Canadian Blood Services
Société canadienne du sang

Clinical Guide to Transfusion

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Clinical Guide to Transfusion

Fourth Edition

Gwen Clarke and Morris Blajchman

We are excited to present to the transfusion medicine community this much-anticipated fourth edition of the Canadian Blood Services' (CBS) ***Clinical Guide to Transfusion***. The last edition of the *Clinical Guide* was published under the auspices of the Canadian Red Cross Society (CRCS) in 1993, with Dr. Anita Ali as editor. The 1993 *Guide* has always been a much appreciated and practical addition to the available information related to transfusion, but it is now outdated. Since 1993 there has been a radical change in the delivery of blood components in Canada. CBS has succeeded CRCS, and there has been a major evolution in the nature of the blood products provided to hospitals.

This fourth edition of the *Clinical Guide* is the result of efforts by CBS to identify the educational needs of health care workers relating to the provision of blood products and transfusion medicine services. The Blood Education Resource Group, a CBS *ad hoc* committee of technologists, nurses and physicians, helped to prioritize the various educational initiatives that were identified. This group indicated that a new edition of the ***Clinical Guide to Transfusion*** was the lead educational priority, along with the need for a transfusion medicine web site. Both were thus developed with the intention of providing current and reliable information about blood, blood components, and transfusion medicine practice in Canada.

The new ***Clinical Guide to Transfusion*** incorporates important changes in content and format from that of previous editions. For example, for the first time the *Guide* will be available as a PDF document attached to the CBS transfusion medicine website (**www.transfusionmedicine.ca**). This will allow for regular updates of the *Guide* as knowledge about blood products and transfusion medicine practices evolve.

The authors of the various sections of the *Guide* are experts in their fields of endeavour. They have provided an excellent and very practical summary of our current knowledge of blood components and transfusion medicine practices. We hope you find their contributions to be clear and useful. Above all, we trust that this *Guide* will help to increase safety for those Canadians who require blood products and add confidence for those who provide the services.

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AFFP	fresh frozen plasma, apheresis
ALI	acute lung injury
aPTT	activated partial thromboplastin time
BU	Bethesda units
CBS	Canadian Blood Services
CCI	corrected count increment (for platelets)
CMVIG	CMV immune globulin
CMV	cytomegalovirus
CPB	cardiopulmonary bypass
CPD	citrate phosphate dextrose
CPDA-1	citrate phosphate dextrose adenine
CP2D	citrate phosphate-2-dextrose
CRYO	cryoprecipitated AHF
CSPL	cryosupernatant plasma
DIC	disseminated intravascular coagulation
ECMO	extracorporeal membrane oxygenation
EDTA	ethylenediamine tetra-acetic acid
EKG	electrocardiogram
F	clotting factor
FEIBA	factor VIII inhibitor bypassing agent
FFP	fresh frozen plasma, LR
FNHTR	febrile non-hemolytic transfusion reaction
FP	frozen plasma, LR
h	hours
HBIG	hepatitis B virus immune globulin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFN	hemolytic disease of the fetus and newborn
HIT	heparin induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HTLV	human T-cell lymphotropic virus
HUS	hemolytic uremic syndrome

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ISG	immune serum globulin
IM	intramuscular
ITI	immune tolerance induction
ITP	immune thrombocytopenic purpura
IV	intravenous
IVIG	intravenous immune globulin
LR	leukocyte reduction
NAIT	neonatal alloimmune thrombocytopenia
NAT	nucleic acid testing
pd	plasma derived
PPR	percent platelet recovery
PT (INR)	prothrombin time (International Normalized Ratio)
PTP	post-transfusion purpura
r	recombinant
RBC	red blood cell(s)
RDP	random donor platelets
rFVIIa	recombinant factor VIIa
RhIG	Rh immune globulin
RICE	rest, ice, immobilization, compression, elevation
SAGM	saline adenine glucose mannitol
SBOS	surgical blood order schedule
sc	subcutaneous
SOP	standard operating procedures
T1/2	half-life
TACO	transfusion-associated circulatory overload
TA-GvHD	transfusion-associated graft vs host disease
TRALI	transfusion-related acute lung injury
TT CMV	transfusion-transmitted CMV
vCJD	variant Creutzfeld Jakob disease
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZIG	varicella-zoster immune globulin
WNV	West Nile virus

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Robert Barr and Ted Alport

The blood system in Canada is complex, closely integrated and carefully regulated. All whole blood and apheresis donations are voluntary. There are two blood suppliers in Canada: Héma-Québec (HQ) in Quebec and Canadian Blood Services (CBS) for the rest of Canada. These suppliers are responsible for donor recruitment, collection, processing, storage, testing and transportation of blood components and plasma fractionation products to hospitals for administration to recipients in need. Qualified personnel throughout the system strive to ensure that blood collection and transfusion are practised as safely and efficiently as possible, that communications among all involved are clear and timely, and that both donors and recipients receive the necessary information to ensure the safety of the transfused blood component or product.

The blood system is regulated and audited by Health Canada. Government funding for Canadian Blood Services is approved by a provincial committee. Proficiency testing of laboratories and accreditation processes vary from province to province. Hospital transfusion services are licensed and/or accredited by provincial ministries of health.

The CBS Head Office, located in Ottawa, has overall responsibility for:

- developing and implementing Policies/Standard Operating Procedures (SOPs) organized into various divisions including, Quality Assurance and Regulatory Affairs, Manufacturing, Medical/Scientific and Communication;
- monitoring and auditing collection facilities and regional testing laboratories;
- developing contracts with plasma fractionators to fractionate CBS plasma and providing appropriate fractionated and recombinant products to meet the needs of Canadian recipients; and
- storing and shipping these products to CBS centres as requested, followed by distribution to hospitals. Similar functions are the purvue of HQ in Quebec.

Volunteer donors are essential and valued components of the blood system and are responsible for:

- attending fixed and mobile clinic sites;
- honestly and completely responding to the written questionnaire and interview questions;
- providing informed written consent confirming their permission to have their blood, platelets or plasma collected, and their understanding of the questions asked; and
- informing CBS of any illness or new diagnosis after donation that might cause harm to a recipient of their donated unit.

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Regional CBS staff include administrative, medical, nursing, technical and recruitment personnel who are responsible for:

- recruiting, assessing and monitoring donors during blood or apheresis collections;
- processing, storing, distributing and transporting blood components and products to area hospitals to meet recipient needs;
- performing laboratory testing or arranging for centralized laboratory testing as appropriate, and labelling units suitable for issue accordingly;
- conducting quality control and quality assurance activities; and
- maintaining the lookback/traceback programs together with hospital partners.

Recall/Lookback and Traceback Procedures

Information received after the time of donation that may affect the safety of any blood donor or recipient must be reported to CBS. Such information can be received from many sources: donors, hospitals, other blood centres, physicians, third parties, etc. The most common sources of information CBS receives are from donors who become unwell after they donate, or hospitals that report an adverse reaction to a blood product. All reports are fully investigated and several procedures are possible.

A. Inventory Retrieval/Recall/Withdrawal

These are closely related procedures that may be voluntary or mandated by the regulatory agency. They all involve identifying and removing from inventory components, from one or more donations, that could compromise the integrity and safety of the blood supply. The medical director, hospital blood bank director and recipient's attending physician will determine if recipient notification is required when components have already been transfused. One example would be the recall of blood components still stored in the blood bank when a donor reports fever within a few days following the donation.

B. Lookback Investigation

This is the process of identifying and contacting recipients of blood components from a donor who, on a subsequent donation or testing, is confirmed to have tested positive for the presence of an infectious agent.

When CBS learns that a blood donor has tested positive for a transmissible disease, the donor is indefinitely deferred and a lookback procedure is initiated on that donor's previous donations. Hospitals that were sent blood or blood components from these donations are notified and asked to identify any recipients. In turn, treating physicians are asked to test their recipients who were transfused with these products for the infectious agent found in the donor, and to inform CBS of the results.

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C. Traceback Investigation

This is the process of investigating a report of transfusion-associated infection in blood recipients who have already received blood components. The purpose of the investigation is to determine whether any donor who provided blood for that recipient has tested positive for an infectious agent. When CBS learns that a blood recipient has tested positive for a transfusion-transmitted infection (without another known cause), all the donors are identified and located, and arrangements are made to retest the donors for the appropriate transmissible disease.

For both lookback and traceback investigations, identifying individuals with positive tests for transfusion-transmitted infections is important for the safety of the blood supply. It is also essential for the donor so that the individual can receive counselling and avoid transmission of infection to others.

Hospital transfusion laboratories have qualified medical and technical personnel responsible for:

- developing and implementing transfusion policies approved by the hospital or regional transfusion committee;
- requesting blood components and products as needed and ensuring their safe storage and distribution;
- maintaining competence in blood grouping, antibody detection and compatibility testing;
- developing, updating and distributing technical and clinical procedure manuals for laboratory, nursing and medical staff to meet standards for safe blood testing, distribution and transfusion;
- educating health care providers on transfusion policies and practices;
- monitoring transfusion safety and investigating/reporting adverse transfusion reactions as required;
- maintaining adequate transfusion records of the receipt, storage, and distribution of blood components and products and investigation of adverse reactions; and
- responding promptly to requests from the CBS lookback program or other correspondence to identify recipients of previously transfused units with possible infectious risks based on subsequent information from or about the donor. If requested to do so, informing the physician who ordered the suspect unit, and/or the recipient, depending on hospital policies, of the possible risk and need for testing.

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Clinical staff in hospital units where blood is transfused are responsible for:

- providing appropriate and properly identified recipient blood samples to the transfusion laboratory for compatibility testing;
- verifying that the blood component issued for transfusion is compatible with the recipient's blood group;
- infusing the blood component at the specified time and rate, through a suitable administration set, with careful monitoring for any adverse effects; and
- maintaining a record of each transfusion on the recipient's medical record, and reporting any adverse reactions to the recipient's physician and the transfusion laboratory.

The recipient's physician who orders the blood component or product is responsible for:

- carefully assessing the clinical need for each order;
- providing information to each recipient on transfusion benefits, risks and alternatives so that the recipient can provide informed consent, and recording this consent on the recipient's medical record;
- instructing staff responsible for performing the transfusions about the urgency, quantity and rate of administration;
- ensuring that all significant, unexpected reactions are promptly reported and investigated; and
- promptly contacting and arranging for testing, either personally or through the family physician, of any recipients identified by the hospital transfusion laboratory as being at possible risk from a previous transfusion (e.g. CBS lookback program), then reporting on the recipient's status and test results to CBS and public health authorities if required to do so.

The interrelationships between these several agencies and health care representatives are illustrated in Table 1. The system works as well as it does only because competent, caring and committed professionals contribute at all levels. There are opportunities for improved data exchange and computer software integration between CBS and hospitals to enhance blood utilization and inventory management.

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In recent years, transformation initiatives, increased emphasis on quality, and enhanced production/testing methodology have dramatically improved the quality and safety of the blood components issued by the CBS. Despite these advances, potential risks from transfusion remain and blood transfusion should never be considered completely safe. The application of the "precautionary principle" to the blood system suggests that a certainty of harm should not be required for action to be taken. Actions may be taken on the basis of "theoretical risk" to avoid harm.

Decisions that have a major impact on donor recruitment and retention cannot be taken lightly, however, since the supply of blood must be sufficient to keep up with demand. In Canada, only 3.5% of the eligible population are repeat donors, compared to 5% in many other developed countries. Both the recruitment of new donors and the retention of previous donors remain a major challenge. Without these dedicated volunteer donors there would be no blood system, and there would be a major negative impact on the advanced health care provided in Canadian hospitals. It is anticipated that demands for blood will increase and potentially outstrip the ability of the blood donor pool to meet these needs, despite vigorous efforts to increase the number of donors. This potential shortfall requires all involved in the provision and transfusion of blood components to do everything possible to limit waste and improve utilization.

Decisions about blood utilization remain primarily a medical responsibility within Canadian hospitals. The safe collection and testing of recipient samples, and the careful transfusion and monitoring of those receiving blood components rely on nursing and technical personnel. Continuing education for all involved, including recipients, as to risks and benefits of transfusion remains a constant challenge. It is hoped that the information in this *Clinical Guide* will assist to optimize the utilization and the safety of blood components and products.

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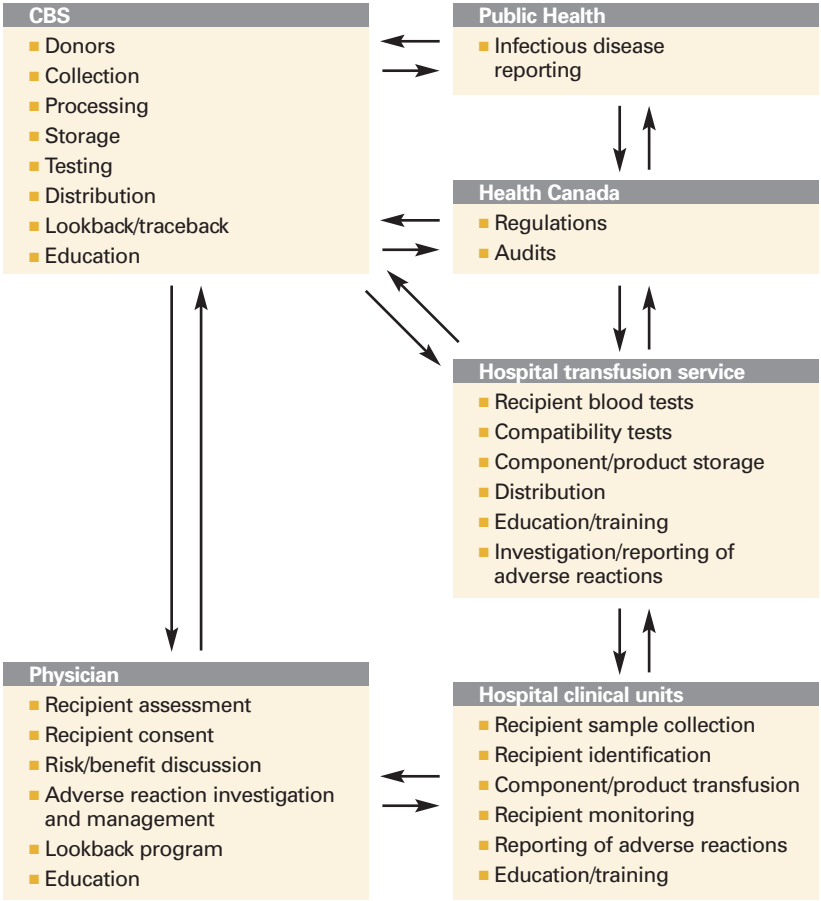
Table 1: Blood donation to blood transfusion: responsible agencies/personnel involved



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Kathy Chambers, Pat Letendre and Lucinda Whitman

Whole blood donations are separated into specific cellular (red blood cells and platelets) and plasma components, to enhance the utilization of individual donations and to decrease the need for whole blood. Transfusing the appropriate combination of components effectively provides for the clinical needs of patients and best utilizes the blood donation.

Whole blood is collected into a multiple bag system in which all bags are connected, allowing blood and components to be moved between bags aseptically. Depending on the number of attached bags, three or four blood components can be prepared, although currently CBS does not prepare more than three components from any single whole blood donation.

