

50-percent dextrose, respectively), thermal injury during blood transport, storage, processing (i.e., use of excessive suction exceeding 150 mm Hg for cell salvage systems or a dysfunctional cell salvage centrifuge) or administration, and inadequate deglycerolization of frozen Red Blood Cells can all cause hemolysis.

### **29. What should be done if urticaria develops during transfusion?**

Urticaria vs severe anaphylaxis is usually due to an idiosyncratic reaction involving transfused allergens in plasma that interact with the patient's tissue mast cells, causing them to degranulate and release various inflammatory mediators. Most reactions are mild. The transfusion should be stopped to ensure that the symptom is not a harbinger of a more serious reaction. Administration of an antihistamine such as diphenhydramine is advisable. The remainder of the unit can often be administered successfully at a slower rate.

### **30. What is the significance of increased temperature occurring during transfusion?**

Fever is associated with several types of transfusion reactions and may be the first indication of either a HTR or administration of a bacterially contaminated blood component. For this reason, transfusion should be stopped and the cause investigated when a rise in temperature of 1°C or greater develops in association with blood transfusion and is not explained by the patient's clinical condition.

If red blood cells are being administered, an HTR should be considered. If platelets are being transfused, bacterial contamination is more likely. The timing of the temperature elevation is important. Fever due to an HTR or bacterial contamination tends to occur following infusion of a small amount of blood and is rarely the only sign of a reaction. Hypotension accompanying a temperature elevation should raise suspicion of an HTR or bacterial contamination. If a HTR is suspected, the transfusion should be stopped, and an immediate clerical check, a direct antiglobulin (Coombs) test and examination for free plasma hemoglobin should be performed. A Gram's stain of the blood component may be useful in diagnosing bacterial contamination. Febrile nonhemolytic

transfusion reactions (FNHTRs) are secondary to infusion of blood-derived cytokines or recipient antibodies to donor leukocytes occur most frequently in patients who require repeated transfusions, and recurrent reactions are common. The diagnosis is usually one of exclusion. While not life-threatening, an FNHTR may be extremely unpleasant for the patient.

### **31. What other adverse reactions may occur as a result of transfusion?**

Transfusion is associated with a number of other acute and delayed reactions, in addition to infection, fever, urticaria and hemolysis.

#### *Allergic and Anaphylactic Reactions*

Allergic, anaphylactoid and anaphylactic reactions involve interaction between an allergen (usually a protein in the plasma of the transfused blood component to which the recipient was previously sensitized) and IgE antibody present on the surface of mast cells and basophils in the tissues and circulation of the recipient. The antigen-antibody interaction takes place on the surface of the cells, activating them and causing release of various mediators of anaphylaxis (anaphylatoxins like leukotrienes, histamine, bradykinin) that cause the signs and symptoms characteristic of the reactions. The severity ranges from mild urticaria to bronchospasm, laryngeal edema, severe hypotension and death — in general, the shorter the interval between initiation of transfusion and the onset of symptoms, the more severe the reaction.

Minor allergic reactions occur in 1 per 20 to 2500 transfusions depending on the components used, definition of reaction and the studied population. Similarly, major reactions range from 1 in 10,000 to 300,000 transfusions for components other than platelets and much higher rates for plasma-containing components.<sup>73,80</sup> Current estimates for the risk of minor allergic reactions after red cell transfusions and pooled platelet transfusions are 0.4% and 4.1% respectively. As for major allergic reactions

(anaphylactoid and anaphylactic), risk estimates are 1 in 23,000 red cell transfusions and 1 in 1,600 platelet pools—platelet transfusion.<sup>73</sup>

In addition to allergy-mediate bronchospasm or laryngeal/glottic edema, the differential diagnosis of acute respiratory distress occurring during or within hours following transfusion includes circulatory overload, transfusion-related acute lung injury (TRALI), the patient's underlying disease or a coincidental event unrelated to transfusion. Severe hypotension beginning soon after initiation of transfusion may be due to a hemolytic transfusion reaction, septic shock from administration of bacterially contaminated blood, or an unrelated clinical event. Fever usually accompanies the first two reactions but not anaphylaxis. Cutaneous manifestations are characteristically associated with anaphylaxis.

Transfusion must be discontinued immediately if an anaphylactic reaction is suspected. Treatment is the same as for other anaphylactic reactions: epinephrine, diphenhydramine and corticosteroids, in addition to appropriate fluid therapy and airway management.

Most anaphylactic and anaphylactoid reactions have no detectable cause. Although only a small percentage of allergic reactions are related to IgA deficiency in the recipient, laboratory evaluation should focus on the possibility that a patient is IgA deficient because of important implications for future transfusion management. Any patient who experiences an anaphylactic reaction should have a pretransfusion serum sample screened to quantify the IgA levels or to detect the presence of anti-IgA (i.e., observed in 30-50% of IgA deficient patients). Testing is performed in reference laboratories, and therefore, results may not be readily available. If anti-IgA is detected or IgA levels are undetectable, the diagnosis of IgA deficiency is confirmed and the patient must be informed, and only blood components from IgA donors should be administered. Until the diagnosis of IgA deficiency is confirmed, only washed or deglycerolized RBC or washed platelets should be administered. Once the

diagnosis is made, however, alloimmunized IgA deficient recipients should only be transfused with components from IgA-deficient donors.

### *Bacterial Contamination*

Bacteria present in stored blood can multiply and may elaborate toxins. Contamination during collection, processing or storage is possible but is more likely to arise from the phlebotomy site or a transient bacteremia associated with an unrecognized infection in the donor. Administration of a bacterially contaminated blood component may result in high fever, tachycardia, hypotension, chills, vomiting and diarrhea. Septic shock, oliguria and DIC can also occur in a subset of patients. Because platelets are stored at room temperature which facilitates bacterial growth, bacteremia is forty times more frequent following platelet administration than transfusion of refrigerated components. However, several fatalities have been reported following transfusion of RBC contaminated with *Yersinia enterocolitica*, a type of endotoxin-producing bacteria that proliferate at 4°C.<sup>73</sup>

### *Febrile Nonhemolytic Transfusion Reaction*

The most likely cause of fever in association with transfusion is FNHTR. The reported frequency of FNHTRs varies according to component, component age, leukocyte content, patient population and degree of surveillance. Overall, about 0.1 to 1 percent of RBC transfusions are associated with FNHTRs, but the incidence is higher in chronically transfused patients.<sup>73</sup> In the past, as many as 20 to 30 percent of platelet transfusions used to cause FNHTRs although more recent studies show significantly less incidence particularly with leukocyte reduced platelets.<sup>80</sup> These reactions usually develop when most of or the entire component has been transfused and are accompanied by chills and rigors. Other symptoms may include headache, nausea and a feeling of discomfort. In some cases, symptoms might be limited to chills and rigors without any fever present.

FNHTRs are immunologically mediated reactions involving leukocyte antibodies in the patient's plasma (stimulated by previous transfusions or pregnancy) and antigens on donor leukocytes, causing

release of endogenous pyrogens by the leukocytes. Cytokines released during component storage are also implicated in causing FNHTRs.<sup>81</sup> Leukocyte reduction of RBC prevents most FNHTRs but is less effective in preventing recurrent reactions associated with platelet transfusions. Pretransfusion prophylaxis and therapy of FNHTRs consist of an antipyretic such as acetaminophen and administration of meperidine for chills.

### *Transfusion-Related Acute Lung Injury (TRALI)*

At a death rate of 30-40 deaths per million units transfused, TRALI is currently the leading cause of transfusion-related death via FDA reporting mechanisms.<sup>70</sup> Clinical presentation of TRALI, in its severe form, is indistinguishable from adult respiratory distress syndrome (ARDS) and is characterized by acute onset (within minutes to 1-2 hours after transfusion), bilateral pulmonary infiltrates and hypoxia without evidence of CHF.<sup>82,83</sup> However, due to differences in the initiating insults and risk factors between TRALI and ARDS, some specific dissimilarities between the two entities exist. In comparison to ARDS, TRALI is characterized by a much shorter time interval between exposure to the precipitating risk factor (transfusion) and onset of clinical manifestations. TRALI resolves much faster and has a lower mortality rate when compared to ARDS. TRALI usually develops within 6 hours (most often less than 2 hours) of a transfusion, usually resolves within 24-48 hours, and has a mortality rate of approximately 5-10%; whereas, ARDS does not usually develop until at least 24 hours after exposure to one of its risk factors, has a duration often longer than 72 hours, and a mortality approaching 30-60%. Because of increasing awareness and identification of TRALI and reductions in the incidence of infectious and hemolytic complications of transfusions, TRALI is now a primary cause of transfusion-associated mortality reported to the FDA and has become a frequent cause of transfusion-related morbidity.<sup>84</sup> It can occur after the transfusion of a variety of blood components such as red blood cells, platelets and FFP but is most often seen after transfusion of the plasma-containing blood components such as FFP and platelets. Symptoms of TRALI can be confused with other transfusion-

and non-transfusion-related events such as anaphylaxis, hemolysis, circulatory overload and cardiac failure.<sup>85</sup> TRALI is believed to have been under-diagnosed and under-reported before, which might explain the great variation in the current risk estimates of 1 in 8,000 to 70,000 units transfused.<sup>73</sup>

Depending on the initiating factor in the transfused component and the inflammatory state of the pulmonary circulation, two different but at times complementary and overlapping pathogenic mechanisms are thought to cause TRALI: “the classical-antibody mediated” for most, and “the two-hit (inflammatory insult)” for some. Most cases of TRALI are due to passive transfer of donor-related anti-leukocyte antibodies directed at HLA or granulocyte-specific antigens on the patient’s leukocytes.<sup>86</sup> This promotes priming and activation of a patient’s granulocytes leading to their pulmonary sequestration and release of proteases, oxidants and leukotrienes which cause alveolar epithelial and microvascular endothelial damage resulting in increased permeability an ultimate development of non-cardiogenic pulmonary edema. The two-hit model of TRALI is similar to that which has been proposed to cause ARDS. In the case of TRALI, however, the specific causative agent in the blood component is unknown although there is growing evidence implicating a bioactive factors or white cell priming lipids: CD40 ligand released by platelets or several reactive lipid-like substances accumulating in red blood cells or platelets during storage. These compounds are referred to as biological response modifiers (BRM) and can be the first pulmonary insult but are more likely the second. The first insult or hit is generally systemic inflammatory condition secondary to major surgery, sepsis, trauma or pulmonary aspiration that causes activation of the pulmonary endothelium and polymorphonuclear lymphocytes (PMN) priming leading to their sequestration in the pulmonary vasculature. The second hit occurs when the primed PMNs are activated by the BRM in the transfused component. Therapy for TRALI is generally supportive and includes administration of high FIO<sub>2</sub>,

endotracheal intubation with mechanical ventilatory support in at least 70% of patients and either volume or vasopressor support of hemodynamics.

Suspected cases of TRALI should be reported to the hospital transfusion service to enable initiation of an appropriate investigation including testing of implicated donors for anti-leukocyte and anti-platelet antibodies and typing recipients for HLA antigens (i.e., via leukocytes in a pre-transfusion blood specimen or buccal swab technique). If donor leukocyte antibodies that react specifically to the patient's leukocytes are found, avoiding future transfusion of plasma-containing components from this donor is recommended. The patient, however, is not at an increased risk of future TRALI reactions with future transfusion.

#### *Posttransfusion Purpura (PTP)*

PTP is a rare disorder characterized by severe thrombocytopenia five to 10 days after transfusion in a patient sensitized by prior transfusion or pregnancy. In most cases, PTP follows administration of Red Blood Cells. The estimated risk is around 1 in 150,000 to 300,000 red cell units.<sup>73</sup> Platelet counts are often less than  $10 \times 10^9/L$ . Patients usually recover spontaneously, although corticosteroids and intravenous immune globulin may be administered. The pathogenesis is unclear, but PTP is presumably related to the development of a platelet-specific antibody in patients who are deficient of a common platelet antigen (e.g. PLA-1) following transfusion.

#### *Transfusion-Associated Graft-versus-Host Disease (TA-GVHD)*

TA-GVHD occurs when immunocompetent donor lymphocytes are transfused to an HLA-incompatible recipient or host (e.g. immunocompromised patients or patients receiving a blood donation from a relative) who is immunologically incapable of eliminating the donor cells. Among the

immunocompromised patients at risk are individuals with congenital cell-mediated immunodeficiencies or Hodgkin's disease, recipients of bone marrow transplants and patients receiving immunosuppressive therapy.<sup>87 88</sup> Immunocompetent recipients of directed donations from biologic relatives may also develop TA-GVHD. Clinical manifestations are usually evident within eight to 10 days after transfusion and include fever, skin rash, diarrhea, liver dysfunction and pancytopenia. Death usually occurs within three to four weeks secondary to bone marrow failure. Irradiation of blood components virtually eliminates the risk of TA-GVHD in susceptible patients.