Apheresis technology may also be used for collection of some blood components, including plasma and platelets. This collection procedure utilizes an automated in-line process in which whole blood enters a collection chamber where flow patterns separate the plasma from cellular blood constituents, or leukocytes, from platelets. Plasma, or platelets suspended in plasma, is collected into a bag while the remaining constituents of the blood are returned to the donor.

All cellular blood products produced by CBS are white cell reduced, referred to as LR, by leukocyte reduction filtration or (in the case of apheresis platelets) during the apheresis procedure. All plasma components prepared by CBS are also LR (by filtration or processing) with the exception of some plasma components produced using the buffy coat extraction method and fresh frozen plasma, apheresis.

This chapter describes the commonly prepared components, their indications, contraindications, storage and transportation requirements; and briefly describes dose, administration and available alternatives. Further information may be found in Chapter 9 and Chapters 11 to 18 of this *Guide* and in the most recent version of the *Circular of Information for the Use of Human Blood and Blood Components*.

Transfusion must be prescribed and administered under medical direction, and documentation of the identity of the units transfused must be retained indefinitely on the recipient's medical record. Documented informed consent should be obtained whenever possible. No medications or drugs, including those intended for intravenous use, may be added to the unit. Infusion of components should begin within 30 minutes of removal from an approved temperature-controlled blood product refrigerator.

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Red Blood Cells (RBC), Leukocytes Reduced (LR)

Description

Whole blood is centrifuged to separate the red cells from the plasma components. Filtration to remove white cells may occur prior to or after centrifugation. RBC, LR contain at least 85% of the original volume of the RBCs of the whole blood and less than 5 x 10^6 leukocytes. A typical unit has a volume of 240–340 mL and hematocrit of less than 0.80 L/L. AS-3 RBC, LR is the primary red cell product prepared by CBS. For other RBC products, consult the latest *Circular of Information for the Use of Human Blood and Blood Components* and see the addendum to this *Guide* regarding buffy coat production of components.

AS-3 Red Blood Cells, LR are prepared from whole blood collected in CP2D anticoagulant, then centrifuged and filtered to reduce leukocytes. After removal of most of the plasma, the additive solution AS-3 (Nutricel®) is mixed with the RBC, LR, CP2D.

Further modification of RBC components such as washing, deglycerolizing, irradiation and cytomegalovirus (CMV) testing are covered in Chapter 15.

Indications

The primary indication for an RBC transfusion is the augmentation of the oxygen-carrying capacity of the blood. Therefore, an RBC transfusion is indicated in patients with anemia who have evidence of impaired oxygen delivery. For example, impaired oxygen delivery in individuals with acute blood loss, chronic anemia with cardiopulmonary compromise, or disease or medication effects associated with bone marrow suppression may be indications for an RBC transfusion. In patients with acute blood loss, volume replacement is often more critical than the composition of the replacing fluid(s).

Effective oxygen delivery depends not only on the hemoglobin level, but on the cardiovascular condition of the individual. Younger people, therefore, will typically tolerate lower hemoglobin levels than older patients. Patients who develop anemia slowly develop compensatory mechanisms to allow them to tolerate lower hemoglobin values than patients who become acutely anemic.

The decision to transfuse anemic patients should be made in each individual case. There is no uniformly accepted hemoglobin value below which transfusion should always occur. An expert working group established by the Canadian Medical Association has published clinical guidelines for transfusion of RBC and plasma. These guidelines are based on the best evidence available at the time, although few randomized trials were available. More recently, in the ICU setting, Hébert et al. found that patients transfused using a liberal threshold (hemoglobin maintained at 100–120 g/L) fared worse in all categories, including mortality rate and organ failure, than those transfused using a restrictive transfusion strategy (hemoglobin maintained at 70–90 g/L).

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Contraindications

RBC should **not** be given for volume replacement or for any reason other than correction of acute or chronic anemia when non-transfusion alternatives have been assessed and excluded. The decision to transfuse should not be based on a single hemoglobin or hematocrit value as a trigger without considering all critical physiologic and surgical factors affecting oxygenation in that patient.

For exchange transfusions in neonates, AS-3 may be removed by concentrating or washing the red cells prior to transfusion. Alternatively, use of RBC, LR collected in CPDA-1 or CP2D could also be considered.

Dose and Administration

RBC compatibility testing must be performed before RBC transfusion unless the situation is life threatening, or unless an infant under four months is being transfused and after initial testing of mother (or newborn) shows the absence of clinically significant red cell antibodies. Recipients must be transfused with ABO group-specific or ABO group-compatible RBC (see Table 1). Rh-positive recipients may receive either Rh-positive or Rh-negative RBC, but Rh-negative recipients should receive Rh-negative RBC except when these units are in short supply, and provided that there is a medically approved policy for switching Rh types. Transfusion of Rh-positive RBC should be avoided for Rh-negative children and for women of child-bearing age. See Chapter 8: Pre-Transfusion Testing and Chapter 9: Blood Administration, for further information

If transfusion will not be initiated within 30 minutes of removal of the unit from the hospital transfusion service or from an approved temperature-controlled blood product refrigerator, the unit should be returned immediately to prevent waste.

Recipient vital signs must be recorded before, during and after transfusion. See Chapter 9: Blood Administration, or the latest version of the *Circular of Information for the Use of Human Blood Components* for further information.

One unit of RBC should increase the hemoglobin concentration by approximately 10 g/L in an average adult. All blood and blood products for intravenous use must be administered through a sterile administration set with a standard pore size (170–260 micron) blood filter to remove clots or other debris.

A physician should specify the rate of infusion. Unless otherwise indicated by the patient's clinical condition, the rate of infusion of RBC should be no greater than 2 mL/minute (or less for pediatric/neonatal patients) for the first 15 minutes of the transfusion. The patient should be observed during this period, since some life-threatening reactions could occur after the infusion of only a small volume of blood. A unit of RBC can be infused over two hours in most patients. The transfusion should not take longer than four hours because of the risk of bacterial proliferation in the blood component at room temperature. If the patient cannot tolerate an infusion rate necessary to complete the transfusion within four hours, a partial unit should be administered. If this is indicated, the hospital transfusion service should be contacted to arrange for a "split" unit, one half of which can be retained in the transfusion service refrigerator until infusion of the first half unit is complete.

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The pediatric infusion rate is usually 2–5 mL/kg/hour. Units are sometimes aliquoted by the hospital transfusion service (depending on hospital services and policies) into several bags or syringes containing small volumes. The hospital transfusion service should be contacted if this is required.

No medications or drugs, including those intended for intravenous use, may be added to the unit. Intravenous solutions administered with RBC must be isotonic and must not contain calcium or glucose. Do not add lactated Ringer's injection (USP) solution. Sterile 0.9% sodium chloride USP solution may be added or infused via a connector to the red cell unit on the order of a physician.

Table 1: ABO compatibility of red cells

Recipient	Donor
A	A,O
B	B,O
AB	AB, A, B, O
O	O

Storage and Transportation

The proper storage and transportation of blood components are critical to safe transfusion. Blood is a biological product and carries a risk of bacterial contamination if stored improperly. Improper storage may also affect the efficacy of blood component therapy.

Table 2 lists the shelf life of RBC components. The shelf life of RBC is dependent on the anticoagulant/nutrient used. Manipulation of the unit, including washing or irradiation, alters the shelf life. The expiry date is documented on each RBC unit collected. If the blood component is opened without the use of a sterile connection device, the shelf life is limited to 24 hours if stored at 1–6°C (or the original expiry date, whichever is sooner), or to four hours if stored at 20–24°C.

Storage of blood products outside the transfusion service in satellite storage refrigerators carries an additional monitoring requirement for the hospital transfusion service. Processes must be in place to ensure satellite storage equipment is monitored, cleaned and calibrated at specified intervals.

RBC components must be stored at 1–6°C in a temperature-controlled refrigerator with an alarm system, air-circulating fan and continuous monitoring device. Records must be kept during storage and transportation that maintain the chain of traceability, in order to follow blood components from their source to final disposition and to ensure that appropriate conditions were present throughout this time frame.

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Maintaining proper storage temperature during transportation is essential. Transportation time should not exceed 24 hours. The allowable temperature limit is 1–10°C during transportation, but the preferable range is 1–6°C. Visual inspection of each blood component to be shipped must be performed and documented. Validated shipping containers and standardized packing procedures are critical to this process. Some hospitals and regions use temperature-monitoring devices in one or more shipping containers in each shipment of blood and blood products to ensure the correct temperature during transportation.

When blood accompanies a patient, the issuing hospital transfusion service is responsible for notifying the receiving hospital transfusion service, which is then responsible for the final disposition documentation.

Table 2: Shelf life of RBC components collected in a closed system

Component	Shelf life
AS-3 red blood cells, LR	42 days from donation
CPDA-1 red blood cells, LR	35 days from donation
CP2D red blood cells, LR	21 days from donation

Additional storage information may be found in the latest version of the *Circular of Information for the Use of Human Blood and Blood Components*.

Available Alternatives

In the treatment of chronic anemia, iron, vitamin B12, folic acid, and erythropoietin therapy may be considered, depending on the underlying cause of the anemia. At the time of publication, alternatives such as perflurocarbons and hemoglobin-based oxygen carriers are not widely available, although some are in late-stage clinical trials for use in select patient groups.

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Platelets

Description

There are two types of platelet preparations, the more common of which is random donor platelets. Random donor platelets are prepared from whole blood donations and are labelled platelets, leukocytes reduced (LR).

Platelets, LR are prepared from a concentrate of platelets separated from a single unit of whole blood collected in a CP2D anticoagulant solution and filtered to reduce leukocytes. The platelets are suspended in 40–70 mL of original plasma. The typical unit of platelets, LR contains at least 55 x 10^9 platelets and less than 8.3 x 10^5 leukocytes per bag. Trace amounts of red blood cells may also be present. Platelets, LR are commonly referred to as random donor platelets (RDP).

Platelets apheresis, LR, approximately equivalent to a pool of four to eight RDP, are prepared by an automated in-line process using a chamber with flow patterns that separate the leukocytes from the platelets. The typical unit of platelets apheresis, LR contains at least 300 x 10^9 platelets per bag with a residual leukocyte count of less than 5 x 10^6 per container.

Indications

Platelets, LR are indicated in the treatment of patients with bleeding due to severely decreased platelet production and for patients with bleeding due to functionally abnormal platelets.

Platelets, LR should be used for patients with platelet consumption only if there is severe bleeding. Decreased platelet counts due to dilution, with accompanying impairment of platelet function, occasionally complicate massive transfusion. Treatment with platelets, LR and/or specific coagulation factor components may be useful when bleeding is related to their depletion. In most instances of dilutional thrombocytopenia, bleeding stops without transfusion.

Platelets, LR may be useful if given prophylactically to patients with rapidly falling or low platelet counts (usually less than 10 x 10^9/L) secondary to bone marrow disorders or chemotherapy. Transfusion of platelets, LR may also be useful in selected patients with microvascular perioperative bleeding (platelet count less than 50 x 10^9/L).

Indications for platelets apheresis, LR are similar to those for platelets, LR. Platelets apheresis, LR may be selected on the basis of similar HLA typing to the recipient's when a recipient fails to respond to platelet transfusion because of demonstrated anti-HLA antibodies (alloimmune refractoriness). CBS maintains a national registry of HLA/HPA-typed donors to respond to these special clinical needs.

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The clinical effectiveness of platelet transfusions should be judged by clinical observation and post-transfusion increments. Theoretically, a 20-minute to one-hour post-transfusion increment in platelet count of 5–10 x 10^9/L is predicted following each unit of random donor platelets given to an adult patient. Transfusion of platelets apheresis, LR should result in increments of about five times those of a random donor unit (RDP). In practice, the post-transfusion platelet count often does not rise to the expected level. Sepsis, alloimmunization, fever, immune thrombocytopenic purpura (ITP) or disseminated intravascular coagulation (DIC) may contribute to a suboptimal response.

Contraindications

Platelet transfusions are not usually effective or indicated in patients with rapid platelet destruction associated with immune thrombocytopenic purpura (ITP) unless a life-threatening bleeding episode is probable. Heparin-induced thrombocytopenia (HIT) and thrombocytopenic purpura (TTP) are thrombotic disorders with thrombocytopenia. Platelets are not recommended in these disorders as they may aggravate the underlying condition.

Dose and Administration

Compatibility tests before transfusion are not necessary; however, blood grouping is required. It is important to use these components within their short expiry date; therefore ABO identical transfusion may not be the primary consideration when selecting platelets for transfusion. The donor plasma in the platelet unit should be ABO compatible (but not necessarily group-specific) with the recipient's red blood cells. The same compatibility guidelines are used for platelets and plasma components. See Table 5 for plasma and platelet component compatibility.

Platelets, LR, if pooled by the hospital transfusion service, may have a single pool number and the label will indicate the number of units in the pool. This number and the number of units in the pool must be documented. If no pool number exists, each donor unit serial number must be documented on the recipient's medical record.

Platelet components must be administered through a blood administration set with a standard blood filter. Infusion should be as rapid as can be tolerated by the patient or as specified by the ordering physician. The infusion must be completed within four hours of removal from the transfusion service. Recipient vital signs must be recorded before, during and after transfusion.

The usual dose for an adult patient with bleeding and a platelet count below 20 x 10^9/L is five units. In most hospitals in Canada platelets, LR are pooled just prior to administration. Another way to calculate dosage is to infuse one unit per 10 kg of body weight up to a usual maximum of five units. A repeat platelet dose may be required in one to three days because of the short lifespan of transfused platelets (three to four days).

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Monitoring patient response by platelet counts (a post-transfusion platelet count) approximately one hour after infusion may identify patients who become refractory. Failure to obtain an improvement in hemostasis, or an increment in platelet count of less than 2.5 x 10^9/L/m^2, may signify that the patient is refractory to platelets from unmatched donors.

The corrected count increment (CCI) is a more precise method for measuring platelet response. This method determines the increase in platelet count adjusted for the number of platelets infused and the size of the recipient. A CCI of at least 7.5 x 10^9/L is expected following a standard platelet transfusion. Poorer responses are sometimes seen. The formula for CCI is as follows:

$$CCI = \frac{(\text{platelet increment}) \times (\text{body surface area})}{(\#\text{ of platelets transfused} \times 10^{11})}$$

For example:

A patient with a nomogram-derived body surface area of 1.40 m^2 is transfused with a unit of platelets apheresis, leukocytes reduced. The collecting facility label indicates a platelet dose of 4.5 x 10^{11}. The pre-transfusion platelet count was 2 x 10^9/L. The patient's platelet count from a sample of blood collected 15 minutes after transfusion was 29 x 10^9/L.

$$CCI = \frac{29 - 2}{4.5 \times (10^{11})} \times 1.40 = 8.4$$

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Storage and Transportation

Platelet components must be stored at **20–24°C under continuous agitation**. Their shelf life is five days from the date of collection. Once pooled or opened, the expiry time is four hours from the time of opening. The collection and expiry dates must be indicated on the label of each pack.

Platelet components carry an increased risk of bacterial contamination because of their storage at room temperature. Platelets apheresis, LR are cultured for bacteria using an automated blood culture system prior to release for patient use by CBS. Some hospital transfusion services also use a method for detection of bacteria in platelets, LR prior to issuing for transfusion.

Platelets that have not been agitated for more than 24 hours (e.g. during transportation) should not be used for transfusion.

Platelet agitators and incubators are required for storing platelet components. If the agitator is not contained in a platelet incubator, the ambient temperature must be recorded manually using a calibrated thermometer every four hours as long as platelet components are stored.

Additional information on storage may be found in the latest version of the *Circular of Information for the Use of Human Blood and Blood Components.*

Available Alternatives

Platelets apheresis, LR may be used instead of platelets, LR whenever supply and demand allow.

There are no known alternatives to platelet concentrates.

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Plasma and Plasma Components

Description

The four main types of plasma components produced by Canadian Blood Services are described in Table 3.

Table 3: Description of plasma components produced by CBS

Type	Description
Frozen plasma, LR (FP)	At least 100 mL of plasma separated from an individual unit of whole blood and placed in a freezer at ≤18°C within 24 hours after donation; contains all coagulation factors except has slightly reduced amounts of factor VIII.
Fresh frozen plasma, LR (FFP)	At least 100 mL of plasma separated from individual units of whole blood and placed in a freezer at ≤18°C **within eight hours** of donation containing all clotting factors including at least 0.70 IU/mL of factor VIII.
Fresh frozen plasma, apheresis (AFFP)	200–600 mL of plasma collected by apheresis and frozen within eight hours of donation. Trisodium citrate or ACD-A anticoagulant is added during the apheresis process. Fresh frozen plasma, apheresis normally contains a minimum of 0.70 IU/mL of factor VIII.
Cryosupernatant plasma LR (CSPL)	At least 100 mL of plasma separated from an individual unit of whole blood prepared following cryoprecipitated AHF production; contains all coagulation factors but has reduced levels of the high molecular weight von Willebrand's factor (vWF) multimers.

Immediately following collection from a normal donor, plasma contains approximately 1 unit/mL of each of the coagulation factors as well as normal concentrations of other plasma proteins. Coagulation factors V and VIII, known as the labile coagulation factors, are not stable in plasma stored for prolonged periods at 1–6°C; therefore, plasma is stored in the frozen state at –18°C or lower. FFP, i.e. plasma placed in a freezer within eight hours of collection, contains about 87% of the factor VIII present at the time of collection, and according to Canadian standards must contain at least 0.70 IU/mL of factor VIII. FP, i.e. plasma placed in a freezer within 24 hours of collection, contains factor VIII levels that are approximately 70–75% of the levels present at the time of collection. The levels of factor V, as well as the levels of other coagulation factors, are not significantly decreased from baseline in plasma frozen within 24 hours of collection.

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Indications

Given the fact that FFP is no longer used to treat patients with an isolated factor VIII or von Willebrand's factor deficiency and that the studies have shown that the levels of factor VIII in FP are only slightly lower than those in FFP, in most clinical situations where these products are indicated, FP and FFP may be used interchangeably.

There is broad general consensus that the appropriate use of FFP/FP is limited almost exclusively to the treatment or prevention of clinically significant bleeding due to a deficiency of one or more plasma coagulation factors. Such situations potentially include the treatment of:

- bleeding patients or patients undergoing invasive procedures who require replacement of multiple plasma coagulation factors (such as patients with severe liver disease or DIC);
- patients with massive transfusion (replacement of patient's blood volume in less than 24 hours) with clinically significant coagulation abnormalities;
- patients on warfarin anticoagulation who are bleeding or need to undergo an invasive procedure before vitamin K can reverse the warfarin effect;
- patients with rare specific plasma protein deficiencies for which no more appropriate alternative therapy is available.

FFP or FP may be used in the preparation of reconstituted whole blood for exchange transfusion in neonates. If using CP2D FFP or FP, glucose levels during and after exchange transfusion should be measured.

Cryosupernatant plasma, LR is used in the treatment of thrombotic thrombocytopenic purpura and adult hemolytic uremic syndrome (HUS) by plasma exchange, or may be used in treatment of multifactor deficiency. FFP is usually used in these situations when CSP is not available. FP may be used if neither CSP nor FFP is available and the attending physician deems this appropriate.

Table 4 shows indications for the use of plasma components by condition/clinical circumstance.

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Table 4: Indications for plasma component transfusion by condition/ clinical circumstance

Condition/clinical circumstance	Type of plasma component indicated			
	FP	FFP	Apheresis FFP	Cryosupernatant plasma
Urgent reversal of warfarin therapy	X	X	X	
Correction of microvascular bleeding when PTT and INR are greater than 1.5 to 2 times normal	X	X	X	
Liver disease	X	X	X	
Massive transfusion with demonstrated deficiency of factor VIII		X	X	
Exchange transfusion in neonates	X	X	X	
TTP or adult HUS plasma exchange therapy (see above text)		X	X	X

Guidelines have been established in Canada for indications for transfusion of RBCs and plasma by an expert working group of the Canadian Medical Association. See also Chapter 17: Hemostatic Disorders and/or the latest version of the *Circular of Information for the Use of Human Blood and Blood Components* for further information.

Contraindications

Plasma component transfusion is **not** indicated for volume replacement alone or for a single coagulation factor deficiency if specific recombinant products or plasma-derived virally inactivated products are available.

FFP/FP should not be used to treat hypovolemia without coagulation factor deficiencies. In those situations, hypovolemia should be treated with other plasma volume expanders such as 0.9% sodium chloride injection (USP); lactated Ringer's injection (USP); albumin; or 10% pentastarch.

Do not use FFP or FP when coagulopathy can be more appropriately corrected with specific therapy such as vitamin K, cryoprecipitate, or specific coagulation factor replacement.

Do not use cryosupernatant plasma for conditions that require factor VIII or von Willebrand's factor replacement.

Note that FFP rather than FP should be used when plasma is required for the treatment of thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS). FP may be used if the attending physician deems this appropriate.

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Dose and Administration

The volume transfused depends on the clinical situations, recipient size, and when possible should be guided by serial laboratory assays of coagulation function. In general the dose to achieve a minimum of 30% of plasma clotting factor concentration is attained with the administration of 10–15 mL/kg of body weight, except for the treatment of warfarin reversal in which 5–8 mL/kg body weight will usually accomplish the desired outcome.

Plasma components must be ABO compatible with the recipient's blood type but not necessarily group specific (see Table 5). To be compatible, the plasma component should not contain ABO antibodies that may be incompatible with the ABO antigens on the patient's RBC. If there is no ABO group available for the recipient, a type and screen will be required to determine compatibility.

Thawing may take 20–30 minutes depending on the thawing method used by the hospital transfusion service. (FFP apheresis will take longer to thaw because of the volume, and length of time to thaw is dependent on thawing equipment used.) Upon completion of thawing, transfuse immediately or store in an alarmed, continuously monitored refrigerator at 1–6°C for up to 24 hours. Once thawed, plasma components cannot be refrozen.

If transfusion of the plasma unit will not be initiated within 30 minutes of removal from the temperature-controlled blood product refrigerator, it should be returned immediately to prevent waste.

Plasma components must be administered through a blood administration set with a standard blood filter. Infusion should be as rapid as can be tolerated by the patient or as specified by the ordering physician.

Recipient vital signs must be recorded before, during and after transfusion.

Table 5: ABO compatibility for plasma and platelet component recipients

Recipient ABO group	Donor ABO group
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

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Storage and Transportation

Frozen plasma components must be stored in a controlled, monitored freezer. Units must not be out of the controlled blood storage freezer for longer than 30 minutes. Thawed units must not be refrozen. See Table 6 for the shelf life of plasma components.

Table 6: Shelf life of plasma components

Component	Shelf life when frozen	Shelf life when thawed
Frozen plasma (FP), LR	12 months at –18°C or colder	24 hours stored at 1–6°C
Fresh frozen plasma (FFP), LR	12 months at –18°C or colder	24 hours stored at 1–6°C
Apheresis FFP	12 months at –18°C or colder	24 hours stored at 1–6°C
Cryosupernatant plasma (CSP), LR	12 months at –18°C or colder	24 hours stored at 1–6°C

Additional information on storage may be found in the latest version of the *Circular of Information for the Use of Human Blood and Blood Components*.

Available Alternatives

Fresh frozen plasma (FFP), LR and apheresis FFP may be used instead of frozen plasma (FP), depending on indication, supply and demand.

Vitamin K should be used for warfarin reversal when the patient is not bleeding and does not require an invasive procedure.

Pentaspan® is available as an alternative for volume replacement. Specific concentrates are available and are described in Chapter 5: Coagulation Factor Concentrates and Chapter 17: Hemostatic Disorders of this *Guide*.

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Cryoprecipitated AHF, LR (Cryoprecipitate)

Description

Each 5–15 mL bag of cryoprecipitated AHF (cryo) contains a minimum of 80 IU of factor VIII and at least 150 mg of fibrinogen.

Indications

Over the last 15 years, several factors have completely changed the clinical indications for the use of cryoprecipitate. These factors include a better understanding of the coagulation system; more attention to the non-factor VIII factors within cryoprecipitate; concern about viral inactivation; and the development of alternative products.

The current primary uses of cryoprecipitate are for fibrinogen replacement in acquired hypofibrinogenemia or as empiric therapy in a bleeding patient. Generally, a plasma fibrinogen level of less than 1.0 g/L, as might occur in DIC or fibrinolysis, provides an objective basis for cryoprecipitate therapy.

Apart from the historical use of cryoprecipitate as a factor VIII concentrate for hemophilia and von Willebrand's disease, there are no prospective studies demonstrating evidence-based outcomes for the use of cryoprecipitate. See the "Available Alternatives" section below for information on use of recombinant products for these conditions.

Despite the paucity of evidence, cryoprecipitate is widely accepted as one of the products used to treat bleeding due to hypofibrinogenemia. These conditions include rare cases of hypofibrinogenemia or dysfibrinogenemia and, more commonly, acquired conditions with multiple factor deficiencies (e.g. DIC, post-thrombolytics, massive transfusion, or liver disease). These are complicated conditions and cryoprecipitate is only one part of the clinical management of such patients. Fibrinogen deficiency should be documented, and the product should only be used if there is active bleeding or a planned surgical procedure. While studies documenting efficacy in these settings is very limited, these are relatively common conditions and there is considerable clinical experience using cryoprecipitate.

Contraindications

Do not use cryoprecipitated AHF, LR unless results of laboratory studies indicate a specific hemostatic defect for which this product is indicated. Specific factor and/or recombinant concentrates are preferred, when available, because of the reduced risk of transfusion-transmissible diseases.

Cryoprecipitated AHF, LR should not be used to make fibrin glue. Virally inactivated commercial products should be purchased for this purpose.

Cryoprecipitate is not recommended in the treatment of hemophilia A, or in most cases (see below) in the treatment of vWD.

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Dose and Administration

One unit of cryoprecipitate contains 150 mg fibrinogen. The amount of cryoprecipitate required for transfusion will depend on the severity and nature of the bleeding condition. The amount of cryoprecipitate needed to raise the fibrinogen concentration of plasma can be calculated as follows:

Weight of the patient (kg) **x** 70 mL/kg **=** blood volume in mL

Blood volume in mL **x** (1.0 **–** patient hematocrit)
= plasma volume in mL

Desired fibrinogen **–** actual fibrinogen **x** plasma volume (mL)
= mg fibrinogen required

mg fibrinogen required **/** 150 mg per cryoprecipitate unit
= units of cryoprecipitate required.

Some facilities use the generic dose of up to one unit of cryoprecipitate/5 kg (2 U/10 kg) body weight, as required to maintain fibrinogen >1 g/L and **monitored by fibrinogen levels**, as directed by the hospital transfusion service medical director for treatment of hypofibrinogenemia.

The same standards as for the other blood components concerning prescription, informed consent and addition of medications apply to cryoprecipitate.

The component is usually pooled by the hospital transfusion service personnel or may be given sequentially. Small quantities of normal saline USP are introduced to rinse each bag in the pooling process. Pooled cryoprecipitated AHF may have a single pool number and the label will indicate the number of units in the pool. This number and the number of units in the pool must be documented. If no pool number exists, each donor unit serial number must be documented on the medical record.

If the transfusion will not be initiated within 30 minutes of removal from the temperature-controlled blood product refrigerator, the product should be returned immediately to prevent deterioration and waste.

Cyroprecipitated AHF, LR may be administered through a blood administration set with a standard blood filter or as a bolus injection by trained personnel. Infusion should be as rapid as can be tolerated by the patient or as specified by the ordering physician.

Recipient vital signs must be recorded before, during and after transfusion.

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Storage and Transportation

Cryoprecipitated AHF must be stored in a controlled, monitored freezer. See Table 7 for shelf life of cryoprecipitated AHF stored in a closed system. If the cryoprecipitate is pooled, all units will have been opened and must be used within four hours.

Additional information on storage may be found in the latest version of the *Circular of Information for the Use of Human Blood and Blood Components*.

Table 7: Shelf life of cryoprecipitated AHF

Component	Shelf life when frozen	Shelf life when thawed
Cryoprecipitated AHF	12 months at –18°C or colder	Up to 4 hours stored at 20–24°C

Note: Units must not be out of the controlled environment of the blood storage freezer for longer than 30 minutes, and they must not be refrozen.

Available Alternatives

Alternative (virally inactivated) and recombinant products are available in most settings.

In Canada, use of cryoprecipitate for hemophilia has been effectively replaced by DDAVP for the treatment of patients with mild hemophilia A and commercial recombinant factor VIII concentrates for patients with more severe disease. Cryoprecipitate is not recommended in the treatment of hemophilia A.

The treatment of vWD and its variants (three types, several subtypes and variants) is complex. DDAVP is the product of choice and is effective in 80–85% of all von Willebrand's disease. Commercial factor VIII concentrate rich in von Willebrand's factor (e.g. Humate-P™) is effective in most other cases. The only possible role for cryoprecipitate may be in rare, emergency settings or unusual cases that have not previously responded to DDAVP and factor VIII/vWF concentrate. The Association of Canadian Hemophilia Clinic Directors Guidelines include the following statement: "In rare instances, the use of Factor VIII concentrate fails to stop the bleeding episode. In such cases the use of Cryoprecipitate, potentially supplemented by platelet concentrates, should be considered."

For the replacement of fibrinogen, factor XIII, and treatment of von Willebrand's disease, commercial viral-inactivated concentrates such as fibrinogen concentrate, factor XIII concentrate and Humate-P are the preferred treatment. However, apart from Humate-P, these products are not licensed in Canada. They are available from blood centres only through the Special Access Program of Health Canada.

Congenital factor XIII deficiency is rare and a commercial factor XIII concentrate is available (unlicensed) for use in such patients. Acquired factor XIII deficiency is also rare, and treatment options include FFP, factor XIII concentrate, cryoprecipitate, immunosuppressives and steroids.

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Cryoprecipitate as a fibrinogen source, combined with thrombin, has been used to prepare in-house fibrin glue. With availability of commercial preparations (virally inactivated), cryoprecipitate should no longer be used for this purpose.

Cryoprecipitate does contain fibronectin that has been suggested and used to improve reticuloendothelial function in critically ill patients with sepsis. There is, however, insufficient information to warrant its use in this setting.