### *Immunomodulation*

The beneficial immunomodulatory effects of allogeneic transfusion in improving renal allograft survival have been known for many years, but considerable controversy exists regarding the question of adverse immunomodulatory effects related to transfusion. Numerous retrospective reports suggest an increased incidence of postoperative infection and earlier recurrence of resected malignancies in transfused patients, but the same notion has not been confirmed by available controlled trials.<sup>89</sup> Critical evaluation of the reports has led some investigators to question whether transfusion causes these deleterious effects or whether the adverse effects are related to factors, such as the need to be transfused. Donor leukocytes are the prime suspect in immunomodulation. Leukoreduction may decrease postoperative infections in certain patient groups, especially those undergoing cardiac surgery.<sup>90,91</sup> At this time, circumstantial evidence suggests an association of allogeneic transfusion with infection and cancer recurrence, but a causal relationship has not been proven.

### *Other adverse events*

Other adverse events and complications of transfusions include alloimmunization, serologic reactions, volume overload, electrolyte (e.g. hyperkalemia) or acid/base abnormalities and

hemochromatosis. Transfusion of an incorrect blood component (not necessarily ABO-incompatible) is another risk associated with transfusions. Examples of this risk include erroneous transfusion of blood units with positive infection disease test results or issuance of allogenic blood to patient when autologous blood is available.<sup>92</sup>

## **MASSIVE TRANSFUSION**

Massive transfusion can be defined as the acute replacement of more than one blood volume or more than 10 units of PRBC within several hours.<sup>93,94</sup> A dynamic definition of massive transfusion, such as the transfusion of four or more red cell concentrates within one hour when ongoing need is foreseeable, or the replacement of 50% of the total blood volume within three hours, may be more appropriate in the acute clinical setting.<sup>95</sup> The most common clinical situation leading to massive transfusion is extensive trauma; however, it also may occur in non-trauma settings during surgical procedures causing large blood loss especially after cardiothoracic surgery. Beside surgery, blood transfusion is a main therapy option for the treatment of acute traumatic shock. However, in trauma patients, the ideal solution to manage hypovolemia and anemia involves administration of fresh whole blood since this approach restores not only oxygen carrying capacity and oxygen delivery but also hemostasis via maintenance of normal levels of coagulation factor and platelets. Fresh whole blood is very difficult to provide by the blood bank due to logistical and testing issues. The incorporation of blood transfusion in resuscitation protocols for trauma victims is supported in the Advanced Trauma Life Support (ATLS) guidelines of the American College of Surgeons.<sup>96</sup> However, massive transfusion affects multiple homeostatic functions of the body which are described in section 32.

### **32. What mechanisms lead to coagulopathy during massive transfusion?**

The etiology of coagulopathy during massive transfusion is multifactorial. Coagulation defects develop not only from dilution of platelets and coagulation factors when crystalloid, colloid and red blood cells are used to replace lost volume but also from hypothermia, tissue hypoperfusion with resultant lactic acidosis and other trauma-related events (e.g. DIC triggered by release of tissue factor from apoptotic cells).<sup>95</sup> Coagulopathy associated with massive transfusion is clinically characterized by the presence of microvascular bleeding or oozing from the mucosa, wound, and puncture sites. The development of acidosis, DIC, hypothermia and, rarely, a hemolytic transfusion reaction may accompany massive transfusion and complicate the ability to effectively manage the coagulopathy.<sup>97</sup> Thus, empiric formulas using ratios of various components to volume lost or administered are inadequate to treat or prevent coagulopathy related to massive transfusion. Treatment of the coagulopathy should include restoration of systemic perfusion, maintenance of normal temperature, resolution of acid-base abnormalities and blood component therapy when supported by abnormal laboratory tests in the setting of active bleeding.

### **33. Are prophylactic platelets and fresh frozen plasma indicated in massive transfusion?**

Platelets should not be routinely administered during massive transfusion.<sup>33,98</sup> While thrombocytopenia may develop in massively transfused patients, administration of platelets should be reserved for the patient exhibiting microvascular bleeding, and a platelet count less than  $50 \times 10^9/L$ . Platelet transfusion may be necessary for patients with intermediate platelet counts ( $50-100 \times 10^9/L$ ) if the risk for more bleeding is significant.<sup>33</sup> It should be noted, however, that prophylactic administration of platelets is not warranted but rather “pre-emptive” use is advocated. For example, if a patient is massively bleeding one does not wait until the platelet count drops to less than 50K or until the INR is greater than 2 to start to address the coagulopathy especially since it can take 30-45 minutes to prepare plasma (thaw) in the laboratory.

FFP also should not be administered prophylactically for massive transfusion.<sup>33,99</sup> In the massively transfused patient, clinical bleeding associated with coagulation factor deficiencies is unlikely until factor levels fall below 20 percent of normal. In the clinical setting, this usually does not occur until greater than one blood volume has been replaced and the PT and PTT are greater than 1.5 -1.8 times control values based on studies performed in the trauma and cardiac surgical settings.<sup>56,98,100,101</sup> Conversely, in a trauma patient with massive bleeding a rise in the PT may be a “late” sign that the patient is developing a severe dilutional coagulopathy.<sup>102,103</sup> In the event that the PT and PTT cannot be obtained in a timely fashion, FFP may be administered for correction of microvascular bleeding in patients transfused with more than one blood volume.<sup>33</sup>

The exact role of off-label use of recombinant activated factor VII to manage bleeding that cannot be controlled by conventional measures remains to be clarified. However, preliminary results from case reports and case series are promising.<sup>95</sup> Until more safety data is published, clinicians should use this agent judiciously as a “rescue therapy” in patients with life-threatening (i.e., > 1 liter/hour) bleeding that is unresponsive to routine hemostatic therapy (e.g. platelets, FFP, etc.) and does not have an identifiable surgical source.<sup>104</sup> For trauma patients presenting with exsanguinating hemorrhage, coagulopathy correction beginning with aggressive FFP administration early in pre-ICU phase may improve ICU resuscitation response and outcome.<sup>105</sup> It may be appropriate to include the administration of RBC, FFP and platelets at fixed ratio in early (pre-ICU) resuscitation protocols for bleeding trauma patients; however this practice has to be verified in a large scale clinical trial.<sup>106</sup> It has to be emphasized that once bleeding is controlled and the patient is hemodynamically stable, the transfusion of blood and blood components should be guided by bedside and laboratory tests as well as the clinical status of the patient.<sup>106</sup>

### **34. How should coagulation be monitored during massive transfusion?**

There is no single coagulation test that will give complete information on coagulation function during massive transfusion. The use of routine coagulation tests to evaluate protein coagulant activity or quantitative factor deficiencies such as PT, PTT and thrombin time, have not reliably predicted perioperative bleeding,<sup>107</sup> but they can identify patients with deficiencies of coagulation factors.<sup>56</sup> These standard laboratory tests along with platelet count and fibrinogen level should guide the component therapy. The bleeding time is not predictive of perioperative bleeding and is rarely accessible in the operating room setting.<sup>108</sup> The activated clotting time (ACT) is influenced by hypofibrinogenemia and coagulation factor deficiencies and this lack of specificity limits ACT as a useful test during massive transfusion.

Whole blood clotting analysis, as assessed with the Thromboelastograph® (TEG) and Sonoclot®, provides a dynamic picture of the entire clotting process. Both the TEG and Sonoclot® measure the viscoelastic properties of blood as it clots. These tests evaluate the development of a blood clot from the initial fibrin strands to eventual clot retraction or lysis. The clinical utility of use of a TEG during liver transplantation<sup>109</sup> and cardiac surgery<sup>51,110,111</sup> to guide component therapy has been demonstrated. Other emerging tests that assess qualitative platelet abnormalities (i.e., such as the PFA-100, Ultegra, Ichor) may be useful to identify patients who may benefit from platelet augmentation (e.g. platelet transfusion, DDAVP). The usefulness of TEG or Sonoclot® during massive transfusion has not been established.

### **35. What metabolic problems occur during massive transfusion?**

The potential metabolic problems resulting from blood transfusion are hyperkalemia, citrate toxicity, hypothermia, hypomagnesemia, acidosis and impaired oxygen-carrying capacity of hemoglobin.<sup>112-114</sup> Potassium increases in the plasma of stored blood as potassium leaves viable erythrocytes. After 21 days of storage, plasma potassium concentrations approach 25 to 30 mEq/L. However, hyperkalemia is rarely a problem in adults for two reasons: 1) there is very little plasma in Red Blood Cells and 2) the potassium that is present leaves the intravascular space of the recipient and rapidly moves intracellularly unless there is a starting hyperkalemic state as related to renal insufficiency. Current technology allows for blood infusion rates at greater than 500 mL/min. These infusion rates may limit the time available for potassium redistribution to occur without resulting in hyperkalemia.<sup>115</sup> Also, infants may receive disproportionately higher volumes of blood cells rapidly and will be at increased risk of acute hyperkalemia from stored blood. Washing the cells before administration removes the potassium. The electrocardiogram should be monitored in all patients for signs of electrolyte abnormality during rapid infusions. Hyperkalemia exacerbates the cardiovascular effects of hypocalcemia. Administration of calcium rapidly antagonizes hyperkalemia by promoting transfer of potassium into cells while administration of sodium bicarbonate, glucose/insulin and beta-2 agonists are also administered to lower blood potassium levels.

Citrate toxicity occurs when ionized calcium is significantly reduced by citrate present in anticoagulant preservative solutions. The liver rapidly metabolizes citrate, and endogenous calcium stores are released to help prevent a fall in ionized calcium. However, in states of shock, these mechanisms may be impaired. Citrate toxicity is potentiated by the rapid administration of large volumes of citrated blood components.<sup>116</sup> Low ionized calcium levels may cause hypotension, narrowing of the pulse pressure, increased cardiac filling pressures, gross muscle tremors and electrocardiogram changes (prolonged Q-T interval). Toxicity is enhanced by hypothermia and a

depressed hepatic function that slows the normal rate of citrate removal by the liver. Administration of exogenous calcium is indicated during massive transfusion when the measured ionized calcium is low and there is evidence of cardiovascular compromise (hemodynamic or prolonged Q-T interval) not attributable to other causes. Citrate also has an affinity for the magnesium ion; and the occurrence of hypomagnesemia in the setting of massive transfusion has been reported.<sup>112</sup>

Stored blood is acidic (pH of 6.6 to 6.9) due to the citric acid in the anticoagulant and the accumulation of carbon dioxide and lactic acid from erythrocyte metabolism.<sup>113</sup> The acid load resulting from transfusion is rapidly reversed in the presence of normal tissue perfusion. Patients with adequate perfusion are likely to become alkalotic as the lactate and citrate are metabolically converted to bicarbonate by the liver. However, monitoring of blood pH is helpful to ensure normal arterial pH since the acid-base response is variable during transfusion. Prophylactic administration of alkalinizing agents such as sodium bicarbonate or tris-hydroxymethyl aminomethane (THAM) is unnecessary and may cause serious alkalosis and hypernatremia.

The erythrocyte concentration of 2,3-diphosphoglycerate (2,3-DPG) decreases with storage, reducing the delivery of oxygen to the tissues (leftward shift of the oxyhemoglobin dissociation curve or to the confirmation shape change of the red cell from decreases in intracellular 2,3-DPG and ATP).<sup>113</sup> However, over a period of eight to 24 hours after transfusion, 2,3-DPG is restored to normal. Studies in healthy humans receiving massive transfusions reveal no evidence of impaired oxygen delivery. However, in patients with impaired blood flow to the heart, brain or other organs, a reduction in oxygen transport due to reduced 2,3-DPG could be deleterious. The consequences of massive transfusion are beyond the immediate coagulation and metabolic abnormalities. Massive transfusion has been

implicated as a cause of TRALI, modulation of the immune system (immunosuppression), GVHD and systemic inflammatory reaction.<sup>93</sup>

### **36. Is it necessary to utilize blood warmers during massive transfusion?**

When massive transfusion is required, hypothermia (temperatures below 35°C) is likely to occur. Low ambient temperature, large open wounds, initial infusion of room temperature fluids, and blood stored at 4°C are contributory factors.<sup>117</sup> The potential effects of hypothermia include ventricular dysrhythmias, shivering, increased oxygen consumption, cardiac arrest and citrate toxicity secondary to reduced metabolism of citrate and lactate. Hypothermia contributes to coagulopathy in the operating room by causing reversible platelet dysfunction, altering coagulation, and enhancing fibrinolysis. Unfortunately, the contribution of hypothermia to the hemorrhagic diathesis may be overlooked because coagulation testing is usually performed at 37°C.<sup>118</sup> Warming of blood, as well as all other fluids during massive transfusion are essential to prevent systemic hypothermia. Warming blood also enhances the intracellular transfer of potassium. High efficiency intravenous fluid warming units are required during rapid, large volume blood replacement.<sup>119</sup>

## **CARDIOVASCULAR AND TRANSPLANT SURGERY**

The hemostatic management of patients undergoing cardiac surgery is a complex issue because of the need to maintain a delicate balance between *anticoagulation* for cardiopulmonary bypass (CPB) and *hemostasis* after CPB. These two opposing processes must be managed carefully and modified with respect to the patient's hematologic status, time during cardiac surgery, and desired hemostatic outcome. During CPB, optimal anticoagulation dictates that coagulation is antagonized and platelets are prevented

from activating, so that microvascular clots do not form on the extracorporeal circuit. Following surgery, coagulation abnormalities, platelet dysfunction, and fibrinolysis occur and create a patient in whom hemostasis integrity must be restored. This complex system of anticoagulation with heparin, antagonism with protamine, and postoperative hemostasis therapy could not be performed without careful and accurate laboratory monitoring.<sup>120</sup> In cardiovascular surgery, transfusion practices should be guided by analysis of laboratory parameters and physiologic parameters such as those listed in section 16.