Uremic bleeding is associated with a multifactorial hemostatic defect with the major problem being acquired platelet dysfunction. One or two articles in the early 1980s suggested some correction with cryoprecipitate but other studies showed inconsistent results. There has been no recent literature supporting such use. Most often, such bleeding is associated with the anemia often seen in such patients. Correction of the anemia with erythropoietin (or RBC transfusions) together with dialysis for the underlying renal failure should ameliorate such bleeding.

In summary, the primary use of cryoprecipitate is for fibrinogen replacement, or empirically in a bleeding patient or patient with new vascular bleeding. Cryoprecipitate may still have a small role in rare cases of von Willebrand's disease where other products have failed. Alternative (virally inactivated) products are available in most other settings.

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Addendum: Buffy Coat Blood Components

David Howe and Bev Pearce

Canadian Blood Services will be implementing the buffy coat method for component production of whole blood donations. This implementation will introduce changes to the components available for transfusion to patients. The implementation of buffy coat component production began in 2005 and will be completed by the end of 2006 or early 2007, subject to Health Canada approval.

Changes to Anticoagulant and Red Blood Cell Preservative

The collection pack configuration will change, and all whole blood donations will be collected into one of two collection sets:

- buffy coat collection system, and
- whole blood filtration system.

There will be one anticoagulant for all whole blood donations. Citrate-phosphate-dextrose (CPD) will replace the current anticoagulants CP2D and CPDA-1. The additive solution for red blood cells will change to saline adenine glucose mannitol (SAGM) from the current AS-3 preservative.

Component Production Changes with the Buffy Coat Collection System

CPD whole blood donations intended for platelet production will be rapidly cooled to room temperature after collection. After transportation to the production site, the units will be centrifuged and separated into red blood cells, plasma, and a buffy coat. The buffy coat is the layer of cells between the red blood cells and the plasma and contains platelets and white blood cells.

After separation, the red blood cells will be mixed with the SAGM additive solution and filtered to remove leukocytes to produce SAGM red blood cells, LR. The plasma from the whole blood separation will be frozen to produce CPD frozen plasma. CPD frozen plasma is frozen within 24 hours of collection and will not be leukocyte-reduced by filtration. The residual leukocyte level in the CPD frozen plasma is on average $< 5 \times 10^6$/L.

The buffy coats from four donations, along with plasma from one of the same four donations, will be pooled together and then further processed and leukocyte-reduced by filtration to produce platelets, pooled LR. The pooled platelets are produced within 28 hours of collection and have a unique pool number identifier. CPD platelets, pooled LR typically will have a volume of approximately 340 mL, a platelet yield $>240 \times 10^9$, and have a shelf life of five days from the date of collection. Pooling platelets at the hospital will not be required for this product.

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Component Production Changes with the Whole Blood Filtration System

The whole blood unit will be filtered and centrifuged to separate the red blood cells from the plasma component. SAGM will be added to the red blood cells. The plasma will be frozen within 24 hours of collection to produce CPD frozen plasma. The CPD frozen plasma may be further processed into cryoprecipitate and cryosupernatant plasma.

Changes to Components Available

Whole blood will no longer be produced as a component for transfusion. All red blood cells will be processed into SAGM red blood cells, LR. The shelf life for SAGM red blood cells, LR is 42 days from donation. Fresh frozen plasma from whole blood donations will no longer be produced. Plasma for transfusion from all whole blood will be CPD frozen plasma or cryosupernatant plasma. Cryoprecipitated AHF will be renamed cryoprecipitate to reflect its modern clinical use. All platelets derived from whole blood donations will be processed as platelets, pooled LR. Single unit random donor platelets will no longer be produced.

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Susan Nahirniak

Albumin has been used as a therapeutic agent since the 1940s. For much of this time, the utility of albumin, as well as a general controversy regarding its risks and benefits, compared with crystalloids has continued.

Albumin has a molecular weight between 63 000 and 69 000 daltons with a low serum viscosity due to its shape. It is a highly soluble net negatively charged molecule capable of binding to both cations and anions. Total body albumin measures about 300 g, of which 40% (120 g) is in the plasma compartment.

Serum albumin is synthesized in the liver. Daily albumin synthesis in a normal adult approximates 16 g. Several hormones have the ability to increase the body's ability to synthesize albumin, but malnutrition, stress, medications and aging all potentially decrease production. For each 500 mL of blood lost, only 12 g (4% of body total) of albumin is lost; thus albumin in the setting of a four-unit hemorrhage will be entirely replaced by normal synthesis in three days.

Albumin is responsible for about 80% of the total plasma oncotic pressure. Generally, one gram of albumin attracts 18 mL of water by its oncotic activity. Infusion of 100 mL of 25% albumin expands the plasma volume by 450 mL.

Product Description

Albumin is supplied as a sterile solution with a physiologic pH and a sodium concentration of 130–160 mmol/L. Stabilizers are present but preservatives are not commonly included in the final product. Viral inactivation processes occur during the fractionation process. Albumin is available in two concentrations: 5% and 25%. Five percent albumin is isosmotic with plasma but 25% albumin is hyperoncotic and is roughly equivalent to a plasma volume four- to five-fold higher than the infused volume.

Indications

The University Hospital Consortium has developed a consensus statement on indications for albumin use. These include:

- volume replacement in non-hemorrhagic shock unresponsive to crystalloid;
- volume replacement after the first day in patients with extensive burns (>50%) unresponsive to crystalloid;
- volume replacement after removal of large volumes (>4 L) of ascitic fluid in patients unresponsive to crystalloid;
- replacement of ascitic fluid volume or treatment of ascites and peripheral edema postoperatively in hypoalbuminemic liver transplant recipients;
- replacement fluid for large volume therapeutic plasma exchange;
- volume replacement in patients with severe necrotizing pancreatitis; and
- diarrhea (>2 L/d) in hypoalbuminemic patients on enteral feedings, unresponsive to short chain peptide supplementation.

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Contraindications

- Patients who would not tolerate a rapid increase in circulating blood volume.
- Patients with a history of an allergic reaction to albumin.

Dose and Administration

The volume and rate of infusion should be determined by the clinical situation. If an oncotic deficit is present, 25% albumin is the product of choice; 5% albumin is used in conditions associated with volume deficit alone.

Infusion is through a standard blood set or line set supplied with the product. The line set must contain an integral airway to prevent foaming. (Also see chapter 9, page 73.)

Albumin is compatible with standard electrolyte and carbohydrate intravenous solutions such as normal saline, Ringer's lactate and D5W, but should not be co-infused with alcohol-containing solutions or protein hydrolysates.

Due to its hyperosmotic nature, 25% albumin should not be infused faster than 2 mL per minute in a 70 kg adult and proportionately slower in younger or smaller patients.

Once opened, the vial of albumin should be infused within four hours or be discarded.

Storage and Transportation

Albumin is usually stored at room temperature providing temperatures do not exceed 30°C. The shelf life can range from two to five years depending on the manufacturing process. An expiry date is stated on each package and the expiration date of each unit should be checked prior to administration.

The product should not be administered if:

- the solution has been frozen;
- the solution is turbid;
- vials are damaged; or
- particulate material (glass or cork) is visible within the solution.

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Alternatives

Alternatives to albumin therapy include both crystalloids and other colloid solutions. Generally, plasma volume expanding therapeutic agents used clinically can be classified into three broad categories:

- crystalloid;
- colloid; and
- hypertonic solutions (as alternatives to 25% albumin).

The most common crystalloids in clinical use are normal saline and Ringer's lactate. The advantages of crystalloid therapy over most colloid solutions include: decreased expense, increased urine output and the chemical simplicity that allows for simple metabolism and excretion. The disadvantages of crystalloid are primarily seen in situations requiring large volumes for clinical resuscitation, which may lead to peripheral and pulmonary edema, and a potential for hyperchloremia in patients with renal dysfunction.

Colloids differ from crystalloids in that they have an increased ability to hold water in the intravascular compartment. If there is normal membrane permeability, colloids preferentially increase plasma volume and do not enter interstitial or intracellular compartments. Colloids currently available in Canada for therapeutic use include:

- Albumin (5% and 25%)
- Dextrans (D40, D70)
- Gelatins (plasma gel, hemacel)
- Hydroxyethyl starches (pentastarch, hetastarch)

Table 1: Plasma volume expansion versus infusion volume

Infused fluid	PV	ECF	ICF
D5W 1000 mL	70 mL	280 mL	650 mL
Ringer's lactate 1000 mL	214 mL	786 mL	0 mL
5% albumin 500 mL	375 mL	125 mL	0 mL
Pentaspan 500 mL	500 mL	0 mL	0 mL

Legend PV – Plasma volume ECF – Extravascular fluid ICF – Intracellular fluid

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Potential disadvantages with colloid therapy include:

- cost, with colloids significantly more expensive than crystalloids;
- decreased recipient hemoglobin concentration following infusion;
- dilution of plasma proteins including coagulation factors; and
- circulatory overload.

Side effects specific to albumin include decreased serum calcium following infusion and a small risk of anaphylaxis. There have been no reports of HIV, hepatitis or other viral transmission at the time of writing, but a theoretical risk of vCJD transmission exists.

Two meta-analyses in the late 1990s indicated that albumin use for the treatment of hypovolemia is associated with an increase in mortality. The data is based on small RCTs which do not show a statistical increase in mortality over patients receiving crystalloid. The results of a large RCT, the SAFE trial, failed to show an increase in mortality related to albumin use in adult ICU patients. The study also failed to demonstrate any clear efficacy advantage of albumin over saline.

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Intravenous Immune Globulin (IVIG)

General Information

Intravenous immune globulin (IVIG) preparations are sterile solutions or lyophilized concentrates of human immunoglobulin that have been processed to remove polymers of immune globulin thus allowing for intravenous transfusion. Since their development in the early 1980s, they have largely replaced immune serum globulin as the therapeutic agent for patients with congenital immune deficiency. The distribution of IgG subclasses is similar to that found in normal plasma. Depending on the method of preparation, some products may also contain trace amounts of IgA and IgM. Most IVIG products are not recommended in IgA deficient patients with anti-IgA antibodies.

Product Description

Table 1: IVIG products currently supplied by Canadian Blood Services (CBS)

Product Name	IGIVnex	GAMMAGARD S/D®	IVEEGAM EN®	GAMUNEX, 10%™
Manufacturer	Talecris Biotherapeutics Inc	Baxter Bioscience	Baxter Bioscience	Talecris Biotherapeutics Inc
Supplied as	Liquid	Lyophilate	Lyophilate	Liquid
Sugar/stabilizer	Glycine	2% Glucose	5% Glucose	Glycine
Viral inactivation	Caprylate	Solvent/ Detergent	PEG Trypsin	Caprylate
Percentage IgG	≥ 98%	≥ 98% 95% monomers	> 90%	> 98%
IgA content	46 µg/mL	< 2.2 µg/mL	< 10 µg/mL	40 µg/mL
Half life	35 days	22–52 days	23–29 days	35 days
Storage	Room temp or 2–8°C	Room temp < 25°C	Refrigerate 2–8°C	Room temp or 2–8°C
Shelf life	36 months	24 months	24 months	36 months
Reconstitution time	N/A – liquid preparation	< 5 min at room temp > 20 min if cold	< 10 min at room temp	N/A – liquid preparation
Administration	10% solution Compatible with D5W	5% or 10% solution Compatible with D5W	5% solution Compatible with D5W or NaCL	10% solution Compatible with D5W
Maximum infusion rate	0.14 mL/kg/min (8.4 mL/kg/h)	4 mL/kg/h if 5% 2 mL/kg/h if 10%	2 mL per minute	0.14 mL/kg/min (8.4 mL/kg/h)

***Also see package insert for specific details and additional product information.**

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Indications

The licensed indications for IVIG use are limited. Many off-label indications account for much of the IVIG use in Canada. Requests for IVIG should be based on specific clinical indications. Local practice (such as British Columbia's IVIG Utilization Management Program) may dictate specific prerequisites and authorization prior to the release of IVIG products for off-label non-approved indications.

The currently licensed indications for intravenous immunoglobulin available in Canada include:

- Primary immunodeficiencies.
- Secondary hypogammaglobulinemia:
  - chronic lymphocytic leukemia with hypogammaglobulinemia, in those patients who have had at least one episode of major infection; and
  - hypogammaglobulinemia in post bone marrow transplant recipients.
- Immune thrombocytopenic purpura (ITP) in the following circumstances:
  - life-threatening bleeding;
  - pre-operative steroid refractory patients;
  - failed splenectomy with bleeding; and
  - AIDs related ITP.
- Kawasaki syndrome.
- Guillain-Barré syndrome.

Intravenous immune globulin is often used as an off-label therapy for diseases that may have an immune mediated or unknown pathogenic mechanism. New "indications" for the use of this product are frequently identified. A Canadian consensus working group suggested that IVIG may be considered first-line treatment for the following disorders: pure red cell aplasia, polymyositis, dermatomyositis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, juvenile rheumatoid arthritis, Stills disease, toxic epidermal necrolysis, chronic parvovirus infection, streptococcal toxic shock syndrome and alloimmune fetal thrombocytopenia.

Contraindications

IVIG is contraindicated in patients known to have had anaphylactic or severe systemic responses to IVIG previously and for individuals with selective IgA deficiency who have anti-IgA antibodies.

Administration

Dosing for IVIG infusion is dependent on the clinical indication.

Generally the immune replacement dose is 400 mg/kg/3–4 weeks whereas the immuno-suppressive dose is 1–2 g/kg over 1–2 days. Local practice guidelines and manufacturer's recommendations provide specific information on dose and duration of therapy for specific indications.

IVIG may be issued from the hospital transfusion service in individual vials or as a pooled product.

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IVIG must be administered intravenously at an infusion rate specified by the ordering physician. Complications during administration of IVIG may be related to infusion rate. Reactions can be prevented or controlled in many cases by slowing the infusion rate.

Protocols for IVIG infusion are based upon the following principles:

- Start with a slow infusion rate and monitor vital signs frequently.
- As tolerated, increase the infusion rate at regular intervals with progressively less frequent monitoring of vital signs.

The patient's response to the infusion will dictate an individualized maximum tolerable rate of infusion that may be lower than the manufacturer's recommendation.

Alternatives to IVIG therapy include IM administration of immune serum globulin for immunodeficient patients. For other indications, alternatives depend on the underlying condition.

Rh Immune Globulin

Product Description

Rh immune globulin (RhIG) is a freeze-dried preparation of human gamma globulin with antibody specificity directed against the Rh (D) antigen. This product is prepared from pooled human plasma derived from donors selected for high titers of anti-D. Although most RhIG products have high purity without high levels of complement activity, some products will contain residual antibodies against other Rh antigens.

The available vial sizes include: 120 µg (600 IU), 300 µg (1500 IU) and 1000 µg (5,000 IU) anti-D.

*** See the package insert for additional product specific details.**

Indications

There are two broad categories of clinical use: prevention of alloimmunization to the D antigen; and treatment of selected patients with immune thrombocytopenic purpura (ITP).

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A. Prevention of alloimmunization to the Rh (D) antigen:

- Prophylaxis for Rh hemolytic disease of the newborn during pregnancy
  - All Rh-negative mothers at 28–32 weeks gestation, unless they have pre-existing immune anti-D. A repeat dose may be considered if the fetus remains in utero after 40 weeks gestation.
  - All Rh-negative mothers of Rh-positive or weak D (Du) positive babies within 72 hours of delivery. If more than 72 hours elapse prior to RhIG administration, RhIG should not be withheld but should be administered as soon as possible up to 28 days after delivery.
  - At time of delivery, additional dosing may be recommended if the initial fetal-maternal hemorrhage screen is positive and a quantitative test demonstrates greater than 30 mL of fetal maternal hemorrhage.
- Rh-negative pregnant women following:
  - spontaneous or therapeutic abortion, or threatened abortion;
  - amniocentesis or chorionic villus sampling;
  - ectopic pregnancy, molar pregnancy or stillbirth;
  - obstetrical manipulations which may result in a transplacental hemorrhage; and
  - blunt abdominal trauma.
- Prophylaxis against anti-D formation following transfusion. RhIg administration should be considered whenever Rh-positive platelets or RBCs are transfused to an Rh-negative recipient. In particular, RhIg administration may be considered for recipients of Rh-positive blood products (platelets or RBCs) when they are pediatric patients under 16 years of age or female patients of child-bearing age who may become pregnant.

B. Immune thrombocytopenic purpura (ITP)

Administration of RhIG for the purposes of ITP differs from its other uses in that the patient must be Rh (D) antigen positive and must have an intact and functional spleen. In addition, intravenous administration is required.

Contraindications

A. For prevention of Rh (D) alloimmunization

- Rh (D) positive individuals;
- Rh (D) negative women who are Rh (D) immunized as evidenced by a positive antibody screening test and a demonstrated anti-D; and
- individuals with a history of anaphylactic or other severe reactions to immune globulin.

B. For immune thrombocytopenic purpura

- Rh-negative patients;
- patients with prior splenectomy; or
- individuals with known hypersensitivity to plasma products.

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Dose and Administration

WinRho SDF™ Rh immune globulin can be administered by either an intravenous or intramuscular route for most indications.

A. Prevention of Rh (D) alloimmunization

	Indication	Dose (IM or IV)
Pregnancy	28 weeks gestation	1,500 IU or 300 µg
	Postpartum with Rh+ infant	1,500 IU or 300 µg or as calculated following quantitation of fetal maternal hemorrhage
Obstetrical	Abortion – therapeutic, threatened or spontaneous	1,500 IU or 300 µg
	Amniocentesis or chorionic villus sampling(CVS) < 34 weeks gestation	1,500 IU or 300 µg
	Amniocentesis, CVS or other manipulations >34 weeks	600 IU or 120 µg
Transfusion		Rule of thumb: 300 µg (1500 IU) is required for each 15 mL RBC or 30 mL whole blood

B. Idiopathic thrombocytopenic purpura

Dosing will vary between 25–75 µg/kg depending on the patient's baseline hemoglobin and local practice. Administration must be via an intravenous route for efficacy in this disorder.

Monitoring of hemoglobin concentration post-administration should be undertaken to detect significant hemolysis.

Storage

2–8ºC

Use within four hours of reconstitution.

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Hyperimmune Globulins

General Information

These fractionation products are created from pools of human plasma specifically selected for high titers of antibodies with selected specificities, and undergo various viral inactivation procedures depending on manufacturing processes.

Contraindications for hyperimmune globulins include:

- IgA deficiency;
- previous severe or allergic reaction to product; and
- any condition that would contraindicate intramuscular injections.

Refer to manufacturer's product insert for most up-to-date information on dose, administration, and potential side effects.

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Table 2: Hyperimmune globulins

Product Name	Manufacturer	Description	Dose and administration	Indication
Varicella-Zoster Immune Globulin (VZIG)	Massachusetts Public Health Biologic Laboratories	Liquid formulation S/D treated Vials = 1.25 mL (125 IU) or 6.25 mL (625 IU) Store at 2–8°C	Intramuscular administration Wgt(kg) Dose(IU) 0-10 125 10.1-20 250 20.1-30 375 30.1-40 500 >40 625 Should be administered within 96 hours of exposure	Passive immunization in susceptible patients following significant exposure to Varicella Zoster
Hepatitis B Immune Globulin (HBIG; BayHep B®)	Talecris Biotherapeutics Inc.	Liquid formulation S/D treated Vials = 1 or 5 mL vial or a 0.5 mL neonatal syringe with ≥ 217 IU/mL Store at 2–8°C	Intramuscular administration *See insert dose = 0.06 mL/kg For neonatal prophylaxis 0.5mL within 12 hours of delivery	Post exposure prophylaxis for individuals without known anti-HBs following: sexual contact, needle stick injury, mucus membrane contact and household exposures Infants born to HBsAg positive mothers
Anti-RSV Immune Globulin Respigam®	Massachusetts Public Health Biologic Laboratories	Liquid formulation S/D treated Vials = 20 and 50 mL vials with concentration of 50±10 mg/mL Store at 2–8 C	Intravenous administration Maximum monthly dose = 750 mg/kg Maximum infusion rate = 6.0 mL/kg/h	Prophylaxis against respiratory syncitial virus (RSV)
Cytomegalo-virus Immune Globulin (CMVIG, Cytogam®)	Massachusetts Public Health Biologic Laboratories	Liquid formulation S/D treated Vials = 20 & 50 mL Conc.=50±10 mg/mL Store at 2–8°C	IM or IV administration Maximum total dose of 150 mg/kg Use within 6 hours of entering vial	Immuno-compromised individuals – for prevention and treatment of CMV, especially following solid organ transplantation

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Further Reading

1. Roifman C, et al. Present and future uses of IVIG: A Canadian multidisciplinary consensus building inititiative. Canadian Journal of Allergy & Clinical Immunology 1997; 2: 176-207.
2. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev 2003; 17: 241-251.
3. Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0)(D) immune globulin intravenous administration for immune thrombocytopenic purpura. Blood 2005; 106: 1532-1537.
4. Intravenous immune globulin (IVIgG) package inserts.
5. Rh immune globulin package insert.

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Man-Chiu Poon

General Description

Coagulation factor concentrates available to Canadian patients as either licensed products or unlicensed concentrates are listed in Table 1. The unlicensed products and some licensed products that have not undergone Health Canada batch release are obtained under the Health Canada Special Access Program (SAP) (see Legend, Table 1). Readers are also referred to the World Federation of Hemophilia (WFH) annually updated registry on worldwide availability of clotting factor concentrates for the treatment of congenital clotting factor deficiency (Kasper CK, Costa e Silva M. Registry of clotting factor concentrates [**www.wfh.org** ➜ Publications ➜ Treatment Products]).

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Table 1: Coagulation factor concentrates available or potentially available in Canada*

No	Factor concentrate (†Health Canada licensed)	Manufacturer	Viral inactivation procedure	Maximum specific activity, IU/mg protein (‡human serum albumin in formulation)	Storage temp (°C)/RT storage period (m)#	Av. recovery (U/dL per IU/kg infused)¶	Av. $T_{1/2}$	Comments
	Factor VIII recombinant							
1	Kogenate FS®†	BayerHealthcare	Solvent detergent/ high salt hold	>3000	2–8/3##	~2	15h	Full length FVIII, no vWF
2	Helixate FS®†	ZLB-Behring	Solvent detergent/ high salt hold	>3000	2–8/3##	~2	15h	Full length FVIII, no vWF
3	Recombinate®†	Baxter BioScience	No specific step§	>3000‡	2–8/6	2.4	14.6h	Full length FVIII, no vWF
4	ReFacto®†	Wyeth	Solvent detergent	13,700	2–8/3	2.4	14.5h	B-domain deleted FVIII, no vWF
5	rAHF-PFM (Advate®)	Baxter BioScience	Solvent detergent	4,000–10,000	2–8/6	2.4±0.5	12±4.3h	Full length FVIII, no vWF
	Factor VIII High Purity							
6	Monoclate-P®†	ZLB-Behring	Pasteurization	>3000‡	2–8/6	1.9	17.5h	No vWF
7	Hemofil M®†	Baxter BioScience	Solvent detergent	>3000‡	2–8	2	14.8h	No vWF
8	Porcine VIII (Hyate:C®)**	IPSEN, Inc	None; end product cell culture viral screen§	≥140	–15 to –20	1.5	10-11h	

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Table 1: Coagulation factor concentrates available or potentially available in Canada* (continued)

No	Factor concentrate (†Health Canada licensed)	Manufacturer	Viral inactivation procedure	Maximum specific activity, IU/mg protein (‡human serum albumin in formulation)	Storage temp (°C)/RT storage period (m)#	Av. recovery (U/dL per IU/kg infused)¶	Av. $T_{1/2}$	Comments
	Factor VIII/vWF concentrate							
9	Humate P™†	ZLB-Behring	Pasteurization	FVIII 1.3–2.6‡ Rcof 3.3–6.6	2-8	2.0/1.9 (FVIII/ Rcof)	10.3/12.2h (FVIII/Rcof)	vWF to FVIII ratio: >2.2
10	Immunate®	Baxter BioScience	Pasteurization/ detergent	FVIII 70±30‡	2–8/3	~2	12h (FVIII)	vWF to FVIII ratio: >0.5
11	Alphanate®	Grifols	Solvent detergent/ dry heat	FVIII 140‡	2–8/2	2.1/2.9 (FVIII/Rcof)	23.8/6.5h (FVIII/ Rcof)	vWF to FVIII ratio: 1–2.6
	Factor IX recombinant							
12	BeneFIX®†	Wyeth	Nanofiltration	≥9200	2–8/6	0.80 (>15y age); –0.65 (≤15y age)	19.4h	
	Factor IX (high purity)							
13	Immunine®†	Baxter BioScience	Pasteurization/ detergent	100±50	2–8/3	1.11 (>15y age); 0.91 (≤15y age)	17h	
14	Mononine®†	ZLB-Behring	Sodium thiocyanate/ ultra filtration	>190	2–8/1	1.23	22.6h	
15	Alphanine SD/Virus Filtered®	Grifols	Solvent detergent/ nanofiltration	246±47	2–8/1	0.96	21h	

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Table 1: Coagulation factor concentrates available or potentially available in Canada* (continued)

No	Factor concentrate (†Health Canada licensed)	Manufacturer	Viral inactivation procedure	Maximum specific activity, IU/mg protein (‡human serum albumin in formulation)	Storage temp (°C)/RT storage period (m)#	Av. recovery (U/dL per IU/kg infused)¶	Av. $T_{1/2}$	Comments
	Prothrombin Complex Concentrate							
16	Prothromplex-T®	Baxter BioScience	Vapor heat	IX: 2.5; II:2.5; VII: 2.5; X:2.5	2–8	~1/~2/~2 (IX/II/X)		Heparin, AT added ~1 IU FX, 1 IU FII, I IU FVII per IU FIX
	Activated Prothrombin Complex Concentrate							
17	FEIBA®†	Baxter	Vapor heat	0.75–2.5	2–8/6		6–12h	No heparin added
	Fibrinogen							
18	Haemocomplettan®	ZLB-Behring	Pasteurization	0.68 mg/mg‡	2–8	1.38–1.45	3d	
	Factor VII							
19	Factor VII Concentrate TIM 4	Baxter BioScience	Vapor heat	1.5–10	2–8	~2	3.5h	
	Factor VIIa Recombinant							
20	Niastase®†	Novo Nordisk	Detergent	50 KIU/mg	2–8	45.6%/43.5% (non-bleeding/ bleeding state)	3.1/2.6h (adult/ children)	
	Factor XI							
21	Hemoleven®	LFB (France)	Solvent/detergent nanofiltration		2–8	~2	35h	Heparin, AT, C1-inactivator added
22	Factor XI concentrate	BPL (UK)	High dry heat	35	2–8/1 week	2.4	48h	Heparin, AT added

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Table 1: Coagulation factor concentrates available or potentially available in Canada* (continued)

No	Factor concentrate (†Health Canada licensed)	Manufacturer	Viral inactivation procedure	Maximum specific activity, IU/mg protein (‡human serum albumin in formulation)	Storage temp (°C)/RT storage period (m)#	Av. recovery (U/dL per IU/kg infused)¶	Av. $T_{1/2}$	Comments
	Factor XIII							
23	FibrogamminP®	ZLB-Behring	Pasteurization	3.6–8.9‡	2–8	1.6	9.3d	
	Antithrombin							
24	Antithrombin III Immuno®†	Baxter BioScience	Vapor heat	1–2.5	2–8	~2	2.5d	
25	Kybernin P®	ZLB-Behring	Pasteurization	5.26	2–8	1.5	2.5d	
	Protein C							
26	Ceprotin®	Baxter BioScience	Pasteurization/ detergent	~11.8‡	2–8	~0.83	5.6h	

* Ordering: Canadian Blood Services (CBS) for licensed products; Health Canada Special Access Program (www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_sap_drugs_e.html; Tel–office hours: 613-941-2108; off hours 613-941-3061) for all unlicensed and some licensed products not yet batch-released by Health Canada.

Abbreviations: pd = plasma-derived; r=recombinant; h=hour(s) d=day(s).

† Health Canada licensed.

‡ Contains human serum albumin in formulation – final specific activity therefore would be lower.

RT = room temperature <30°C. Manufacturers recommend against refrigeration once stored at RT and to mark date removed from refrigeration on box.

§ Specific viral inactivation procedures are not used, but some of the manufacturing or purification steps have virus reduction or removal capability.

¶ Recovery (activity in IU/dL recovered in circulation after 1 IU/kg infused) and $T_{1/2}$ (half-life) in patients with severe congenital deficiency (not in patients with acquired deficiency) and for AT and protein C recovery and $T_{1/2}$ are expected to be lower during acute thrombotic events). Recovery and $T_{1/2}$ provided here are provided as rough guides only—the precise recovery and $T_{1/2}$ for a particular patient may be different and can be determined by pharmacokinetic studies to help with more precise dosing and dosing intervals (see Chapter 17). Recovery tends to be lower in children with higher plasma volume.

Approved by the FDA for storage in room temperature for up to 3 months. Approval by Health Canada pending.

** Porcine VIII (Hyate:C®) may not be available long-term.

Plasma-Derived vs. Recombinant Concentrates

Plasma-derived (pd)

The majority of clotting factor concentrates are manufactured from pooled screened donor plasma. As indicated in Table 1, the purity of different products differs and, in the case of very high purity products, human serum albumin (HSA) may be added as a stabilizer in the final formulation.

Recombinant (r)

Recombinant clotting factor concentrates are manufactured by biotechnology. Clotting factors are expressed in cultured mammalian cells transfected with vectors carrying the clotting factor gene, and the clotting factor protein secreted into the culture medium is purified and formulated for therapeutic use.

First generation recombinant products: human/animal proteins are present in the manufacturing process with human serum albumin in the final formulation. Example: Recombinate® (FVIII).

Second generation recombinant products: human/animal proteins present in the manufacturing process but not in the final formulation. Examples: Kogenate® FS/Helixate®-FS, ReFacto® (all FVIII) and recombinant FVIIa (manufactured in the presence of fetal calf serum but is purified and formulated without human proteins).

Third generation recombinant products: human and animal proteins are not present in the manufacturing process or in the final formulation. Examples: BeneFIX® (rFIX, Wyeth), ReFacto AF® (rFVIII, Wyeth). Another third generation FVIII product Advate® (rAHF-PFM, Baxter) is already licensed by the FDA and is awaiting Health Canada licensure.