### **37. How should coagulation be monitored during and after cardiopulmonary bypass?**

Heparinization for cardiopulmonary bypass can be monitored using functional tests of anticoagulation and quantitative measures of the level of circulating heparin. The anticoagulant effect of heparin should be monitored functionally before placing the patient on CPB. The activated clotting time (ACT) is a clot-based assay performed on whole blood using an activator and an endpoint detection method. The ACT result may have an artifactual prolongation by hemodilution, hypothermia, and extreme degrees of thrombocytopenia, but despite its substantial limitations, it is still considered a gold standard for monitoring anticoagulation. Heparin concentration monitoring can be performed using an automated, whole blood protamine titration assay and a clot-based detection system. Heparin concentration monitoring is useful when heparin levels are low yet the ACT is prolonged due to other clinical conditions (sepsis, DIC, quantitative coagulation factor or platelet abnormality). The confirmation of heparin neutralization is also most accurately done using heparin concentration monitoring or an ACT assay that incorporates a heparin-neutralizing agent into it to serve as a control. (i.e. heparin-neutralized thrombin time, heparinase ACT).

### **38. How should transfusion in cardiac and complex vascular patients be directed?**

The [Society of Thoracic Surgeons Blood Conservation Guideline Task Force](#) has recommended that transfusion of hemostatic allogeneic blood products after cardiac surgery should be based upon laboratory parameters that are measured as part of a transfusion algorithm.<sup>121</sup> Clinical and physiologic parameters such as those listed in section 16 should also be used for transfusion decision. Transfusion algorithms coupled to point-of-care or laboratory-based testing have been studied in cardiac surgery and have been very successful in reducing transfusion of blood products.<sup>51,111,122-125</sup> The tests included in the algorithm should be those that most closely measure the hematologic abnormalities that are felt to be most common for that surgery. For example, tests of platelet number and/or platelet function are often studied first. The particular tests used in the algorithm are not as important as the careful and wise application of such algorithm. The thromboelastograph (TEG®), PFA-100® and point-of-care PT monitors are a few of the monitors that have demonstrated efficacy in cardiac surgery transfusion algorithms. Hemostasis management of patients undergoing cardiac transplantation is similar to that for any complex cardiac surgery. Many cardiac transplantation surgeries are re-operations and require explantation of a ventricular assist device. For these reasons, careful hemostasis monitoring is especially critical during and after cardiac transplantation.

Cardiac surgery in patients having recently ingested clopidogrel can result in excessive bleeding, hemorrhage, increased transfusion requirements, and excessive morbidity postoperatively.<sup>126,127</sup> This is due to the synergistic platelet defect of CPB plus the anti-aggregatory effects of the drug clopidogrel. Observational studies have shown excess morbidity associated with the use of clopidogrel prior to CPB, but do not support the empiric transfusion of platelet concentrates. The [Society of Thoracic Surgeons Blood Conservation Guideline Task Force](#) has recommended discontinuation of anti-platelet (e.g.

clopidogrel, IIb/IIIa antagonist) or antithrombotic (e.g. direct thrombin inhibitors, LMWH) agents at different time intervals prior to surgery based on their pharmacodynamic half-life.

### **39. How should transfusion in Liver transplantation patients be directed?**

Patients undergoing liver transplantation have a variety of coagulation abnormalities that render them hypocoagulable.<sup>128</sup> They have deficiencies and dysfunction of the proteases that participate in the coagulation cascade (i.e., coagulation factor, anticoagulant molecules), as many of these factors are made in the liver. Hepatic transplantation is also associated with hypersplenism and platelet sequestration leading to thrombocytopenia. Primary fibrinolysis is also common after reperfusion of the grafted liver. Liver transplant surgical patients can potentially consume a large volume of allogeneic blood product transfusions during and after surgery and may benefit from careful management with point-of-care coagulation testing. The TEG is the coagulation monitor that has been studied to the greatest extent and measures many aspects of the hemostatic system from coagulation to fibrinolysis.<sup>109</sup>

## **AUTOLOGOUS TRANSFUSION**

### **40. In which patients is preoperative autologous donation indicated?**

Although the medical indications for predonation of blood for autologous transfusion are limited, patients who might benefit from predonation of autologous blood include:

- those with multiple red blood cell antibodies,
- those with a rare blood phenotype,
- those who are scheduled for elective high blood loss procedures.

The collection of autologous blood should be based on the anticipated need for each patient, taking into account that patient's medical condition, the scheduled surgical procedure and the transfusion history of the particular procedure. Patients should not be encouraged to donate autologous blood components for surgical procedures such as routine cholecystectomies, routine hysterectomies, uncomplicated pregnancies or other cases in which there is very low or no likelihood of the patient requiring transfusion unless the patient has multiple alloantibodies and a rare RBC phenotype. The MSBOS (see section 2) can be used to help determine the expected transfusion needs for a given surgical procedure. Cases best suited for preoperative donations of autologous blood include major orthopedic surgical procedures — total knee replacement, total hip replacement and scoliosis correction. Also appropriate for preoperative autologous donation are major urologic and gynecologic oncology cases for which transfusion is anticipated.

Criteria used for accepting patients for autologous donation are less stringent than those used for selecting allogeneic donors. The AABB standards state that a patient may donate autologous whole blood if his or her level of hemoglobin is 11 g/dL or greater.<sup>21</sup> Although other screening criteria, such as age and weight, are left to the judgment of the patient's physician, young children, especially those under 45 kg, may need special consideration due to their smaller blood volumes. Patients who pre-donate blood for autologous transfusion should have the last donation no later than 72 hours prior to surgery to allow re-establishment of intravascular volume. Further, the patient should not have an active infection or bacteremia at the time of donation. Certain medical conditions may be considered contraindications to preoperative autologous blood donation. Patients with severe aortic stenosis, unstable angina and severe left main coronary artery disease are often disqualified for autologous donation. These patients may not tolerate a sudden shift in blood volume or a decrease in oxygen-carrying capacity (hemoglobin level) without adverse consequences. In addition, any patient with any active infection is deferred from donation to avoid re-infusion of bacterially contaminated blood.

Autologous transfusion is not without risk. Clerical errors can occur. Predonated blood can still be mislabeled and mistransfused or bacterially contaminated. Further, if the red cell volume is not expanded with erythropoietin, folic acid and iron therapy prior to surgery, the patient might become anemic by the time of surgery as a result of multiple autologous donations. The indications for transfusion of autologous blood are supposed to be the same as allogeneic blood but sometimes people use them more liberally due to reduced transfusion-related risks including infectious disease transmission and alloimmunization.<sup>33</sup> Use of autologous blood has reduced over the last several years possibly due to the public perception of increased safety of the allogeneic blood supply and its' high costs (Note: Autologous units transfused in the institution in which they were collected need not be tested for infectious disease markers.)

#### **41. What is acute normovolemic hemodilution?**

Acute normovolemic hemodilution (ANH) is a technique in which blood is collected from the patient prior to operative blood loss with simultaneous replacement of cell-free solutions to maintain intravascular volume and a normovolemic state. Utilization of ANH may reduce the need for and the potential risks associated with allogeneic blood while providing a source of fresh autologous whole blood for transfusion. In addition, the decrease in the patient's hematocrit and blood viscosity as a result of ANH potentially improves tissue perfusion and reduces intraoperative red cell loss (blood lost contains fewer red cells per unit volume). Despite 30 years of experience with ANH, the safety and efficacy of ANH is still actively debated.<sup>129</sup>

There is potential risk associated with a decrease in hemoglobin and subsequent reduction in arterial oxygen content ( $\text{CaO}_2$ ). The primary compensatory mechanism to maintain oxygen delivery to the tissues with ANH is an increase in cardiac output. With the oxygen content of the blood supply to the myocardium reduced and an augmented cardiac output increasing myocardial oxygen consumption, the most significant potential complication from ANH is myocardial ischemia.<sup>130</sup> However, these risks are

minimized with normovolemic hemodilution over pre-autologous donation since the systemic and myocardial oxygen consumption is reduced under general anesthesia.

Patient selection for ANH is based on a number of factors including expected blood loss (surgery where a T&C is needed), preoperative hemoglobin concentration and the relative absence of significant and poorly controlled cardiac, pulmonary, renal or hepatic disease.<sup>130</sup> In addition, the patient should be free of infection and have normal clotting function. Concerning expected blood loss, it should be anticipated that the patient will lose greater than or equal to 1500 mL or an equivalent of 30 percent of estimated blood volume.

Various formulas have been used to determine the amount of blood to be withdrawn to reach a desired hematocrit. While a linear formula fails to correct for the successive decrease in hematocrit accompanying hemodilution, a simplified formula has been developed that approximates the more accurate natural logarithm between the initial and final hematocrits as follows:<sup>131</sup>

$$\text{Volume to be removed} = \text{EBV} \times (\text{H}_0 - \text{H}_f) / \text{H}_a$$

EBV represents the patient's estimated blood volume;  $H_0$  is the patient's initial hematocrit;  $H_f$  is the final or desired hematocrit after blood withdrawal;  $H_a$  is the average of the initial and final hematocrits. The blood may be withdrawn from a central or large peripheral vein or an artery and collected in standard blood bags containing anticoagulant solution.

Crystalloid or colloid, or both, are infused simultaneously during blood withdrawal. When crystalloid is used, an amount approximately three times the volume of blood withdrawn must be infused due to the almost instantaneous redistribution of crystalloid into the extracellular, extravascular compartment. This carries the potential risk of acute fluid overload and tissue edema.<sup>130</sup> Colloid solutions remain in the intravascular space and may be infused in equal volume to the amount of blood

withdrawn. The collected units of blood may be stored at room temperature up to eight hours or at 1° to 6 °C for a maximum of 24 hours if storage at 1° to 6 °C is begun within eight hours of collection. Normovolemic hemodilution is frequently performed via the venous cannulae of the cardiopulmonary bypass circuit just prior to initiation of flow during cardiac surgical procedures. In these type of procedures (i.e., cardiac operations), the patient will also potentially benefit from a hemostatic perspective via preservation of coagulation proteins and platelets within the collected units.<sup>132</sup>

#### **42. When is intraoperative blood salvage indicated for autotransfusion?**

Intraoperative blood salvage and reinfusion is used in an effort to reduce allogeneic blood transfusion. It is indicated in a variety of surgical procedures whenever major blood loss is anticipated.<sup>133</sup> Intraoperative blood salvage usually becomes cost-effective when 1,500 mL or more of blood is collected; however, it does eliminate some of the risks of allogeneic blood transfusion (see sections 27 and 28), even when smaller volumes are salvaged and allogeneic blood can be avoided. It is also indicated if the patient has a rare blood type and adequate amounts of allogeneic blood cannot be found. Intraoperative blood salvage is often acceptable to Jehovah's Witnesses, provided the salvaged blood remains in continuity with the patient's circulation. When intraoperative blood salvage is utilized, the patient should be free from bacterial infection and the operative field from contamination by malignant cells. (*Note: Currently available red cell recovery instruments are not designed for direct re-infusion and do not have air detectors. Caution must be exercised to prevent fatal air embolism, and red cells from these devices should never be administered under pressure.*) A risk of blood salvage during obstetrics delivery as related to risk of amniotic fluid infusion.

Intraoperative blood salvage is typically accomplished with a semicontinuous flow device that utilizes special suction tubing that allows mixing of recovered blood with an anticoagulant solution. Blood is collected in a reservoir and then centrifuged to separate the blood components, and the red blood cells are washed and then directed to a collection bag for transfusion. Blood can also be

collected with canister systems and reinfused following washing or only filtration both intraoperatively and post-operatively. Other limitations or complications of cell salvage include:

- hemolysis via a dysfunctional centrifuge or use of high suction pressures (>150 mm Hg)
- inadequate removal of either cellular debris or anticoagulant via dysfunctional or low volume (< 3 bowel volumes) processing which can lead to either DIC, a generalized systemic inflammatory response or hypotension (i.e., with citrate)
- bleeding (i.e., with heparin) related to inadequate removal of blood thinner used,
- infection via contamination of disposable circuits or loss of platelets or coagulation factors if process volumes are extreme (> 2-3 liters) in the setting of use to process cardiotomy bleeding during cardiac surgery.

## **ARTIFICIAL OXYGEN CARRIERS (BLOOD SUBSTITUTES) (AOC) AND PHARMACOLOGIC ALTERNATIVES**

### **43. What oxygen-carrying blood substitutes are available?**

Although advances in transfusion medicine have improved the safety of administering donated blood components, transfusion-related risks persist. A safe substitute for the red blood cell therefore remains desirable. The development of clinically useful red cell substitutes (also called “oxygen therapeutic agents”) has mostly focused on **hemoglobin-based oxygen carriers (HBOCs)** and a class of compounds called **perflurochemicals (PFCs)**.