Viral Safety

The chromatographic purification processes used during fractionation remove viruses. Additionally, virus inactivation/partitioning procedures are incorporated into the manufacturing process of all plasma-derived concentrates and most of the recombinant concentrates (see Table 1). The virus inactivation procedures are all effective against important human pathogens such as HIV, HCV and HBV, and no case of HIV or HCV transmission because of concentrate use has occurred since 1987 and 1988 respectively. However, no virus inactivation procedure is expected to inactivate all viruses. In particular non-enveloped viruses such as parvovirus B19, a pathogen in immunosuppressed patients, can be resistant to viral inactivation. Patients with congenital coagulation deficiency expected to receive any blood product(s) should be immunized against hepatitis B virus (HBV) and hepatitis A virus (HAV).

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Prevention of Thrombotic Complications

Clotting factor concentrates affect hemostasis by correcting the underlying clotting defect. Patients with coexisting risk factors for thrombosis and DIC as well as coagulation factor deficiency may develop thrombotic complications when the hemostatic mechanism is corrected. Prothrombin complex concentrate, factor XI concentrate and rFVIIa should be used with caution in patients with risk factors for thrombosis and DIC, such as sepsis, crush injury, atherosclerosis and advanced age. The dosage for FEIBA should not exceed 200 IU/kg/day and that of FXI concentrate should not exceed 30 IU/kg per dose. Thrombosis has been reported even in patients with von Willebrand's disease treated to raise factor VIII level in excess of 2 U/mL in the surgical setting. Antifibrinolytic therapy should be avoided when using prothrombin complex concentrates including FEIBA.

Allergy Precautions

As with infusion of any protein products, allergic reactions may occur. Minor allergic reactions may be prevented by pre-medication with antihistamine. When an allergic reaction occurs, a similar concentrate from a different manufacturer can be tried for subsequent therapy and may not result in an allergic response. Patients on home-therapy should have epinephrine (e.g. Epipen®) on hand to deal with serious allergic reactions or anaphylaxis. Some concentrates may contain trace amounts of proteins of hamster (all recombinant products), or bovine (first and second generation recombinant products) origin or mouse immunoglobulins (products that incorporate mouse monoclonal antibodies in the purification processes, e.g. all presently available recombinant FVIII, Monoclate-P, Hemofil M, Mononine). The manufacturers advise caution in the use of their respective products in patients with known allergy to these proteins. Hemophilia B patients may have severe allergic responses (including anaphylaxis) to factor IX containing concentrates at the time inhibitors are developed. In susceptible severe hemophilia patients, inhibitors develop usually early on with factor IX concentrate treatment. It is advisable to treat newly diagnosed severe hemophilia B patients in a setting equipped for management of severe allergic reactions during the first 20 or so treatments.

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Storage and Transportation

All but a few coagulation factor concentrates are stable to the printed expiration date when stored refrigerated at 2–8°C (Table 1). Long distance transportation occurs in validated transport containers cooled with cold packs. Some, but not all, concentrates can be stored at room temperature (usually less than 30°C) for a specified period (see Table 1). When it is necessary to store at room temperature, the date when the box is removed from refrigeration must be clearly marked on the box, and the manufacturers do not recommend returning these room temperature stored concentrates to refrigeration. Freezing should be avoided except for porcine FVIII, which must be stored and transported frozen at –15 to –20°C.

Reconstitution

Almost all clotting factor concentrates available to Canadian patients are supplied in packages containing a kit for reconstitution and infusion, usually the appropriate diluent, double-ended needles for transferring diluent to the vial containing the lyophilized concentrate, and filter needle or spike for withdrawing the dissolved concentrate to syringes for infusion. Kogenate FS® (Bayer), Recombinate® (Baxter) and Advate® (Baxter) are supplied with proprietary needle-less reconstitution sets (BIOSET® from Bayer, BAXJECT® from Baxter), which allow transfer of diluent and withdrawal of dissolved concentrate without multiple punctures of the vials. The reconstitution instructions in the product insert must be followed and aseptic techniques must be observed. In general, the vials of diluent and concentrate should be pre-warmed to 20–37°C before mixing and the diluent should, if possible, be allowed to flow down the side of the vial wall, and the mixture should then be swirled gently to allow dissolution of the concentrate. Shaking may create bubbles, resulting in denaturation of the proteins that must be avoided. Diluent (sterile water) is not supplied for the fibrinogen concentrate Haemocompletten (Aventis-Behring).

Specific Properties and Indications of Factor Concentrates

Table 1 provides the properties and other characteristics of individual factor concentrates, and Table 2 provides indications, monitoring, contraindications/ precautions and available alternatives for different classes of factor concentrates.

For specific product information refer to the package insert provided by the manufacturer of each concentrate.

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Table 2: Use of coagulation-factor concentrates

Item No (refer to Table 1)	Factor concentrate	Indications (for treatment and prevention of bleeding)	Monitoring	Contraindications/precautions (allergy precautions under general description)	Available alternatives
1-5	Recombinant FVIII	▪ Hemophilia A	▪ FVIII level	▪ Not for vWD – no vWF	▪ Pd FVIII ▪ Desmopressin for responsive mild patients ▪ Cryoprecipitate
6-7	High purity pd FVIII	▪ Hemophilia A	▪ FVIII level	▪ Not for vWD – no vWF	▪ rFVIII ▪ Desmopressin for responsive mild patients ▪ Cryoprecipitate
8	Porcine FVIII	▪ Hemophilia A with inhibitor ▪ acquired FVIII inhibitor	▪ FVIII level	▪ May cause platelet agglutination & thrombocytopenia – from small amount of porcine vWF present ▪ Inhibitor to porcine FVIII may develop	▪ rFVIIa ▪ FEIBA
9-11	pd FVIII/vWF concentrate	▪ Von Willebrand's disease ▪ Hemophilia A	▪ FVIII level, vWF:Rcof level ▪ FVIII level	▪ FVIII:vWF ratio varies (see Table 1) ▪ Keep FVIII <2 U/ml (thrombosis precaution) especially in surgical setting	▪ Desmopressin for responsive types 1 and 2A vWD patients and for responsive mild Hemophilia A ▪ Cryoprecipitate
12	Recombinant FIX	▪ Hemophilia B	▪ FIX level	▪ ~50% FIX inhibitor patient may develop severe allergic reaction at time of inhibitor development ▪ These patients may develop nephrotic syndrome with ITI	▪ High purity pd FIX

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Table 2: Use of coagulation-factor concentrates (continued)

Item No (refer to Table 1)	Factor concentrate	Indications (for treatment and prevention of bleeding)	Monitoring	Contraindications/precautions (allergy precautions under general description)	Available alternatives
13–14	High purity pd FIX	■ Hemophilia B	■ FIX level	■ See rFIX above	■ rFIX
15-16	Prothrombin complex concentrate (PCC), non activated	■ Rapid reversal of warfarin overdose, vitamin K deficiency ■ FX deficiency ■ FII deficiency	■ INR ■ FX level ■ FII level	■ Thrombotic precaution (see General Description)	■ Plasma ■ Vitamin K ■ Plasma
17	Activated prothrombin complex concentrate	■ FVIII inhibitor ■ FIX inhibitor	■ Clinical	■ FVIII inhibitor: may cause anamnesis – do not use while patient is waiting for ITI ■ FIX inhibitor: do not use if patient has allergic reactions to FIX ■ Thrombotic precaution – limit dosage to 200 IU/kg/d	■ Porcine FVIII and rFVIIa for FVIII inhibitor ■ rFVIIa for FIX inhibitor
18	pd Fibrinogen concentrate	■ Congenital fibrinogen deficiency	■ Fibrinogen level		■ Cryoprecipitate (~200 mg/bag)
19	pd FVII concentrate	■ FVII deficiency	■ FVII level		■ rFVIIa
20	Recombinant FVIIa	■ FVIII inhibitor ■ FIX inhibitor ■ FVII deficiency (50 IU/microgram)	■ Clinical ■ Clinical ■ FVII level	■ Thrombosis precaution – see General Description	■ FVIII inhibitor: porcine FVIII, FEIBA ■ FIX inhibitor: FEIBA ■ FVII deficiency: pd FVII

Table 2: Use of coagulation-factor concentrates (continued)

Item No (refer to Table 1)	Factor concentrate	Indications (for treatment and prevention of bleeding)	Monitoring	Contraindications/precautions (allergy precautions under general description)	Available alternatives
21-22	pd XI concentrate	▪ FXI deficiency	▪ FXI level	▪ Thrombosis precaution – limit dosage to ≤30 IU/kg	▪ Plasma
23	pd FXIII concentrate	▪ FXIII deficiency	▪ FXIII level		▪ Plasma ▪ Cryoprecipitate
24-25	pd antithrombin concentrate	▪ AT deficiency in high thrombotic risk situation such as surgery ▪ Overwhelming sepsis with DIC/thrombosis	▪ Antithrombin level		▪ Plasma
26	pd protein C	▪ Homozygous protein C deficiency ▪ Overwhelming sepsis with DIC/thrombosis	▪ Protein C level		▪ Plasma ▪ Activated protein C concentrate

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Further Reading

The product monograph (package insert) should be consulted for further information about the various products discussed in this chapter.

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Mindy Goldman

Donor Screening

All blood transfused in Canada is collected from volunteer donors. Donors are questioned about medical conditions and behaviors to determine if their donation would pose an increased risk for their own health or the health of the recipient. At registration donors must provide identification, and computer records are checked to see if a deferral code has been attributed to that donor after previous donations. Donors are provided with a pamphlet explaining the donation process, the testing that will be done on their blood, and the obligatory Health Canada requirement for reporting certain testing results to public health authorities. The pamphlet also explains the risk factors for HIV and hepatitis transmission and the possibility that testing may fail to identify individuals who are in the early stage of infection.

After reading the pamphlet, the donor's medical history is assessed by means of a standard questionnaire. Donors are asked about risk factors for transfusion-transmissible diseases and about illness in major organ systems that may put them at increased risk of an adverse reaction at the time of donation. As screening tests have been improved, the importance of the health assessment questionnaire in eliminating donors at risk for HIV and hepatitis has decreased. However, at the present time, the questionnaire is the only means of excluding donors with a risk of CJD, vCJD, malaria, Chagas disease, babesiosis, or leishmaniasis, since testing is not performed for these agents. In addition, donors taking teratogenic medications are identified and excluded from donation. Depending on the magnitude of the risk, donors may be deferred temporarily or indefinitely. For example, people who have taken illegal drugs by injection are indefinitely deferred, while travellers to a region where malaria is considered endemic are deferred from donation of cellular blood components for only one year.

Donors must be at least 17 years old (18 in Quebec) and weigh 50 kg or more. Blood donors may donate whole blood every 56 days. The time for phlebotomy varies from 10 to 15 minutes. Approximately 18% of donors are considered ineligible at the collection site, with inadequate hemoglobin levels accounting for close to half of these deferrals. Approximately 3% of donors are indefinitely deferred, with travel to regions considered at risk for vCJD constituting the largest single cause for indefinite deferral. It is estimated that three in 100 people eligible to donate in Canada actually are active blood donors, and the average donor donates approximately twice a year.

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The Whole Blood Donation Process

A donor's blood pressure, pulse, and temperature are taken prior to donation and must be normal. A measure of the donor's hemoglobin level is done. The acceptable minimum hemoglobin is 125 g/L for both men and women. Approximately 450 mL of blood are taken per whole blood donation.

Prior to donation, both arms are examined for signs of injection intravenous drug use (IDU). The donor's skin is disinfected using a two-step method. A scrub step, using a small scrub brush imbibed with 70% isopropyl alcohol, is followed by a preparation step using an ampoule containing tincture of iodine. Chlorhexidine and 70% isopropyl alcohol are used for donors allergic to iodine. Phlebotomy is performed using a sterile single-use kit that contains an anticoagulant nutritive solution. The first few millilitres of blood are directed to a diversion pouch before filling the main collection bag. The diversion pouch has been shown to decrease the penetration of skin flora into the main collection bag. The blood in the diversion pouch is used for the serological and infectious disease testing performed on each blood unit.

Apheresis Donations

Criteria for apheresis donations are very similar to those for allogeneic whole blood donation. Several additional criteria are present to ensure the safety of the donor and the quality of the component. Plateletpheresis donors must have a platelet count of 150 x 10^9/L prior to undergoing each procedure. Plateletpheresis may be performed every 14 days for a maximum of 24 donations in a calendar year. Plasmapheresis donors must be demonstrated to have a total serum protein of over 60 g/L and a normal serum protein composition. These tests must be repeated every four months. Donors may make weekly plasmapheresis donations. The maximum quantity of plasma that may be collected per donation and during a six-month period is dependent on the donor's weight.

All plateletpheresis products in Canada are tested for bacterial contamination using an automated blood culture system. Due to the volume of product required for this testing, it is not practical to perform automated blood cultures on individual whole blood derived platelet units at this time. Some hospitals may choose to utilize methods to confirm sterility prior to issue of the units for transfusion. Following the change to buffy coat component production platelets, pooled LR will be tested for bacterial contamination using the same automated blood culture system as is used for plateletpheresis products.

Tests Performed on Blood Donations

The tests performed on each blood donation may detect antigen, antibody or nucleic acid of the infectious agent (Table 1). Antibody and antigen testing are done on individual donor samples, while nucleic acid testing (NAT) is done in pools of 24 samples for HIV and HCV, or pools of six samples for WNV. As new technology is developed, it is possible that single unit NAT may be performed in the future. In particular, single unit NAT testing may be necessary to optimize sensitivity for West Nile virus.

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Table 1: Transfusion transmissible disease testing

Pathogen	Screening tests	Additional tests
HIV 1/2	▪ Anti-HIV 1/2 chemiluminescent assay ▪ Pooled nucleic acid amplification (NAT) testing	▪ Western blot ▪ Resolution to single unit of pool
Hepatitis B	▪ Hepatitis B surface antigen (HBsAg) chemiluminescent assay ▪ Anti-hepatitis B core (HBc) chemiluminescent assay	▪ Neutralization assay ▪ None available, experimental NAT
Hepatitis C	▪ Anti-hepatitis C Virus (HCV) chemiluminescent assay ▪ Pooled NAT testing	▪ Recombinant immunoblot assay (RIBA) ▪ Resolution to single unit of pool
HTLV I/II	▪ Anti-human T-cell lymphotrophic virus (HTLV) I/II chemiluminescent assay	▪ Western blot
Syphilis	▪ Micro-hemagglutination assay for *Treponema pallidum* (MHATP)	▪ Fluorescent treponemal antibody absorption (FTA-ABS), ▪ MHATP performed by public health labs
West Nile virus	▪ Pooled NAT testing	▪ Resolution to single unit of pool
Cytomegalovirus (CMV)	▪ Anti-CMV particle agglutination assay	▪ None available

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Antigen and Antibody Testing

Donors who have initially reactive results on antigen or antibody testing have repeat testing performed twice on the same sample. If one of these two repeats is positive, the donation is discarded and additional testing is performed. Confirmatory tests, such as western blots or radioimmunoprecipitation assays (RIBA), are more specific than the initial screening tests. They may give positive, negative, or indeterminate results. At the present time, donors are indefinitely deferred after one repeat reactive result, with the exception of anti-HBc testing. Since the false positive rate is considerably higher for anti-HBc, a modified approach is used by CBS. Donors with repeat reactive anti-HBc results, who are also anti-HBs and/or HBV NAT positive on supplemental testing, are indefinitely deferred. Donors with anti-HBc repeat reactive results alone are deferred only after obtaining repeat reactive results on two positive donations. Deferred donors are informed of their testing results and excluded from future allogeneic blood donation. Inventory retrieval and notification of the hospitals that received components of previous donations may be necessary.

Approximately 0.2% of donors are repeat reactive for a transfusion transmissible marker and 0.05% of donors are confirmed positive. An additional 0.6% to 0.8% of donors are repeat reactive for anti-HBc. Deferral for false positive test results is an important source of donor dissatisfaction and donor loss. Re-entry protocols may be developed to address this problem. Testing for antibodies to cytomegalovirus (CMV) is performed on a subset of donations in order to provide CMV seronegative components for at-risk patient groups.

Nucleic Acid Amplification Testing (NAT)

If NAT testing is positive on a pool, each individual sample in the pool will be retested alone. False positive results on individual samples are extremely rare.

Blood Group Determination and Antibody Detection

ABO and Rh(D) grouping are performed using an automated hemagglutination assay. Manual confirmatory typing is done for first-time donors found to be Rh(D) negative, and donors are tested for the presence of D and weak D antigens. Testing is also performed for unexpected red cell antibodies. The methods used may be less sensitive than those required in pre-transfusion antibody detection. In recipient testing, a low level of antibody may be of clinical importance, since an anamnestic response may occur. In donor testing, only a small amount of passive antibody transfusion will occur and in most instances it is insignificant, therefore a weak antibody is of minimal importance.

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Pathogen Reduction Systems

Pathogen reduction systems are under development for plasma, platelets and red cell components. Pathogen inactivation methods for plasma include solvent-detergent treatment of plasma in pools and methylene blue followed by UVA irradiation for single unit plasma. Pathogen reduction methods for platelets include S59 plus UVA irradiation and riboflavin plus UV light irradiation. Pathogen reduction has been demonstrated to decrease bacterial, viral and protozoal pathogens by several logs. At this time, cellular components that have undergone pathogen reduction are not currently licensed for use in Canada. Plasma that has undergone pathogen reduction using solvent-detergent has recently been licensed and may soon be available.

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Barbara Hannach

General

Traditionally all plasma fractionation products were derived from pooled human plasma. More recently, products made with recombinant technology have become available. Proteins are expressed in cultured mammalian cells transfected with vectors carrying the particular gene of interest. The protein secreted into the culture medium is purified and formulated for therapeutic use.

"First generation" recombinant products contained a small amount of human plasma protein, usually albumin, to provide for product stability. Advances in the manufacturing process have evolved so that most, but not all, of the recombinant products currently available no longer contain any human protein and are manufactured without exposure to human or animal proteins.

Not all of the products available in Canada have been licensed by Health Canada, nor are products always used for licensed indications. It is up to the manufacturer to submit products with their indications for use to Health Canada for licensing. If the product is new or has a very limited application, the manufacturer may not apply for a license in every jurisdiction where it is sold. For this reason, a few products can only be issued for use by a specific patient with a Special Product Release (SPR) from Health Canada. Permission must be obtained from Health Canada by the treating physician or his/her delegate before the product can be sent to the hospital.

This section will discuss in general terms the various methods and principles by which fractionated products are made.

The reader is advised to consult the product monograph or package insert for details concerning specific products.

Recombinant Products

Factors VIII, IX, VIIa and activated protein C are currently available as recombinant products. They are manufactured by inserting the appropriate gene into hamster ovary cells that are grown in cell culture. The gene product is then harvested, stabilized, purified and packaged for use. As with any pharmaceutical product, multiple steps are in place to ensure the safety, potency and efficacy of the product. Chapter 5: Coagulation Factor Concentrates has detailed information on the available recombinant clotting factor proteins.

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Plasma Derived Products

These products are made by pooling the plasma from large numbers of donors (>10,000) and then separating out, or fractionating, the different constituents. The Cohn fractionation process, developed during World War II, varies the temperature, pH and ethanol concentration to precipitate the various plasma fractions in a stepwise manner. The supernatant or waste from one precipitation step becomes the starting material for the next one. Each fraction is then processed separately to remove impurities, stabilize the product, inactivate and/or remove pathogens and ensure sterility. The basic Cohn-Oncley fractionation process is very efficient and with modifications is still in use today. Improvements and additions to the basic process such as liquid chromatography and monoclonal affinity columns have increased the yield and purity of the final product.

Disease Reduction Steps

Although zero risk cannot be guaranteed, manufacturers incorporate multiple steps at various points before, during and after the manufacturing process to reduce the risk of transfusion transmissible disease. These multiple steps ensure a many-fold (often more than 10 log) reduction of any agent they are designed to reduce in the final product.

Donor Screening

The mainstay of preventing disease transmission, whether plasma is derived from a whole blood donation (recovered plasma) or is obtained by apheresis technology, is donor health screening. This is done through a health assessment at the time of donation and laboratory testing of a sample of blood at the time of each donation.

In Canada, whole blood donors have a sample from each donation tested for syphilis, hepatitis B surface antigen (HBsAg) and antibodies to human T cell lymphotrophic virus I/II (HTLV I/II), human immunodeficiency virus 1/2 (HIV 1/2) and hepatitis C (HCV). Recently sensitive nucleic acid tests (NAT) for HCV, HIV and West Nile virus (WNV) have been added and are done on pooled donor samples. Anti-hepatitis B core (anti-HBc) antibody testing has been implemented recently.

Apheresis plasma donors, because they can donate up to 31 L/year, have a serum protein determination performed with each donation, quarterly testing of immunoglobulin levels and an annual physical examination by a physician, in addition to the health assessment performed on all blood donors. In Canada, the same infectious disease studies performed on whole blood donations are also done on apheresis plasma (see Chapter 6: Donor Screening and Pathogen Reduction).

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Not all fractionated products are derived from plasma originating from Canadian donors. Commercial products made with plasma from non-Canadian donors may not have the exact same screening procedures or tests performed as in Canada. They would, however, meet their local and/or United States Food and Drug Administration (FDA) licensing requirements for donor screening and testing. Usually products available in Canada meet local, FDA and Health Canada licensing requirements.

Refer to the product monograph for details about a specific product.

Additional Testing

In addition to individual donor sample testing that is done before the plasma is sent for fractionation, there are a number of tests that may be performed by manufacturers. Recently, sensitive tests for non-lipid enveloped viruses have been introduced. Parvovirus B19 and hepatitis A virus are examples of non-lipid enveloped viruses that are difficult to inactivate. Currently there is no testing for hepatitis A. However for parvovirus B19, donor plasma that has very high titers of virus is removed from further manufacture. This ensures that the final product contains less than an infectious dose of virus. All products are tested to ensure that they are pyrogen-free and sterile.

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Pathogen Inactivation/Reduction Processes

There are a variety of methods available to decrease the risk of viral transmission. Most manufacturers use a combination of two or more complementary processes. The degree of effectiveness is validated by determining virus recovery from microbially contaminated test samples following the pathogen inactivation process.

Some commonly used pathogen inactivation/reduction methods include:

Heat treatment: This can be dry, steam or wet (pasteurization) depending on the product. The specific temperature, pressure and length of time are predetermined for each product so that specific pathogens are inactivated without undue loss of product activity.

Solvent-detergent treatment: This method, although used by most manufacturers, is only effective against viruses with a lipid envelope. In this process water immiscible solvents are used in combination with detergents to disrupt the lipid membrane of viruses. As these reagents are mildly toxic, they must be removed at a later stage in the manufacturing process.

Pathogen reduction: The fractionation process itself decreases bacterial and viral contamination, as the changes in pH, temperature and ethanol concentration keep microbial contamination low and lead to the physical separation of viruses from proteins. Additional processes such as chromatography and nanofiltration are often used in addition to fractionation to obtain even greater removal of pathogens and enhance the purity of the product.

Conclusion

Although zero risk of disease transmission cannot be guaranteed, the fractionation products currently available are manufactured following Good Manufacturing Practices using validated processes and with sufficient quality control testing to ensure that they meet the ever-rising standards for purity, potency, efficacy and safety.

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Debra Lane

Introduction

Pre-transfusion testing refers to the laboratory tests required to ensure compatibility between the blood of the transfusion recipient and the blood component intended for transfusion. This process entails the collection and labelling of a blood sample from the patient, laboratory testing to determine the blood group and identify the presence of alloantibodies and, for some blood components, compatibility testing between the recipient and the donor blood. The pre-transfusion testing is completed when a compatible component, "tagged" or labelled with the name and identification number of the intended recipient, is issued from the transfusion service ready for transfusion.

Specimen Collection

The first step in pre-transfusion testing is the collection of a blood sample from the intended transfusion recipient. It is essential that hospitals and clinics collecting samples for pre-transfusion testing have a specific policy and procedure for positive patient identification and appropriate labelling of the sample in the presence (at the bedside) of the patient. Samples must be labelled with two unique identifiers. Often these include first and last name and either the hospital number or provincial health insurance number. Specific local policies related to labelling requirements should be consulted prior to blood collection. The sample must be labelled according to these requirements immediately following collection and in the presence of the patient.

A non-hemolyzed sample of blood is required for testing. The samples used for patient testing may be anticoagulated in EDTA (preferred) or may be clotted blood and serum, depending on local policy. Compatibility testing results generally expire three days following collection. Retesting is necessary after three days to ensure compatible blood availability for the patient. This testing frequency is required because of the possibility of antibody development in patients exposed to red cell antigens by transfusion or pregnancy during this interval. If the patient has not been recently transfused or is not currently pregnant, samples for pre-transfusion testing may be tested in advance and the validity of compatibility testing results extended beyond the three-day expiry. Local policies may vary, but this extension of an in-date crossmatch is sometimes used for surgical pre-admission patients who may have their blood drawn for compatibility testing several days or weeks before the planned surgical date. If they are not transfused in the interim period, the results are considered valid and compatible blood can be available on the anticipated surgical date on the basis of this prior testing.

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Pre-Transfusion Testing

Pre-transfusion tests include ABO and Rh typing of the recipient's RBCs and an antibody screen. The latter is a method to detect clinically significant RBC antibodies in the recipient's plasma. Most clinically significant antibodies are IgG and usually appear following exposure to foreign RBC antigens during transfusion or pregnancy.

Before a non-emergency transfusion, compatibility testing is also performed. The compatibility test may be a serological crossmatch or may involve only the use of a computer to ensure that an appropriate component has been prepared for the intended recipient. The latter is known as an electronic crossmatch.

ABO Typing

ABO typing involves testing the recipient RBC for the presence of A and B antigens using anti-A and anti-B antisera (forward grouping). Testing of the recipient plasma for the presence of anti-A and anti-B using known group A and group B cells (reverse grouping) is also part of routine ABO blood group testing.

Rh Typing

The Rh (D) type of the transfusion recipient is also determined by testing recipient RBC with anti-D. A significant proportion of the population lack the Rh (D) antigen on their RBC. Seventy percent of Rh (D) negative recipients may develop antibodies to the D antigen if exposed to D containing RBCs. It is, therefore, imperative to provide Rh-negative (D negative) blood to any Rh (D) negative individual. In particular, Rh (D) negative women of child-bearing age should be prevented from receiving Rh (D) positive blood components as development of anti-D in these recipients could contribute to hemolytic disease of the fetus and newborn (HDFN) in future pregnancies.

Antibody Screening

Alloantibodies to RBC antigens lacking on an individual's red cells may develop in anyone who has been exposed to foreign RBC antigens through pregnancy or transfusion. To detect these antibodies, a sample of the patient's plasma or serum is tested against selected group O cells that bear most or all clinically significant antigens. This screening test usually takes 30 to 60 minutes to complete. Many techniques are currently available for the detection of antibodies. Some methods involve addition of testing reagents such as saline, albumin, low ionic strength saline (LISS), or polyethylene glycol (PEG). Some use gel cards or microtiter well plates with bound RBC antigens to enhance antibody detection.

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Antibody Investigation

If a clinically significant antibody is found in a recipient's plasma it is usually identified. This process involves testing the antibody reactivity with a panel of group O RBCs with known antigen types. Antibody identification can involve multiple steps designed to exclude particular antibodies, determine the optimal temperature of antibody reactivity and determine the presence of autologous reactivity of the antibody. Following antibody identification, donor RBC units are screened to identify those that lack the antigens corresponding to the antibody identified in the recipient. Crossmatch of this antigen negative blood is the final step in procuring blood suitable for transfusion. If crossmatch compatible blood can not be found, the medical director of the hospital transfusion service may authorize the release of incompatible units if the need for transfusion outweighs the risk of transfusing incompatible blood. Depending on the number and complexity of the antibodies present in recipient plasma, a variable amount of additional time may be required to find compatible blood. In most cases, compatible allogeneic RBCs safe for transfusion can be identified. Consultation with a reference laboratory experienced in antibody investigation may be necessary in some cases, which could contribute to a potential delay in availability of blood. When compatible blood is very difficult to obtain, rare units or frozen units may be accessed. In some cases either autologous donation or directed donations from close family members may be required to ensure that adequate amounts of compatible blood are available.

Crossmatch

The term crossmatch is used to describe a method of confirming compatibility between the patient's blood (plasma) and the donor RBCs. The crossmatch is meant primarily to detect and prevent ABO incompatibility. A crossmatch may involve either the direct mixing of donor RBCs with recipient plasma (serological crossmatch) or utilizing a computer system to ensure that the recipient and donor testing are complete and that the donor units selected for a particular recipient are compatible. This is known as the electronic or computer-assisted crossmatch. The latter may be used only in the setting of a computer system that has been validated to prevent release of incompatible units and for a recipient with a negative antibody screen.

Type and Screen, or Crossmatch?

For patients who are unlikely to require blood transfusion in a given medical or surgical setting, a common approach is to determine the recipient ABO and Rh type and perform an antibody screen (type and screen). If this screen is negative, no further testing would occur, but a crossmatch could be performed and blood components provided quickly in the event that they were needed. In this situation RBCs do not have to be crossmatched when experience has shown that blood transfusion is infrequently required. For patients where a positive antibody screen is present, further testing as outlined above together with a crossmatch would be undertaken to ensure timely availability of compatible blood.

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A crossmatch should be requested for those patients for whom a blood transfusion is intended or definitely anticipated. This order should include the number of RBC units required. In the laboratory a crossmatch order results in blood grouping and antibody screening as well as compatibility testing with preparation and labelling of the RBC units for transfusion to the particular recipient.

Emergency Blood Release

When the urgency of the transfusion requirement prevents initiation or completion of pre-transfusion testing, emergency release of unmatched blood may be considered. If ABO and Rh testing have been completed, group-specific uncrossmatched blood may be provided. If no testing has been initiated when blood is required, group O Rh-negative unmatched blood could be released. A sample for compatibility testing should be obtained as soon as clinical circumstances permit. This allows appropriate switching to group-specific crossmatched blood and helps to prevent overuse of the limited group O Rh-negative supply.

Standard Blood Order Schedule (SBOS)

The standard blood order schedule is a guide to indicate how many RBC units should be crossmatched for a particular surgical procedure. This is usually determined by calculating the average number of units transfused for a specific surgical procedure, and should be agreed upon by the surgical and transfusion medical staff. A type and screen procedure is recommended for procedures where blood is not routinely needed. Development of this type of schedule prevents unnecessary work in testing and labelling of blood products that are unlikely to be transfused, while ensuring blood availability for any recipient who may require it.