HBOC solutions have been developed from animal, recombinant and human sources. The potential advantageous of these agents involve use with trauma or battlefield scenarios, in patients who either refuse blood or who cannot get compatible blood (rare phenotypes or multiple alloantibodies) or as an adjunct with one or more of the following: normovolemic hemodilution, radiation therapy, as a contrast medium for image enhancement, with carbon monoxide poisoning or treatment for acute lung injury. Many studies demonstrate a substantial reduction in transfusion requirements when blood substitutes have been used with normovolemic hemodilution during cardiac surgery.<sup>134,135</sup> While promising, basic

problems related to HBOCs include the toxicity of hemoglobin solutions, a short half-life, increased vasoactivity (i.e., vasospasm) and a relatively high colloid oncotic pressure and affinity for oxygen. Initial trials of purified hemoglobin were plagued with many complications including renal dysfunction, which were partly attributed to free hemoglobin molecules in plasma. Modification of the hemoglobin molecules (i.e., polymerization, tetramer encapsulation, conjugation) was proposed to reduce these complications and aldehydes and other cross-linking reagents were used to make first-generation polymerized hemoglobin solutions.<sup>136</sup> Other advances have led to solutions with greater purity through elimination of stromal contaminants; a P50 near the normal range; increased half-life using conjugation with other macromolecules such as polyethylene glycol and a molecular size sufficiently large to prevent the osmotic diuresis that was seen with earlier solutions.<sup>136,137</sup> Some examples include PolyHeme®, Hemopure® and Hemospan®. While approved in some other countries, Hemopure® trial is on clinical hold in the US. Published results of a phase III clinical trial on PolyHeme® are expected in 2007 and Hemospan® is entering phase III clinical trial.<sup>136</sup> Concerns still exist, however, about the safety, side effects and efficacy of these newer products and these concerns must be resolved in the ongoing and coming clinical trials before any of the oxygen-carrying solutions will be approved for general use in humans. Other HBOCs such as hemoglobin vesicles and nanoparticles have been also proposed, but their development has been slowed by many complexities.<sup>136,138</sup>

PFCs are synthetic compounds that have high oxygen solubility. They contain no hemoglobin or proteins and transport oxygen dissolved in the plasma rather than bound to hemoglobin. The first-generation PFCs (e.g., Fluosol®) had limited usefulness due to a number of problems, including activation of complement, a short half-life and the necessity for concurrent administration of a high inspired oxygen concentration and it was withdrawn.<sup>137</sup> Second-generation emulsified PFCs such as Oxygent® have greater oxygen-carrying capacity, but Oxygent® use was found to be associated with neurologic complications and further research was suspended. It is a matter of debate however, if the observed complications were due to Oxygent or other trial-related factors.<sup>139</sup> Other variants of PFCs

have been developed and are under investigation, but the role of these compounds as temporary oxygen carriers remains to be defined.<sup>137</sup>

#### **44. What volume expanders are available?**

Normal saline and lactated Ringer's solution are the most commonly used volume substitutes. Noncrystalloid volume expanders currently available in the United States include albumin, hydroxyethyl starch, dextrans and purified protein fractions. All of these substances are effective volume expanders that distribute throughout the extracellular space and not solely in the intravascular space; however, they do not provide oxygen-carrying capacity and they can produce coagulopathy via dilution or via an acquired vWD state.<sup>140</sup> The debate over colloids versus crystalloids administration for volume expansion in surgery has persisted for over 40 years.

**Albumin**, a protein solution of approximately 95% albumin and 5% other plasma proteins, is available as a 5-percent or 25-percent solution and has been widely used for its oncotic properties. The 25-percent solution has an oncotic equivalent to five times that of plasma. Serum albumin is prepared from pooled human plasma and is heat-treated to eliminate viral and bacterial contamination. There have been no reports of cases of hepatitis or HIV transmission by albumin. Albumin (5-percent) can be used as a volume expander in patients with adequate oxygen-carrying capacity but should not be used to correct nutritional deficiencies. Some Jehovah's Witnesses will not accept albumin.

The safety of albumin use was seriously questioned when the Cochrane Injuries Group performed a meta-analysis on data from 30 randomized trials comparing the use of albumin with other fluid regimens for intravascular volume replacement in critically ill patients.<sup>141</sup> Excess mortality of 6.8% was identified in the patients that received albumin compared to other fluid therapy whereby suggesting the increased mortality was related to fluid therapy (relative risk of mortality 1.68; 95% confidence interval: 1.26, 2.23). As a result, the Food and Drug Administration (FDA) issued a Letter to Healthcare Providers expressing concern over the safety of albumin administration to critically ill patients.

Subsequently, the SAFE study, which was the largest randomized but not blinded controlled trial to date on the safety of albumin, has been published. The SAFE study found no difference in mortality rate of patients in the general intensive care unit (ICU) that received albumin versus normal saline (relative risk of mortality 0.99; 95% confidence interval: 0.91, 1.09).<sup>142</sup> There were 6997 critically ill study participants who were randomized to receive either 4% albumin or normal saline for intravascular fluid resuscitation. Secondary analysis of pre-specified subgroups of patients with ARDS, severe sepsis, and trauma also showed no differences concerning albumin or normal saline administration.

**Hydroxyethyl starch (HES)**, a synthetic polymer derived from the starch amylopectin, is available in a 6-percent solution in normal saline. HES is available in two forms in the United States, HES in normal saline, Hespan®, and HES in Lactated Ringers, Hextend®. HES has a large molecular weight and its volume expansion effect lasts 24 hours (equal to albumin), with trace amounts detectable in the circulation up to 17 to 26 weeks. It is recognized that HES can affect coagulation as evidenced by increases in PTT, PT and bleeding time and decreases in Factor VIII, fibrinogen and von Willebrand factor.<sup>143-145</sup> While a number of studies have found no increase in blood loss when HES is administered as compared to other colloids in non-cardiac surgical patients, , recent evidence demonstrates that HES administration was associated with increased bleeding in cardiac surgical patients especially if volumes exceed 15 mL/kg are administered.<sup>146</sup> As a result, the United States FDA required a new warning on the package insert for 6% HES in normal saline that states that this solution “is not recommended for use as a cardiac CPB pump prime, while the patient is on CPB or in the immediate period after the pump has been discontinued because of the risk of increasing coagulation abnormalities and bleeding in patients whose coagulation status is already impaired.”<sup>147</sup> There are other HES, gelatin and dextran formulations available outside of the USA which may not have the coagulation effects of the first generation, high molecular weight, HES currently used in the USA.<sup>148</sup> In a review of HES, the authors conclude that it is difficult to recommend a maximum safe dose because patient response may be idiosyncratic and published data do not support the 20 mL/kg safe guidelines for Hespan.<sup>149</sup>

**Dextrans**, large glucose polymers, are available as dextran 40 (molecular weight 40KD) or dextran 70 (molecular weight 70KD). Dextrans can interfere with platelet function, red cell function or blood crossmatching and are associated with the potential for anaphylaxis. Therefore, dextrans are rarely used as volume expanders. Promit®, dextran 1 (molecular weight 1KD), should be administered prior to dextran 40 or dextran 70 to reduce the risk of anaphylaxis. Dextran 1 acts as a hapten that binds with dextran 40 or dextran 70. Dextrans can improve microvascular circulation by decreasing blood viscosity and coating endothelial cells to minimize platelet and red blood cell aggregation.<sup>145</sup>

**Purified protein fractions (PPFs)** consist of 88 percent albumin as well as 12 percent globulin fractions not contained in albumin preparations. PPF is heat-treated like albumin to eliminate the risk associated with viral or bacterial contamination.

## **PHARMACOLOGIC MANIPULATION OF COAGULATION**

### **45. What drugs are available to promote hemostasis, and how are they used clinically?**

Research continues to find pharmacologic agents that may reduce blood loss and help in the management of coagulopathies. Pharmacologic adjuncts that have such a clinical application include: DDAVP; lysine analogues [epsilon-aminocaproic acid (EACA), tranexamic acid (TXA)] serine protease inhibitors (aprotinin); and recombinant human factor VIIa.

DDAVP was designed for use in the treatment of diabetes insipidus. It was created as an analogue of the antidiuretic hormone vasopressin but was found to affect coagulation: DDAVP causes the release of both components of the Factor VIII complex — Factor VIII:C (coagulant portion) and the von Willebrand factor (vWF) from vascular endothelial cells.<sup>150</sup> The released vWF consists chiefly of large multimers that are potent stimulants of platelet adhesion. DDAVP is helpful in the treatment of bleeding in patients with mild-to-moderate hemophilia A and may be given prophylactically to decrease surgical blood loss in these patients.<sup>150</sup> Because DDAVP releases preformed Factor VIII:C from

endothelial cells, it is most helpful in mild hemophilia patients who have a supply of Factor VIII to be released. Severe cases of hemophilia, who have less than 1 percent of normal Factor VIII:C activity, show little response to DDAVP. Patients with the Type I form of vWD (80 percent of the patients with vWD) present with a quantitative deficiency of vWF but with normal multimeric composition. These patients benefit from DDAVP therapy. Type IIA (low to normal plasma levels of vWF but decreased or absent high- and medium-weight vWF multimers) show a variable response. Type IIB patients sometimes develop a transient severe thrombocytopenia due to extreme platelet aggregation mediated via release of very high molecular weight multimers; DDAVP is contraindicated in these patients. DDAVP is not effective in type III vWD patients and those with severe forms of type I and II. Benefits and limitation of DDAVP therapy in vWD are being further evaluated in a number of studies.<sup>151</sup>

Although DDAVP can shorten the bleeding time in patients with uremia,<sup>152</sup> widespread use of recombinant erythropoietin has made this abnormality of hemostasis much less frequent than it was previously since increased hematocrit results in increased platelet and vessel wall interaction.<sup>153</sup> In 1986, Salzman et al.<sup>154</sup> demonstrated that DDAVP reduced blood loss and transfusion requirements by approximately 30% compared to placebo during complex cardiac surgery. Unfortunately, clinical benefit of DDAVP in reducing blood loss and transfusion requirement in cardiac and non-cardiac surgeries in patients without pre-existing coagulation disorders has not been confirmed in meta-analyses.<sup>155</sup> Overall, available evidence does not support empiric use of DDAVP in patients without bleeding disorders undergoing surgery.

DDAVP has few side effects. If given rapidly by IV administration, it can produce hypotension via release of endothelial prostacyclin, and because of its antidiuretic hormone (ADH)-like activity, DDAVP may induce hyponatremia. Theoretically, DDAVP could lead to thrombotic events due to its enhancement of platelet adhesion. Increased risk of myocardial infarctions has been reported in some meta-analyses,<sup>156</sup> but not in others.<sup>157</sup> Nonetheless, use of DDAVP in patients with ischemic heart disease should be cautioned.

The lysine analogues and aprotinin are helpful in controlling bleeding from the action of plasmin, the fibrinolytic enzyme produced by the conversion of plasminogen to plasmin by plasminogen activators. Therefore, these agents had been expected to be useful in a variety of conditions or procedures that are associated with either 1) excess fibrinolysis, such as surgery involving CPB or liver transplantation, or 2) involve tissues in the body that contain high concentrations of tissue plasminogen activator.

The lysine analogues and aprotinin have been used in cardiac surgery for a number of years and have been shown to decrease blood loss and transfusion requirements.<sup>156,158-162</sup> Although the initial rationale for their use was based on a belief that CPB-induced hemostatic defects were primarily due to increased fibrinolysis, subsequent investigation has demonstrated that platelet dysfunction plays a significant role in the coagulopathy associated with CPB as well. Of the commonly available agents, aprotinin is the only agent FDA approved, the most expensive, and there were early reports of a possible increase in early saphenous vein graft closure in patients undergoing reoperative CABG associated with aprotinin therapy.<sup>163</sup> However, a large randomized trial involving over 800 patients and use of postoperative catheterization to evaluate graft patency only showed a small increase in vein graft occlusion by aprotinin which was not significant when all covariates were included in a multivariate analysis.<sup>164</sup> Although there is no evidence of an increase in thrombotic complications when either EACA or TXA is administered to patients undergoing cardiac surgery, results from several of the meta analyses revealed that there was a trend for either an increase in myocardial infarction or death with either half-dose aprotinin or EACA; these observations support the notion that there may be an undiagnosed subset of patients with hypercoagulability who may be at risk for thrombotic complications in the setting of inhibition of fibrinolysis, an important clot breakdown pathway.<sup>165</sup>

Antifibrinolytic agents have been also employed to decrease blood loss during surgical procedures that involve tissues of the body that contain high concentrations of tissue plasminogen activator.

Release of tissue plasminogen activator increases local fibrinolysis (plasmin production) and bleeding. Tissue plasminogen activator is found in high concentration in the saliva of the mouth, in the brain, in gastric mucosa and in the prostate gland. The antifibrinolytic agents have been employed in hemophilia patients undergoing dental surgery, in patients with a subarachnoid hemorrhage to prevent rebleeding, in those patients with gastritis or peptic ulcer disease, and in those undergoing surgery on the prostate gland to decrease bleeding. Excellent results are obtained in the hemophilia patients undergoing dental surgery in which the antifibrinolytic mouthwashes dramatically reduce perioperative bleeding.<sup>166</sup>

The two synthetic antifibrinolytic lysine analogues EACA and TXA bind reversibly to both the precursor molecule, plasminogen, and to plasmin, inducing conformational changes in both. Binding to plasminogen blocks the ability of plasminogen to bind to fibrin and its enzymatic conversion to plasmin. Binding to plasmin can displace or prevent this molecule from binding to fibrinogen or a fibrin surface. Therefore, these antifibrinolytic agents can prevent the proteolytic digestion of fibrinogen to fibrin and, likewise, of fibrin to fibrin degradation products as well as preserve GP Ib receptors, Factors V, VIII and fibrinogen which are consumed by plasmin. Effects of TXA is more potent and long-lasting than EACA in *in vitro* and it is generally used more widely.<sup>167</sup> More recent studies have confirmed that prophylactic administration of TXA (and to less extent EACA) can reduce blood loss and/or transfusion requirement in cardiac,<sup>167,168</sup> liver<sup>169</sup> and orthopedic<sup>170</sup> surgeries. Their low cost and rare risks and side effects make lysine analogues (particularly TXA) attractive prophylactic regents to promote hemostasis in surgeries.

Aprotinin, isolated from bovine lung tissue, is a naturally occurring inhibitor of serine protease enzymes. Mechanism of action of aprotinin is complicated and still under investigation. It has been suggested that by binding to plasmin, aprotinin prevents the degradation of fibrin and fibrinogen, and it may also help to preserve platelet function by preventing plasmin-induced degradation of platelet glycoprotein 1b, which is the platelet receptor for vWF. In addition, at higher doses aprotinin also

inhibits tissue and plasma kallikrein. Because kallikrein participates in contact activation of Factor XII, inhibition by aprotinin would decrease the amount of thrombin generated and effectively produce a weak anticoagulant effect. Thrombin is a powerful platelet aggregator, and therefore, aprotinin may exert a protective effect on platelet function by two different mechanisms.

Several meta-analysis have confirmed aprotinin benefits in reducing blood loss and transfusion in cardiac surgery based on available evidence with a distinct advantage of this agent with respect to statistically reducing reexploration for bleeding and at least some of them demonstrating a superiority with respect to a reduction in either blood loss or transfusion.<sup>162,171</sup> A more recent study by the same group has demonstrated aprotinin superiority over lysine analogues in reducing blood loss and transfusion.<sup>172</sup> Similar benefits have been reported in orthopedic and (with less certainty) liver surgeries.<sup>167</sup> In spite of abundant evidence to support aprotinin benefits, recent safety concerns have shadowed its widespread use. Aprotinin was believed to be generally well-tolerated with major adverse reaction (hypersensitivity) occurring rarely (but increased risk if used repeatedly or within 12 months of previous exposure). However, recent studies have reported increased risk of renal dysfunction, heart attack and stroke in patients receiving aprotinin.<sup>173,174</sup> However, data from the US database encompassing over 4000 randomized patients (Bayer database via web site) as well as data from another recent analysis involving 23,000 patients<sup>175</sup> do not support their findings. Given all these data, FDA has recommended that use of aprotinin be limited to situations where decreased blood loss is necessary in management of the patients and outweighs the potential risks and perhaps judicious use in patients at increased risk for renal complications until more studies are performed. Also, patients receiving aprotinin should be carefully monitored for toxic effects in the kidneys, heart and brain until further evidence becomes available.<sup>176</sup>

Off-label use of recombinant human factor VIIa (rFVIIa) to control bleeding has been rising recently. While rFVIIa is currently indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX or for patients with hereditary Factor VII

deficiency, anecdotal reports suggest its usefulness as a hemostatic agent in management of intractable bleeding in trauma, obstetrics and surgical patients with coagulopathies. Use of rFVIIa as a prophylactic agent to prevent surgical bleeding in patients without pre-existing coagulopathies is controversial.<sup>167</sup> Concerns have been expressed about its potential to cause unwanted thromboses, especially in patients who are thrombophilic. According to a recent consensus panel, off-label use of rFVIIa was rated appropriate only in limited circumstances involving life-threatening bleeding when significant clotting factor or platelet replacement has failed after cardiac, thoracic aortic, or spinal surgery; hepatic resection; hysterectomy; or postpartum bleeding.<sup>104</sup> Other possible appropriate situations include severe multiple trauma (with unsuccessful surgery and blood replacement), nontraumatic intracranial bleeding within 4 hours of symptom onset and traumatic intracranial bleeding associated with anticoagulant use and hematoma expansion. While rise in off-label use of rFVIIa is expected to continue, randomized controlled trials are needed to evaluate its efficacy in preventing blood loss in routine surgeries as well as to adjust dose and timing of administration as well as to evaluate cited concerns regarding safety.<sup>104,177</sup> Considering its rather high cost, cost analyses are also required.

#### **46. What topical hemostatics are available and how are they used clinically?**

There are a variety of commercially available topical hemostatic agents such as absorbable gelatin sponge,<sup>178</sup> collagen based materials,<sup>179</sup> fibrin<sup>180</sup> and oxidized cellulose.<sup>181</sup> Absorbable gelatin sponge (Gelfoam), microfibrillar collagen (Avitene) and oxidized cellulose (Surgicel) are the topical hemostatic agents in widest use.<sup>182</sup> Topical hemostatic agents are of great value to significantly reduce bleeding complications. They are applied when cautery, ligature, or other conventional hemostatic methods are impractical or ineffective.<sup>183</sup>

An ideal hemostatic agent would possess several characteristics. This agent should have a simple, independent mechanism of action, a long shelf-life, easy storage requirements, and should be immediately active. It should have no allergic, anaphylactic, infectious, or toxic potential. It should elicit minimal inflammatory reactions since they can cause granuloma formation. It should effectively treat even severe bleeding and be effective in patients on anti-platelet and anti-coagulant medications. This has been difficult to achieve. Fibrin sealant may be a better topical hemostatic agent in patients undergoing reoperative cardiac surgery<sup>184</sup> and may reduce allogeneic blood transfusions in cardiac surgical patients.<sup>185</sup>

There are several complications associated with the use of topical hemostatic agents of which anesthesiologist should be aware. Local hemostats may absorb body fluid of several times their weight and expand postoperatively. In April 2004, the FDA issued a public health notification of the possible development of paralysis after the use of absorbable hemostatic agents. In all cases the agent was left on or near a “bony neural space,” which resulted in compression of the spinal cord or other neural structures.<sup>186</sup> Another important safety concern is misadministration of topical hemostatic agents. Several deaths have resulted from intravenous administration of topical thrombin.<sup>187</sup>

Many topical hemostatic agents contain protein and allergic reactions can result. The antigenicity of topical collagen is known to be low, but the incidence of allergic reactions was reported as 3.0%.<sup>183</sup> To avoid the risk of human viral transmission, all primarily thrombin compounds available in the United States are bovine derived.<sup>188</sup> These bovine preparations contain bovine prothrombin, thrombin, and a small amount of factor V. Exposure can result in anti-bovine and anti-human antibodies to prothrombin, thrombin, and factor V which would decrease the efficacy of the agent at subsequent dosing and result in life-threatening bleeding as related to antibodies that develop to factor V or

thrombin after re-exposure.<sup>188</sup> These complications may be attenuated with the use of a new recombinant form of thrombin.

Several topical hemostatic agents have compounds that produce either exothermic reactions or otherwise damage tissues. A granular mineral hemostatic agent used in bandages (QuikClot™) has been shown to induce thermal injury to tissues.<sup>189</sup> BioGlue® is a surgical adhesive composed of purified bovine serum albumin that cross-links with glutaraldehyde. It targets tissue proteins independent of the clotting cascade and can damage the tissues upon which it is applied. BioGlue® is FDA approved for topical hemostasis in aortic dissection.

Overall, topical hemostatic agents augment the control of bleeding in the surgical patient and are an important and necessary tool in many surgical procedures. The majority of agents have very few complications.

## **SPECIAL CONSIDERATIONS**

### **47. How should transfusion in Jehovah's Witnesses be directed?**

The management of Jehovah's Witnesses patients provides special challenges. Members of this religious faith have deep convictions against accepting transfusion of blood, and blood components. Many will allow the use of (non-blood-prime) cardiopulmonary bypass, dialysis, or similar equipment if the extracorporeal circulation is uninterrupted. The decision on the use of minor blood components and autologous intraoperative cells salvage blood for Jehovah's Witnesses has long been understood to be left to the individual. The Watchtower Society in 2000 issued a directive stating that the organization would no longer disfellowship members who did not comply with the policy of refusal of blood.<sup>190</sup> The official JW publication, *Watchtower*, defined the "primary components" of blood as red cells, white cells, plasma, and platelets.<sup>191</sup> Members of the Jehovah's Witnesses faith were instructed to continue to refuse transfusion of these "primary components," but individual believers could decide for themselves whether to accept processed fractions of the "primary components." Examples of processed

fractions of the "primary components" include but are not limited to: cryoprecipitate, antithrombin III concentrate and albumin.<sup>192</sup> As a consequence, it is important to discuss with the individual patient what processed fractions of the "primary components" and what procedures (including the use of intraoperative cell salvage) are acceptable and document this discussion. Use of other pharmaceutical agents to prevent bleeding along with isovolemic hemodilution should be considered. If time permits, optimizing the patient's hemoglobin with erythropoietin and iron would also be desirable.

#### **48. How should transfusion in patients with sickle cell disease be directed?**

Sickle cell disease (SCD) is the most prevalent inherited hemoglobinopathy in the United States.<sup>193</sup> Transfusion of blood is a critical part of the multidisciplinary approach necessary in the management of patients with SCD, especially for surgical procedures. SCD is a hemoglobin structure disorder where glutamic acid at the sixth residue of the  $\beta$  chain of hemoglobin is substituted by valine. This results in the formation of a poorly soluble hemoglobin tetramer ( $\alpha_2/\beta_2^S$ ). There are a variety of sickle cell syndromes, such as homozygosity for HbS (the most common) and symptomatic heterozygous states, including HbSC, HbS $\beta$ -thalassemia, and HbSO<sub>Arab</sub>. For all of these disorders, the abnormal hemoglobin molecules associate with each other resulting in the formation of paracrystals within the red blood cells and thus fundamentally altering the cell membrane structure. The formation of paracrystals results in the typical crescent or sickle-shaped appearance owing to deformation by hemoglobin polymers formed while hemoglobin is in the deoxygenated state. SCD causes anemia and vasculopathy that has multiple clinical manifestations. The vasculopathy of SCD results from the increased whole blood viscosity with adherence of red blood cells to the endothelial surface. This results in vaso-occlusion and activation of the coagulation cascade and additional adhesion molecules. The major sources of morbidity and mortality related to SCD are severe anemia, infections, acute painful syndromes, acute chest syndrome, and organ failure.

The indications for blood transfusion in SCD have the common goals of increasing oxygen-carrying capacity lowered by the anemia of SCD and improving end-organ perfusion by decreasing the

proportion of circulating HbS cells. Preparation for major surgery requiring general anesthesia is a common indication for transfusion. The most common operations performed in SCD patients are orthopedic procedures, cholecystectomies, and splenectomies. Serious complications have been reported in as many as 67% of SCD surgical patients, especially after hip replacement.<sup>194</sup> Major surgeries requiring general anesthesia may induce postoperative vaso-occlusive complications and death. In the Cooperative Study of Sickle Cell Disease, 12 deaths occurred among 717 patients who underwent over 1000 surgical procedures.<sup>195</sup> Of the 12 patients who died, 11 had been transfused before surgery, 10 were homozygous for HbS, and all had intra-abdominal surgeries. Use of regional anesthesia was associated with more complications than general anesthesia. A prospective randomized trial comparing aggressive transfusion regimen designed to decrease the hemoglobin S level to less than 30 percent versus conservative regimen designed to increase the hemoglobin level to 10 gm / dL prior to cholecystectomy in SCD patients showed no difference in the incidence of SCD complications.<sup>196</sup> An even larger study of 604 operations in which two groups of SCD patients were prospectively assigned to the aggressive or conservative blood transfusion regimen demonstrated no statistically significant difference in the number of serious complications occurring in the two groups (31% in the aggressive group and 35% in the conservative group).<sup>197</sup> Despite the above data and the risk of alloimmunity secondary to multiple exposure to transfusions, published guidelines for the perioperative prophylactic transfusion of red blood cells need to be reviewed and placed in this context.<sup>198</sup> However, red cell exchange transfusion to reduce Hgb S levels to 30% should be considered in patients at high risk for vasocclusive complications who are undergoing high risk procedures. Availability of compatible blood for these patients is essential and may be problematic since many of these patients have developed alloantibodies related to their extensive transfusion history.

#### **49. How should coagulation testing be used to guide transfusion therapy?**

There is growing concern that the blood collection industry may not be able to meet the needs of patients that need blood. Delays in elective surgical procedures at many institutions have occurred throughout the United States due to shortages of blood products.<sup>199</sup> Multiple consensus conferences

and specialty society task forces on blood transfusion therapy have advocated the use of coagulation tests to guide non-red blood cell and red blood cell transfusions,<sup>33</sup> yet according to a recent survey of anesthesiologists this still may not be commonly done.<sup>200</sup> This survey demonstrated that a major reason that these tests are not done is the time it takes for the test results to become available, the tests are not available at their institution and the long time required for blood components preparation. Point of care testing of coagulation allows rapid test results to be available for clinical decision making. ( For discussion of many of these tests see sections 23, 33, 34, 38,39).

A large percentage of allogeneic blood is transfused in the operating room, especially to cardiac surgery and liver transplant patients<sup>201,202</sup> with 20% of blood transfusions thought to be inappropriate.<sup>203</sup> In the “ASA Practice guidelines for perioperative blood transfusion and adjuvant therapies,”<sup>33</sup> the task force recommended that “A visual assessment of the surgical field should be jointly conducted by the anesthesiologist and surgeon to determine whether excessive microvascular bleeding (i.e., coagulopathy) is occurring.” The [Society of Thoracic Surgeons Blood Conservation Guideline Task Force](#) has recommended that transfusion of hemostatic allogeneic blood products after cardiac surgery should be based upon the existence of microvascular bleeding and laboratory parameters that are measured as part of a transfusion algorithm.<sup>121</sup> Clinical and physiologic parameters such as those listed in section 16 should also be used for transfusion decisions. Six prospective randomized trials compared the use of transfusion algorithms to clinical judgment for administration of non-red blood cell components in cardiac surgery.<sup>51,111,122-125</sup> Each study used different algorithms with different coagulation tests but five of the six studies demonstrated reduction of allogeneic blood exposure with the use of a transfusion algorithm. Two of the studies demonstrated a reduction of blood loss in the intensive care unit in addition to reduced allogeneic blood exposure.<sup>111,122</sup>

## GLOSSARY OF ABBREVIATIONS

2,3-DPG	2,3-dishospyhoglycerate
ACT	activated clotting time
ADH	antidiuretic hormone
AHG	antihuman globulin
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANH	acute normovolemic hemodilution
anti-HBc	antibody to hepatitis B core antigen
anti-HCV	antibody to hepatitis C virus
anti-HTLV-I/II	antibody to human T-cell lymphotropic virus type I/II
aPPT	activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ATIII	antithrombin III
CABG	coronary artery bypass graft
CHF	congestive hearth failure
CMV	cytomegalovirus
CPB	cardiopulmonary bypass
CPD	citrate, phosphate, dextrose (solution)
CPDA-1	citrate, phosphate, dextrose-adenine (solution)
C/T	crossmatch-to-transfusion (ratio)
DDAVP	1-desamino-8-d-arginine vasopressin (desmopressin)
DIC	disseminated intravascular coagulopathy
EACA	epsilon-aminocaproic acid
FDA	Food and Drug Administration
FFP	fresh frozen plasma

FNHTR	febrile nonhemolytic transfusion reaction
HAM	HTLV-I-associated myelopathy
HBOC	hemoglobin-based oxygen carrier
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HES	hydroxyethyl starch
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HTLV-I/II	human T-cell lymphotropic virus type I/II
HTR	hemolytic transfusion reaction
IgA	immunoglobulin A
PFC	perflurochemical(s)
PMN	polymorphonuclear lymphocytes
PPF	purified protein fraction
PRP	platelet-rich plasma
PT	prothrombin time
PTP	posttransfusion purpura
PTT	partial thromboplastin time
Q-T	from QRS complex to end of T wave (interval)
rFVIIa	recombinant human factor VIIa
SCD	sickle cell disease
STS	serological test for syphilis
T&S	type and screen
TA-GVHD	transfusion-associated graft-versus-host disease
TEG	Thromboelastograph®
TP	thawed plasma

TRALI	transfusion-related acute lung injury
TSP	tropical spastic paraparesis
TXA	tranexamic acid
vWd	von Willebrand's disease
vWf	von Willebrand's factor

## REFERENCES

1. Silva M: Standards for Blood Banks and Transfusion Services, 24th Edition. Bethesda, MD, AABB, 2006
2. Saxena S, Shulan I: Resurgence of the blood utilization committee. *Transfusion* 2003; 42: 998-1006
3. Sherman L: Legal issues in blood banking. Elements of informed consent. *Clin Lab Med* 1996; 16: 931-46
4. Thaler M, Shamiss A, Orgad S, Huszar M, Nussinovitch N, Meisel S, Gazit E, Lavee J, Smolinsky A: The role of blood from HLA-homozygous donors in fatal transfusion-associated graft-versus-host disease after open-heart surgery. *N Engl J Med* 1989; 321: 25-8
5. Brecher M, Taswell H, Clare D, Swenke P, Pineda A, Moore S: Minimal-exposure transfusion and the committed donor. *Transfusion* 1990; 30: 599-604
6. Stokol T: Blood component production. Ithaca, NY, Cornell University, Clinical Pathology, College of Veterinary Medicine, 2007
7. Lumadue J, Boyd J, Ness P: Adherence to a strict specimen-labeling policy decreases the incidence of erroneous blood grouping of blood bank specimens. *Transfusion* 1997; 37: 1169-72
8. Shulman I, Downes K, Sazama K, Maffei L: Pretransfusion compatibility testing for red blood cell administration. *Curr Opin Hematol* 2001; 8: 397-404
9. Sazama K: Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion* 1990; 30: 583-90

10. Manno C, Hedberg K, Kim H, Bunin G, Nicolson S, Jobes D, Schwartz E, Norwood W: Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. *Blood* 1991; 77: 930-6
11. Triulzi D, Gilmor G, Ness P, Baumgartner W, Schultheis L: Efficacy of autologous fresh whole blood or platelet-rich plasma in adult cardiac surgery. *Transfusion* 1995; 35: 627-34
12. Repine T, Perkins J, Kauvar D, Blackburne L: The use of fresh whole blood in massive transfusion. *J Trauma* 2006; 60: S59-69
13. Valeri C, Ragno G, Pivacek L, Srey R, Hess J, Lippert L, Mettillie F, Fahie R, O'Neill E, Szymanski I: A multicenter study of in vitro and in vivo values in human RBCs frozen with 40-percent (wt/vol) glycerol and stored after deglycerolization for 15 days at 4 degrees C in AS-3: assessment of RBC processing in the ACP 215. *Transfusion* 2001; 41: 933-9
14. Valeri C, Srey R, Tilahun D, Ragno G: The in vitro quality of red blood cells frozen with 40 percent (wt/vol) glycerol at -80 degrees C for 14 years, deglycerolized with the Haemonetics ACP 215, and stored at 4 degrees C in additive solution-1 or additive solution-3 for up to 3 weeks. *Transfusion* 2004; 44: 990-5
15. Lane T: Leukocyte reduction of cellular blood components. Effectiveness, benefits, quality control, and costs. *Arch Pathol Lab Med* 1994; 118: 392-404
16. Alonso-Echanove J, Sippy B, Chin A, Cairns L, Haley R, Epstein J, Richards M, Edelhauser H, Hedberg K, Kuehnert M, Jarvis W, Pearson M, The Transfusion-Associated Red Eye Syndrome Study Group. Nationwide outbreak of red eye syndrome associated with transfusion of leukocyte-reduced red blood cell units. *Infect Control Hosp Epidemiol* 2006; 27: 1146-52
17. US Food and Drug Administration (FDA). Update on: Leukocyte Reduction of Blood and Blood Components Public Workshop. Rockville, MD, FDA, 2005

18. van de Watering LM, Hermans J, Houbiers JG, van den Broek PJ, Bouter H, Boer F, Harvey MS, Huysmans HA, Brand A: Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. *Circulation* 1998; 97: 562-8
19. Bilgin YM, van de Watering LM, Eijnsman L, Versteegh MI, Brand R, van Oers MH, Brand A: Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. *Circulation* 2004; 109: 2755-60
20. Wallis JP, Chapman CE, Orr KE, Clark SC, Forty JR: Effect of WBC reduction of transfused RBCs on postoperative infection rates in cardiac surgery. *Transfusion* 2002; 42: 1127-34
21. American Association of Blood Banks. *Blood Transfusion Therapy: A Physician's Handbook.*, 8th Edition. Bethesda, MD, American Association of Blood Banks, 2005
22. Grabmer C, Holmberg J, Popovsky M, Amann E, Schönitzer D, Falaize S, Hanske H, Pages E, Nussbaumer W: Up to 21-day banked red blood cells collected by apheresis and stored for 14 days after automated wash at different times of storage. *Vox Sang* 2006; 90: 40-4
23. Weiskopf R, Schnapp S, Rouine-Rapp K, Bostrom A, Toy P: Extracellular potassium concentrations in red blood cell suspensions after irradiation and washing. *Transfusion* 2005; 45: 1295-301
24. Moroff G, Holme S, AuBuchon J, Heaton W, Sweeney J, Friedman L: Viability and in vitro properties of AS-1 red cells after gamma irradiation. *Transfusion* 1999; 39: 128-34
25. Rivet C, Baxter A, Rock G: Potassium levels in irradiated blood. *Transfusion* 1989; 29: 185
26. Goodnough L, Brecher M, Kanter M, AuBuchon J: Transfusion medicine, part II: Blood conservation. *N Engl J Med* 1999; 340: 525-33
27. Shander A, Goodnough L: Objectives and limitations of bloodless medical care. *Curr Opin Hematol* 2006; 13: 462-70

28. Wiesen A, Hospenthal D, Byrd J, Glass K, Howard R, Diehl L: Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. *Ann Intern Med* 1994; 121: 278-30
29. NIH Consensus Conference. Perioperative red blood cell transfusion. *JAMA* 1988; 260: 2700-3
30. Weiskopf R, Viele M, Feiner J, Kelley S, Lieberman J, Noorani M, Leung J, Fisher D, Murray W, Toy P, Moore M: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998; 279: 217-21
31. Weiskopf R, Feiner J, Hopf H, Viele M, Watson J, Lieberman J, Kelley S, Toy P: Heart rate increases linearly in response to acute isovolemic anemia. *Transfusion* 2003; 43: 235-40
32. Metivier F, Marchais S, Guerin A, Pannier B, London G: Pathophysiology of anaemia: focus on the heart and blood vessels. *Nephrol Dial Transplant* 2000; 15 Suppl 3: 14-8
33. 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* 2006; 105: 198-208
34. Stehling L, Zauder H: How low can we go? Is there a way to know? *Transfusion* 1990; 30: 1-3
35. Hebert P, Wells G, Blajchman M, Marshall J, Martin C, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340: 409-417
36. Hebert P, Yetisir E, Martin C, Blajchman M, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I: Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001; 29: 227-34

37. Madjdpour C, Spahn D, Weiskopf R: Anemia and perioperative red blood cell transfusion: a matter of tolerance. *Crit Care Med* 2006; 34(5 Suppl): S102-8
38. Bickell W, Wall M, Pepe P, Martin R, Ginger V, Allen M, Mattox K: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994; 331: 1105-9
39. McCunn M, Dutton R: End-points of resuscitation how much is enough? *Curr Opin Anaesthesiol* 2000; 13: 147-53
40. Pineda A, Rippeteau N, Clare D, Bunkowske B: Infusion flow rates of whole blood and AS-1-preserved erythrocytes: a comparison. *Mayo Clin Proc* 1987; 62: 199-202
41. Ryden S, Oberman H: Compatibility of common intravenous solutions with CPD blood. *Transfusion* 1975; 15: 250-5
42. Brown W, Kim B, Weeks D, Parkin C: Physiologic saline solution, Normosol R pH 7.4, and Plasmanate as reconstituents of packed human erythrocytes. *Anesthesiology* 1978; 49: 99-101
43. Wortham S, Ortolano G, Wenz B: A brief history of blood filtration: clot screens, microaggregate removal, and leukocyte reduction. *Transfus Med Rev* 2003; 17: 216-22
44. Snyder E, Bookbinder M: Role of microaggregate blood filtration in clinical medicine. *Transfusion* 1983; 23: 460-70
45. Vassallo R, Murphy S: A critical comparison of platelet preparation methods. *Curr Opin Hematol* 2006; 13: 323-30
46. Preparation and Storage of Platelet Concentrates. 3rd Edition. Baltimore, Williams and Wilkins, 2002
47. British Committee for Standards in Haematology. Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; 122: 10-23

48. Vilahur G, Choi B, Zafar M, Viles-Gonzalez J, Vorchheimer D, Fuster V, Badimon J: Normalization of platelet reactivity in clopidogrel-treated subjects. *J Thromb Haemost.* 2007; 5: 82-90
49. Hu Z, Yang X, Ho P, Chan S, Heng P, Chan E, Duan W, Koh H, S. Z: Herb-drug interactions: a literature review. *Drugs* 2005; 65: 1239-82
50. Schwartz L, Brister S, Bourassa M, Peniston C, Buchanan M: Interobserver Reproducibility and Biological Variability of the Surgicutt II Bleeding Time. *J Thromb Thrombolysis* 1998; 6: 155-158
51. Shore-Lesserson L, Manspeizer H, DePerio M, Francis S, Vela-Cantos F, Ergin M: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999; 88: 312-19
52. Brecher M: The platelet prophylactic transfusion trigger: when expectations meet reality. *Transfusion* 2007; 47: 188-91
53. Strauss R: Pretransfusion trigger platelet counts and dose for prophylactic platelet transfusions. *Curr Opin Hematol* 2005; 12: 499-502
54. Miller R: *Transfusion Therapy*. 5th Edition. Philadelphia, PA, Churchill Livingstone, 2000
55. Downes K, Wilson E, Yomtovian R, Sarode R: Serial measurement of clotting factors in thawed plasma stored for 5 days. *Transfusion* 2001; 41: 570
56. Despotis GJ, Santoro SA, Spintznagel E, Kater KM, Barnes P, Cox JL, Lappas DG: On-site prothombin time, activated partial thromboplastin time, and platelet count. A comparison between whole blood and laboratory assays with coagulation factor analysis in patients presenting for cardiac surgery. *Anesthesiology* 1994; 80: 338-351
57. Triulzi D: The art of plasma transfusion therapy. *Transfusion* 2006; 46: 1268-70

58. Leonard K, Davey R: Principles of transfusion medicine. New York, NY, Raven Press Ltd, 1995
59. American Association of Blood Banks. Blood Transfusion Therapy: A Physician's Handbook, 5th Edition. Bethesda, MD, American Association of Blood Banks, 1996
60. Leslie SD, Toy PT: Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. *Am. J. Clin. Pathol.* 1991; 96: 770-773
61. Colombo M, Mannucci P, Carnelli V, Savidge G, Gazengel C, Schimpf K: Transmission of non-A, non-B hepatitis by heat-treated factor VIII concentrate. *Lancet* 1985; 2: 1-4
62. Franchini M: Advances in the diagnosis and management of von Willebrand disease. *Hematology* 2006; 11: 219-25
63. Bui JD, Despotis GD, Trulock EP, Patterson GA, Goodnough LT: Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. *J Thorac Cardiovasc Surg* 2002; 124: 852-4
64. Kelly M, Rosenfeld D, Leslie G: Venous surgery in patients with congenital antithrombin III deficiency. *Aust N Z J Surg* 1994; 64: 865-8
65. Klein H: Pathogen inactivation technology: cleansing the blood supply. *J Intern Med* 2005; 257: 224-37
66. Wagner S: Transfusion-transmitted bacterial infection: risks, sources and interventions. *Vox Sang* 2004; 86: 157-63
67. Busch M, Kleinman S, Nemo G: Current and emerging infectious risks of blood transfusions. *JAMA* 2003; 289: 959-62
68. Randal J: "Look back" program initiated for hepatitis C infection. *J Natl Cancer Inst* 1999; 91: 907

69. Madjdpour C, Heindl V, Spahn D: Risks, benefits, alternatives and indications of allogenic blood transfusions. *Minerva Anesthesiol* 2006; 72: 283-98
70. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA: Proceedings of a consensus conference: towards an understanding of TRALI. *Transfus Med Rev* 2005; 19: 2-31
71. Eder AF, Kennedy JM, Dy BA, Notari EP, Weiss JW, Fang CT, Wagner S, Dodd RY, Benjamin RJ: Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross experience (2004-2006). *Transfusion* 2007; 47: 1134-42
72. Alter H, Nakatsuji. Y, Melpolder J, Wages J, Wesley R, Shih J, Kim J: The incidence of transfusion-associated hepatitis G virus infection and its relation to liver disease. *N Engl J Med* 1997; 336: 747-54
73. Kleinman S, Chan P, Robillard P: Risks associated with transfusion of cellular blood components in Canada. *Transfus Med Rev* 2003; 17: 120-62
74. Centers for Disease Control and Prevention and U.S. Public Health Service Working Group. Guidelines for counseling persons infected with human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II). *Ann Intern Med* 1993; 118: 448-454
75. Dellinger E, DA. A: Infectious and immunologic consequences of blood transfusion. *Crit Care* 2004; 8 Suppl 2: S18-23
76. Dodd R: Current safety of the blood supply in the United States. *Int J Hematol* 2004; 80: 301-5
77. Hewitt P, Llewelyn C, Mackenzie J, Will R: Three reported cases of variant Creutzfeldt-Jakob disease transmission following transfusion of labile blood components. *Vox Sang* 2006; 91: 348

78. Linden J, Tourault M, Scribner C: Decrease in frequency of transfusion fatalities. *Transfusion* 1997; 37: 243-4
79. Goodnough L: Risks of blood transfusion. *Anesthesiol Clin North America* 2005; 23: 241-52
80. Robillard P, Nawej K, Jochem K: The Quebec hemovigilance system: description and results from the first two years. *Transfus Apher Sci* 2004; 31: 111-22
81. Davenport R, Kunkel S: Cytokine roles in hemolytic and nonhemolytic transfusion reactions. *Transfus Med Rev* 1994; 8: 157-68
82. Moore S: Transfusion-related acute lung injury (TRALI): clinical presentation, treatment, and prognosis. *Crit Care Med* 2006; 34(5 Suppl): S114-7
83. Kleinman S: A perspective on transfusion-related acute lung injury two years after the Canadian Consensus Conference. *Transfusion* 2006; 46: 1465-8
84. Mair D, Hirschler N, Eastlund T: Blood donor and component management strategies to prevent transfusion-related acute lung injury (TRALI). *Crit Care Med* 2006; 34(5 Suppl): S137-43
85. Shander A, Popovsky M: Understanding the consequences of transfusion-related acute lung injury. *Chest* 2005; 128(5 Suppl 2): 598S-604S
86. Stroncek D: Pulmonary transfusion reactions. *Semin Hematol* 2007; 44: 2-14
87. Nollet K, Holland P: Toward a coalition against transfusion-associated GVHD. *Transfusion* 2003; 43: 1655-7
88. Anderson K: Broadening the spectrum of patient groups at risk for transfusion-associated GVHD: implications for universal irradiation of cellular blood components. *Transfusion* 2003; 43: 1652-4
89. Blajchman M: Transfusion immunomodulation or TRIM: what does it mean clinically? *Hematology* 2005; 10 Suppl 1: 208-14

90. Blajchman M: Immunomodulation and blood transfusion. *Am J Ther* 2002; 9: 389-95
91. Fergusson D, Khanna M, Tinmouth A, Hebert P: Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials. *Can J Anaesth* 2004; 51: 417-24
92. Linden J, Wagner K, Voytovich A, Sheehan J: Transfusion errors in New York State: an analysis of 10 years' experience. *Transfusion* 2000; 40: 1207-13
93. Huber-Wagner S, Qvick M, Mussack T, Euler E, Kay M, Mutschler W, Kanz K: Massive blood transfusion and outcome in 1062 polytrauma patients: a prospective study based on the Trauma Registry of the German Trauma Society. Working Group on Polytrauma of German Trauma Society (DGU). *Vox Sang* 2007; 92: 69-78
94. Karkouti K, Wijeyesundera D, Yau T, Beattie W, Abdelnaem E, McCluskey S, Ghannam M, Yeo E, Djaiani G, Karski J: The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion* 2004; 44: 1453-62
95. Hardy JF, de Moerloose P, Samama CM: Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anaesth* 2006; 53: S40-58
96. American College of Surgeons. Advanced Trauma Life Support for Doctors - Student Course Manual, 7th Edition. Chicago, American College of Surgeons, 2004
97. Ferrara A, MacArthur J, Wright H, Modlin I, McMillen M: Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg* 1990; 160: 515-8
98. Murray D, Pennel B, Weinstein S, Olson J: Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. *Anesth Analg* 1995; 80: 336-342

99. Reed RL, Ciavarella D, Heimbach DM, Baron L, Parlin E, Counts RB, Carrico CJ: Prophylactic platelet administration during massive transfusion. A prospective, randomized, double blind clinical study. *Ann. Surg.* 1986; 203: 40-48
100. Murray D, Olson J, Strauss R, Tinker J: Coagulation changes during packed red cell replacement of major blood loss. *Anesthesiology* 1988; 69: 839-45
101. Ciavarella D, Reed R, Counts R, Baron L, Pavlin E, Heimbach D, Carrico C: Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. *Br J Haematol* 1987; 67: 365-8
102. Hirshberg A, Dugas M, Banez EI, Scott BG, Wall MJ, Jr., Mattox KL: Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *J Trauma* 2003; 54: 454-63
103. Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, Cocanour CS, Balldin BC, McKinley BA: Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma* 2007; 62: 112-9
104. Goodnough L, Lublin D, Zhang L, Despotis G, Eby C: Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; 44: 1325-31
105. Gonzalez E, Moore F, Holcomb J, Miller C, Kozar R, Todd S, Cocanour C, Balldin B, McKinley B: Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma* 2007; 62: 112-9
106. Malone D, Hess J, Fingerhut A: Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma* 2006; 60(6 Suppl): S91-6
107. Reiss R: Hemostatic defects in massive transfusion: rapid diagnosis and management. *Am J Crit Care* 2000; 9: 158-65
108. Lind SE: The bleeding time does not predict surgical bleeding. *Blood* 1991; 77: 2547-2552

109. Kang Y: Thromboelastography in liver transplantation. *Semin Thromb Hemost* 1995; 21: 34-44
110. Welsby I, Jiao K, Ortel T, Brudney C, Roche A, Bennett-Guerrero E, Gan T: The kaolin-activated Thrombelastograph predicts bleeding after cardiac surgery. *J Cardiothorac Vasc Anesth* 2006; 20: 531-5
111. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, Ereth MH: Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. *Anesthesiology* 2001; 94: 773-81
112. McLellan B, Reid S, Lane P: Massive blood transfusion causing hypomagnesemia. *Crit Care Med* 1984; 12: 146-7
113. Crosby E: Perioperative haemotherapy: II. Risks and complications of blood transfusion. *Can J Anaesth* 1992; 39: 822-37
114. Wilson R, Binkley L, Sabo F, Wilson J, Munkarah M, Dulchavsky S, Diebel L: Electrolyte and acid-base changes with massive blood transfusions. *Am Surg* 1992; 58: 535-44
115. Jameson L, Popic P, Harms B: Hyperkalemic death during use of a high-capacity fluid warmer for massive transfusion. *Anesthesiology* 1990; 73: 1050-2
116. Abbott T: Changes in serum calcium fractions and citrate concentrations during massive blood transfusions and cardiopulmonary bypass. *Br J Anaesth* 1983; 55: 753-60
117. Winkler M, Akça O, Birkenberg B, Hetz H, Scheck T, Arkiliç C, Kabon B, Marker E, Gröbl A, Czepan R, Greher M, Goll V, Gottsauner-Wolf F, Kurz A, DI. S: Aggressive warming reduces blood loss during hip arthroplasty. *Anesth Analg* 2000; 91: 978-84
118. Downing L, Ramsay M, Swygert T, Hicks K, Hein H, Gunning T, Suit C: Temperature corrected thrombelastography in hypothermic patients. *Anesth Analg* 1995; 81: 608-11

119. Patel N, Knapke D, Smith C, Napora T, Pinchak A, Hagen J: Simulated clinical evaluation of conventional and newer fluid-warming devices. *Anesth Analg* 1996; 82: 517-24
120. Despotis GJ, Gravlee G, Filos K, Levy J: Anticoagulation monitoring during cardiac surgery: a review of current and emerging techniques. *Anesthesiology* 1999; 91: 1122-51
121. Ferraris V, Ferraris S, Saha S, Hessel E, Haan C, Royston B, Bridges C, Higgins R, Despotis G, Brown J, Spiess B, Shore-Lesserson L, Stafford-Smith M, Mazer C, Bennett-Guerrero E, Hill S, Body S: Society of Thoracic Surgeons Blood Conservation Guideline Task Force and Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion. Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007; 83(5 Suppl): S27-86
122. Despotis GJ, Grishaber JE, Goodnough LT: The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. *Transfusion* 1994; 34: 290-296
123. Capraro L, Kuitunen A, Salmenpera M, Kekomaki R: On-site coagulation monitoring does not affect hemostatic outcome after cardiac surgery. *Acta Anaesthesiol Scand* 2001; 45: 200-6
124. Royston D, von Kier S: Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. *Br J Anaesth* 2001; 86: 575-8
125. Avidan M, Alcock E, Da Fonseca J, Ponte J, Desai J, Despotis G, Hunt B: Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. *Br J Anaesth* 2004; 92: 178-86
126. Yende S, Wunderink R: Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med* 2001; 29: 2271-5

127. Hongo R, Ley J, Dick S, Yee R: The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 2002; 40: 231-7
128. Kang Y: Coagulation and liver transplantation: current concepts. *Liver Transpl Surg* 1997; 3: 465-7
129. Shander A, Perelman S: The long and winding road of acute normovolemic hemodilution. *Transfusion* 2006; 46: 1075-9
130. Shander A, Rijhwani T: Acute normovolemic hemodilution. *Transfusion* 2004; 44(12 Suppl): 26S-34S
131. Gross J: Estimating allowable blood loss: corrected for dilution. *Anesthesiology* 1983; 58: 277-80
132. Nuttall GA, Oliver WC, Ereth MH, Santrach PJ, Bryant SC, Orszulak TA, Schaff HV: Comparison of blood-conservation strategies in cardiac surgery patients at high risk for bleeding. *Anesthesiology* 2000; 92: 674-82
133. Huët C, Salmi L, Fergusson D, Koopman-van Gemert A, Rubens F, Laupacis A: A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac and orthopedic surgery. International Study of Perioperative Transfusion (ISPOT) Investigators. *Anesth Analg* 1999; 89: 861-9
134. Spahn DR, Waschke KF, Standl T, Motsch J, Van Huynegem L, Welte M, Gombotz H, Coriat P, Verkh L, Faithfull S, Keipert P: Use of perflubron emulsion to decrease allogeneic blood transfusion in high-blood-loss non-cardiac surgery: results of a European phase 3 study. *Anesthesiology* 2002; 97: 1338-49
135. Levy JH, Goodnough LT, Greilich PE, Parr GV, Stewart RW, Gratz I, Wahr J, Williams J, Comunale ME, Doblzar D, Silvay G, Cohen M, Jahr JS, Vlahakes GJ: Polymerized bovine hemoglobin solution as a replacement for allogeneic red blood cell transfusion after cardiac

- surgery: results of a randomized, double-blind trial. *J Thorac Cardiovasc Surg* 2002; 124: 35-42
136. Winslow R: Current status of oxygen carriers ('blood substitutes'): 2006. *Vox Sang* 2006; 91: 102-10
137. Dietz N, Joyner M, Warner M: Blood substitutes: fluids, drugs, or miracle solutions? *Anesth Analg* 1996; 82: 390-405
138. Tsuchida E, Sakai H, Horinouchi H, Kobayashi K: Hemoglobin-vesicles as a transfusion alternative. *Artif Cells Blood Substit Immobil Biotechnol* 2006; 34: 581-8
139. Riess J: Perfluorocarbon-based oxygen delivery. *Artif Cells Blood Substit Immobil Biotechnol* 2006; 34: 567-80
140. Roberts J, Bratton S: Colloid volume expanders. Problems, pitfalls and possibilities. *Drugs* 1998; 55: 621-30
141. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; 317: 235-40
142. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, Investigators. SS: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350: 2247-56
143. Dailey S, Dysart C, Langan D, Slye M, Nuttall G, Schrader L, Williams B, Oliver W: An in vitro study comparing the effects of Hextend, Hespan, normal saline, and lactated ringer's solution on thrombelastography and the activated partial thromboplastin time. *J Cardiothorac Vasc Anesth* 2005; 19: 358-61
144. Wilkes NJ, Woolf RL, Powanda MC, Gan TJ, Machin SJ, Webb A, Mutch M, Bennett-Guerrero E, Mythen M: Hydroxyethyl starch in balanced electrolyte solution (Hextend)--

- pharmacokinetic and pharmacodynamic profiles in healthy volunteers. *Anesth Analg* 2002; 94: 538-44
145. Van der Linden P, Ickx B: The effects of colloid solutions on hemostasis. *Can J Anaesth* 2006; 53(6 Suppl): S30-9
146. Wilkes MM, Navickis RJ, Sibbald WJ: Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. *Ann Thorac Surg* 2001; 72: 527-33
147. Haynes G, Havidich J, Payne K: Why the Food and Drug Administration changed the warning label for hetastarch. *Anesthesiology* 2004; 101: 560–561
148. Boldt J: Volume therapy in cardiac surgery: are Americans different from Europeans? *J Cardiothorac Vasc Anesth* 2006; 20: 98-105
149. Warren B, Durieux M: Hydroxyethyl starch: safe or not? *Anesth Analg* 1997; 84: 206-12
150. Mannucci P, Levi M: Prevention and treatment of major blood loss. *N Engl J Med* 2007; 356: 2301-11
151. Federici A, Castaman G, Thompson A, Berntorp E: Von Willebrand's disease: clinical management. *Haemophilia* 2006; 12 Suppl 3: 152-8
152. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS: Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *New England Journal of Medicine* 1983; 308: 8-12
153. Moia M, Mannucci P, Vizzotto L, Casati S, Cattaneo M, Ponticelli C: Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet* 1987; 2: 1227-9

154. Salzman E, Weinstein M, Weintraub R, Ware J, Thurer R, Robertson L, Donovan A, Gaffney T, Bertele V, Troll J, al. e: Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. A double-blind randomized trial. *N Engl J Med* 1986; 314: 1402-6
155. Mahdy A, Webster N: Perioperative systemic haemostatic agents. *Br J Anaesth* 2004; 93: 842-58
156. Levi M, Cromheecke M, de Jonge E, Prins M, de Mol B, Briet E, Buller H: Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; 354: 1940-7
157. Carless P, Henry D, Moxey A, O'Connell D, McClelland B, Henderson K, Sly K, Laupacis A, Fergusson D: Desmopressin for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2004: CD001884
158. Laupacis A, Fergusson D: Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Anesth Analg* 1997; 85: 1258-67
159. Munoz JJ, Birkmeyer NJ, Birkmeyer JD, O'Connor GT, Dacey LJ: Is epsilon-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery?: a meta-analysis. *Circulation* 1999; 99: 81-9
160. Sedrakyan A, Treasure T, Elefteriades J: Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004; 128: 442-8
161. Carless P, Moxey A, Stokes B, Henry D: Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-to-head trials. *BMC Cardiovasc Disord* 2005; 5: 19

162. Brown JR, Birkmeyer NJ, O'Connor GT: Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; 115: 2801-13
163. Cosgrove Dr, Heric B, Lytle B, Taylor P, Novoa R, Golding L, Stewart R, McCarthy P, Loop F: Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg* 1992; 54: 1031-6
164. Levy JH, Pifarre R, Schaff HV, Horrow JC, Albus R, Spiess B, Rosengart TK, Murray J, Clarke RE, Smith P: A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. *Circulation* 1995; 92: 2236-44
165. Slaughter TF, Faghiih F, Greenberg CS, Leslie JB, Sladen RN: The effects of epsilon-aminocaproic acid on fibrinolysis and thrombin generation during cardiac surgery. *Anesth Analg* 1997; 85: 1221-6
166. Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M: Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. *New Engl J Med* 1989; 320: 840-843
167. Ozier Y, Schlumberger S: Pharmacological approaches to reducing blood loss and transfusions in the surgical patient. *Can J Anaesth* 2006; 53(6 Suppl): S21-9
168. Casati V, Guzzon D, Oppizzi M, Cossolini M, Torri G, Calori G, Alfieri O: Hemostatic effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid in primary cardiac surgery. *Ann Thorac Surg* 1999; 68: 2252-6; discussion 2256-7
169. Dalmau A, Sabate A, Acosta F, Garcia-Huete L, Koo M, Sansano T, Rafecas A, Figueras J, Jaurrieta E, P. P: Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg* 2000; 91: 29-34

170. Camarasa M, Olle G, Serra-Prat M, Martin A, Sanchez M, Ricos P, Perez A, Opisso L: Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. *Br J Anaesth* 2006; 96: 576-82
171. Henry D, Moxey A, Carless P, O'Connell D, McClelland B, Henderson K, Sly K, Laupacis A, Fergusson D: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2001: CD001886
172. Carless P, Moxey A, Stokes B, Henry D: Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-to-head trials. *BMC Cardiovasc Disord* 2005; 5: 1-12
173. Mangano D, Tudor I, Dietzel C, Group MSoPIR, Foundation. IRaE: The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354: 353-65
174. Karkouti K, Beattie W, Dattilo K, McCluskey S, Ghannam M, Hamdy A, Wijeyesundera D, Fedorko L, Yau T: A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46: 327-38
175. Furnary AP, Wu Y, Hiratzka LF, Grunkemeier GL, Page US, 3rd: Aprotinin does not increase the risk of renal failure in cardiac surgery patients. *Circulation* 2007; 116: I127-33
176. Food and Drug Administration. FDA Public Health Advisory.- Aprotinin Injection (marketed as Trasylol). 2006
177. O'Connell N, Perry D, Hodgson A, O'Shaughnessy D, Laffan M, Smith O: Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion* 2003; 43: 1711-6
178. Gabay M: Absorbable hemostatic agents. *Am J Health-Sys-Pharm* 2006; 63: 1244-53
179. Schelling G, Block T, Blanke E, Hammer C, Brendel W, Gokel M: The effectiveness of a fibrinogen-thrombin-collagen-based hemostatic agent in an experimental arterial bleeding model. *Ann Surg* 1987; 205: 432-435

180. Jackson M, Gillespie D, Longenecker E, Goff J, Fiala L, O'Donnell S, Gomperts E, Navalta L, Hestlow T, Alving B: Hemostatic efficacy of fibrin sealant (human) on expanded polytetrafluoroethylene carotid patch angioplasty: a randomized clinical trial. *J Vasc Surg* 1999; 30: 461-466
181. Kram H, Nugent P, Reuben B, Shoemaker W: Fibrin glue sealing of polytetrafluoroethylene vascular graft anastomoses: comparison with oxidized cellulose. *J Vasc Surg* 1988; 8: 563-568
182. Scher K, Coil JJ: Effects of oxidized cellulose and microfibrillar collagen on infection. *Surgery* 1982; 91: 301-4
183. Tomizawa Y: Clinical benefits and risk analysis of topical hemostats: a review. *J Artif Organs* 2005; 8: 137-42
184. Rousou J, Levitsky S, Gonzalez-Lavin L, Cosgrove D, Magilligan D, Weldon C, Hiebert C, Hess P, Joyce L, Bergsland J, et al: Randomized clinical trial of fibrin sealant in patients undergoing re-sternotomy or reoperation after cardiac operations. A multicenter study. *J Thorac Cardiovasc Surg* 1989; 97: 194-203
185. Carless P, Henry D, Anthony D: Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2003: CD004171
186. Feigal DJ: FDA public health notification: paralysis from absorbable hemostatic agent., [www.fda.gov/cdrh/safety/040204-hemostatics.html](http://www.fda.gov/cdrh/safety/040204-hemostatics.html), 2004
187. Gershon S, Chang A, Purvis W, et al: Misadministration of topical bovine thrombin. *JAMA* 1999; 282: 1919
188. Schoenecker J, Johnson R, Fields R, et al: Relative purity of thrombin-based hemostatic agents used in surgery. *J Am Col Surg* 2003; 197: 580–590

189. Wright J, Kalns J, Wolf E, Traweek F, Schwarz S, Loeffler C, Snyder W, Yantis LJ, Eggers J: Thermal injury resulting from application of a granular mineral hemostatic agent. *J Trauma* 2004; 57: 224-30
190. Muramoto O: Bioethical aspects of the recent changes in the policy of refusal of blood by Jehovah's witnesses. *BMJ* 2001; 322: 37-9
191. Watch Tower Bible and Tract Society. questions from readers., Watchtower, 2000, pp 29–31
192. Sniecinski R, Chen E, Levy J, Szlam F, Tanaka K: Coagulopathy after cardiopulmonary bypass in Jehovah's Witness patients: management of two cases using fractionated components and factor VIIa. *Anesth Analg* 2007; 104: 763-5
193. Wanko S, Telen M: Transfusion management in sickle cell disease. *Hematol Oncol Clin North Am* 2005; 19: 803-26
194. Vichinsky E, Neumayr L, Haberkern C, Earles A, Eckman J, Koshy M, Black D: The perioperative complication rate of orthopedic surgery in sickle cell disease: report of the National Sickle Cell Surgery Study Group. *Am J Hematol* 1999; 62: 129-38
195. Koshy M, Weiner S, Miller S, Sleeper L, Vichinsky E, Brown A, Khakoo Y, Kinney T: Surgery and anesthesia in sickle cell disease. *Cooperative Study of Sickle Cell Diseases. Blood* 1995; 86: 3676-84
196. Haberkern C, Neumayr L, Orringer E, Earles A, Robertson S, Black D, Abboud M, Koshy M, Idowu O, Vichinsky E: Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. *Preoperative Transfusion in Sickle Cell Disease Study Group. Blood* 1997; 89: 1533-42
197. Vichinsky E, Haberkern C, Neumayr L, Earles A, Black D, Koshy M, Pegelow C, Abboud M, Ohene-Frempong K, Iyer R: A comparison of conservative and aggressive transfusion

- regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. *N Engl J Med* 1995; 333: 206-13
198. Firth P, Head C: Sickle cell disease and anesthesia. *Anesthesiology* 2004; 101: 766–85
199. *The Wall Street Journal* 2002; June 26
200. Nuttall G, Stehling L, Beighley C, Faust R: Current transfusion practices of members of the American society of anesthesiologists - A survey. *Anesthesiology* 2003; 99: 1433-42
201. Goodnough LT, Johnston MF, Toy PT: The variability of transfusion practice in coronary artery bypass surgery. *JAMA* 1991; 265: 86-90
202. Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R, D'Ambra MN, Mangano DT, Spiess BD: Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. *Anesthesiology* 1998; 88: 327-33
203. Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG: Economic impact of inappropriate blood transfusion in coronary artery bypass graft surgery. *Am. J. Med.* 1993; 94: 509-14