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Marina Hamilton and Judith Cleary

This chapter outlines the main principles and safety concerns to be considered by the individual administering blood and blood products.

Pre-Administration

Informed Consent

Justice Krever's recommendations* outlined the importance of informed consent for the administration of blood and blood products. These recommendations stated:

- Patients in Canada, barring incompetency or an emergency surgical procedure, will be informed of the risks and benefits of, and alternatives to, allogeneic blood transfusion.
- Risks, benefits, and alternatives will be presented in language the patient will understand and in a manner that permits questions, repetitions, and sufficient time for assimilation and further questions.

Various hospitals have put in place different policies regarding the documentation of consent for transfusion therapy. Refer to the institution's specific policies about informed consent to determine the approved means of documenting consent.

Refusal of Transfusion

Patients also have the right to refuse transfusion or treatments involving the use of blood or plasma fractionation products. Such a decision should follow an informed discussion of the risks of refusal and the benefits of transfusion. Refusal should be clearly documented on the patient's medical record in accordance with institution-specific policies.

The Jehovah's Witness Patient

Jehovah's Witnesses forbid blood transfusion based on their interpretation of Biblical scripture. For most, this interpretation rules out transfusion of whole blood, red blood cells, white blood cells, plasma and platelets. The use of plasma fractions such as albumin, clotting factors and immune globulins are not absolutely prohibited. Each member of the faith is permitted to decide individually what is personally acceptable. Jehovah's Witnesses do not provide autologous blood donations, but generally do accept use of a closed cardiac bypass circuit as long as it is not primed with blood (autologous or allogeneic) and blood is not stored during the process.

Additional information is available from the Hospital Information Services (Canada) for Jehovah's Witnesses 24-hour emergency line at 1-800-265-0327 or fax 905-873-4510.

*Report of the Commission of Inquiry on the Blood System in Canada (Krever Commission), 1997.

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Physician Orders

Transfusion must be prescribed and administered under medical direction and the transfusion requirements documented in the recipient's chart.

Physician orders for the administration of blood should outline:

- the product to be administered;
- volume or amount to be transfused;
- time over which the product is to be administered; (Some institutions may reference specific policies or procedures such as an intravenous manual that outline the administration procedure including the usual rate.)
- use of pressure infusion devices;
- use of blood warmers;
- modifications to blood components; and
- pre-medications.

IV Access

Blood components and products may be administered through a variety of central venous access devices (CVAD) or peripheral catheters. Considerations when choosing an intravenous (IV) site, either peripheral or central, include:

- Gauge or lumen size: this should be large enough to allow the flow of the component/product within the specified administration time and to prevent damage to the cells. In adults, a 19 gauge or 3 French catheter is often recommended as the minimum size to infuse red blood cells (RBC). In pediatric patients the minimum size is a 25 gauge catheter.
- Confirmation of patency.
- Availability of direct venous access from the line or use of needle-free IV tubing. The blood component should NOT be "piggy-backed" through a needle into a main IV line. However, use of needle-free IV tubing may allow the blood administration set to be connected at the lowest Y-port without damaging the cells. This can be especially beneficial if the patient has a transfusion reaction, as the blood component can be easily disconnected while maintaining IV access.
- Alternate IV sites should be used for other medications or IV fluids, as these should NOT be added to the blood bag or tubing during a transfusion.
- CVADs with multiple lumens may allow blood components or plasma fractionation products to be given through one lumen while other medications or solutions infuse through other lumens. Medications that are frequently linked to hypersensitivity reactions should be used cautiously in conjunction with transfusion, since distinction between medication-related symptoms and a transfusion reaction can be difficult when they are infused simultaneously.
- Availability of non-vented IV administration sets. Vented tubing is to be used only with manufactured products that are transfused directly from a glass bottle (albumin, some IVIG products). Vented tubing should not be used when administering blood components as this may introduce air into the bag.
- In emergency situations it may be necessary to administer various blood components or fractionated blood products concurrently. This should be done using separate IV access. Only ABO compatible plasma and 5% albumin are compatible with other blood components.

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Administration Sets

Various blood administration sets are available on the market for gravity flow or for use with infusion devices. It is important to be familiar with the specific properties and instructions for use of the particular sets at the institution concerned. Blood administration sets must be sterile and pyrogen-free with a filter and drip chamber. Filters should be completely wet and the drip chamber 1/3–1/2 full prior to initiating the transfusion. Many have two ports, one for the component and one for the saline priming solution.

The administration of blood components requires the use of a standard blood filter, which may range in pore size from 170 to 260 microns. These filters are intended to remove clots, cellular debris and coagulated protein. Over time the filter can create an ideal environment for bacterial growth or contribute to sluggish flow, slowing the transfusion. Individual facilities should have policies relating to the frequency of filter or administration set changes. Various standards indicate that blood administration sets should be changed within four hours, eight hours, or up to 24 hours following initiation of the transfusion. Four to eight hours is a reasonable time frame with up to four units being transfused in this interval prior to filter change. When there is a delay between units of an hour or more, it is prudent to replace the administration set.

Administration sets or filter needles that accompany fractionated plasma products should be used as they meet the manufacturer's requirements for administration. If a fractionated product is without accompanying tubing, refer to the product monograph to determine what if any filtration is required.

Leukoreduction and Microaggregate Filters

All cellular blood components issued to hospitals by Canadian Blood Services have undergone a leukocyte reduction by filtration process. This eliminates the need for the use of a leukocyte reduction filter during transfusion (bedside or post-storage leukoreduction).

Microaggregate filters were designed for use with red blood cells to remove fibrin, white blood cells, and platelets. These were often recommended as a method for decreasing febrile non-hemolytic transfusion reactions. The pre-storage leukocyte reduction process is more effective in decreasing the incidence of these reactions and a separate microaggregate filter is not necessary for this purpose.

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Infusion Devices

It is often beneficial to regulate the flow rate of a blood component or fractionated product using an infusion device. Many of the available infusion pumps are safe for use with blood components and do not cause clinically significant hemolysis of red blood cells. Infusion devices have also been recommended for use during the administration of granulocytes and platelets. Infusion devices do not appear to have any negative effects on these components; however, the duration of infusion is usually so short that there probably is no benefit to using an infusion device for these transfusions. Before using an infusion device to administer blood components, validation should be obtained from the manufacturer supporting the safe use of the device with blood components.

Special Products

A number of special blood components may be requested from the transfusion medicine service for patient-specific indications. These include the use of CMV seronegative blood components and the irradiation of cellular blood components. See Chapter 15: CMV Seronegative, Irradiated and Washed Blood Components for further details.

Red Blood Cell Antibodies

Multiple antibodies to red cell antigens that may arise following a prior transfusion or pregnancy can contribute to a complicated and time-consuming process for finding crossmatch compatible red blood cells. For patients with multiple RBC antibodies, a prolonged interval for completion of the crossmatch should be anticipated. If RBCs are required urgently, the transfusion service should be notified.

Patients with Compromised Cardiovascular Status

Consideration should be given to decreasing the rate and volume of transfusion when patients are at risk for congestive heart failure (CHF). While blood transfusions must be completed within four hours of the time of issue, there are some options that may reduce the risk of adverse effects:

- use of diuretics (e.g. furosemide 20–40 mg IV) preceding the transfusion or between units; or
- splitting or dividing units so that only a portion of the unit is issued for transfusion at a given time. The remainder of the unit remains in storage in the appropriate transfusion service refrigerator. Storage of a previously opened unit should be discouraged however, and this must be coordinated with your blood transfusion service.

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Pre-Medications

Although administration of pre-medication is not routinely recommended for a first transfusion, it may be considered if the patient has a history of previous transfusion reactions. Pre-medications are typically administered approximately 30 minutes prior to initiating the transfusion and often include diphenhydramine and/or acetaminophen. An example of a pre-medication order for an adult patient would be:

- diphenhydramine 25–50 mg PO or IV
- acetaminophen 650 mg PO or PR

Blood Warmers

Although routine warming of blood is not recommended, these devices may be used to prevent hypothermia exacerbated by rapid infusion of a large volume of cold blood (more than 100 mL/min over 30 minutes).

It may also be advisable to warm the blood during administration if the patient has cold agglutinin disease. In this setting, warming the blood during infusion may prevent agglutination due to the presence in the recipient of cold reactive antibodies. The blood warmer should be set at 37°C and must trigger an audible or visible alarm if the temperature exceeds 42°C.

Pressure Infusion Devices

Pressure infusion devices may be used to increase the rate of administration in gravity flow infusions. The pressure applied to the blood component should not exceed 300 mmHg as this may result in hemolysis or bag breakage.

Returning Unused Products

Blood components that have been outside of a temperature-controlled environment for more than 30 minutes must be discarded and cannot be placed back into inventory for use in another patient. This means that the blood component must be **returned to a transfusion service refrigerator** within the 30-minute time frame if it is to be re-issued.

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Administration

Review of consent for transfusion, orders to transfuse, timing of transfusion and specific type of component as outlined above should be undertaken prior to retrieving the blood from the transfusion service. Blood must not be stored on the patient care unit or placed in a non-approved or non-monitored refrigerator.

Depending on the product to be administered there will be additional specific items to consider. The following are the general steps for initiating a blood transfusion (see Table 1 for a summary of component specific administration requirements):

- Provide information to patient regarding the planned transfusion.
- Obtain baseline vital signs within one hour prior to the initiation of the transfusion.
- Prime tubing with saline unless administering a fractionated plasma product; in this case refer to the manufacturer's product monograph for compatible IV fluids.
- Visually inspect components for clots, clumps, and discoloration. If present, notify transfusion service and return the product.
- Verify that the product has not/will not expire during the anticipated time for the transfusion.
- Verify the identity of the intended recipient and the blood group and identifiers on the unit of blood.
- Initiate the transfusion.
- Monitor and document vital signs according to institution-specific policies.
- Identify and treat transfusion reactions that may occur.

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Table 1: Initiating the transfusion

Blood components	Indication	Compatibility	Administration
RBC	■ Anemia with impaired oxygen delivery	■ Must be ABO and Rh compatible ■ Crossmatch required	■ Use standard blood filter (170–260 um) and tubing ■ Rate is 2 mL/min (120 mL/hr) for first 15 min. May be increased if well tolerated with no adverse reaction. One unit usually takes 1.5–2 hours to infuse, but may be infused over up to 4 hours in volume sensitive patients.
Platelets	■ Treatment/ prevention of bleeding in patients with decreased or dysfunc-tional platelets	■ Preferred ABO and Rh compatible with donor plasma ■ Must have confirmed blood group. Rh compatibility important for Rh (D) negative women of child-bearing age ■ RhIG administration should be considered if Rh-positive platelets are given to an Rh-negative patient, especially females of child-bearing age	■ Standard blood filter (170–260 um) and tubing ■ Administer as rapidly as tolerated (4 units/ 20 min average in adults)
Plasma	■ Multiple clotting factor replacement ■ Exchange transfusion ■ Therapeutic apheresis	■ Must be ABO compatible ■ Rh compatibility not generally required. Consider RhIG administration when very large volumes of plasma from Rh-positive donors are transfused to Rh-negative individuals, especially females of child-bearing potential. ■ Confirmed blood group required	■ Standard blood filter (170–260 um) and tubing ■ Transfuse as rapidly as clinically tolerated

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Table 1: Initiating the transfusion (continued)

Blood components	Indication	Compatibility	Administration
Cryoprecipitate	■ Diffuse microvascular bleeding and/or bleeding due to hypo-fibrinogenemia, or dys-fibrinogenemia	■ ABO compatibility preferred but not required ■ Confirmed blood group required	■ Standard blood filter (170–260 um) and tubing ■ Transfuse as rapidly as clinically tolerated

Recipient Identification

One of the most frequent severe adverse outcomes of RBC transfusion is an acute hemolytic transfusion reaction. Hemolytic reactions can be the result of ABO incompatibilities or due to incompatibilities in other blood group antigen systems. Patient misidentification is the most common cause of ABO incompatible blood administration. The misidentification of the patient can occur during specimen collection, result reporting, product request, or product issue. The identification process prior to initiating the transfusion is the final opportunity to prevent a transfusion error of this nature.

It is critical that all information associating the blood component with the intended recipient has been matched and verified in the presence of the recipient. This includes:

- verifying ABO and Rh (if applicable) compatibility of the product and recipient (see Tables 2–4 below);
- verifying that the unique patient identifiers on the product match those of the intended recipient; and
- verifying that the unique product identifiers on the product label match those on the accompanying transfusion service form/tag.

Table 2: ABO compatibility of RBC

Recipient	Donor
A	A,O
B	B,O
AB	AB, A, B, O
O	O

Table 3: Rh compatibility of RBC

Rh of recipient	Rh of donor
Rh-positive	Rh-positive or -negative
Rh-negative	Rh-negative

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Table 4: Compatibility of plasma

Recipient	Donor
A	A, AB
B	B, AB
AB	AB
O	O, A, B, or AB

Patient Monitoring

Symptoms of serious transfusion reactions frequently appear within 15 minutes after blood enters the vein; therefore observation of the patient during this time period is of the utmost importance. The patient should be monitored regularly during the transfusion and for a period of time following the completion of the transfusion. Assessment frequency and documentation requirements should be performed according to specific hospital policy.

Continuous Infusion of Coagulation Factors

Coagulation factor replacement by continuous infusion is used in many centres across the country for the management or prevention of serious bleeding in patients with coagulation disorders. As this procedure falls outside recommendations in the product monograph, each institution is required to develop its own policies and procedures to direct and guide this practice. An excellent resource in developing these procedures is the document prepared by the Winnipeg Bleeding Disorders Program: Factor Replacement by Continuous Infusion, Second Edition, 2002.

Principles of Managing a Transfusion Reaction

If a transfusion reaction is suspected:

- Immediately stop the transfusion and maintain vascular access with normal saline. The blood component line should be disconnected from the IV cannula/CVAD to prevent further infusion of the product. Alternatively, connecting the blood administration set to the lowest port on a mainline of normal saline would eliminate the need to disconnect the tubing.
- Notify the physician.
- Treat as directed by physician.
- Assess the patient.
- Verify the recipient/product compatibility.
- Monitor patient until symptoms resolve.
- Obtain post-reaction blood samples and notify the transfusion service of the reaction according to the institution-specific policy.
- Retain administration set until investigation by transfusion service is completed (or send to transfusion service as required).
- Provide the transfusion service with sufficient relevant information to facilitate transfusion reaction reporting to Canadian Blood Services and/or other entities as indicated in your province/territory.

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Post-Administration

To ensure full benefit of the transfusion, the blood administration tubing should be flushed with normal saline to clear remaining blood cells. Following administration of a fractionated plasma product, the tubing should be flushed with a compatible fluid (see manufacturer's product monograph). The administration set should then be discarded to prevent bacterial proliferation within the tubing or filter.

The completion of the transfusion should not be the end of patient monitoring. Continued monitoring is required to identify delayed adverse reactions that may occur. Generally changes in the patient status or vital signs occurring within six hours of the transfusion should prompt consideration of the transfusion as a potential cause of the symptoms or signs and should be reported to the blood transfusion service.

Further Reading

1. Brecher M. AABB Technical Manual 14th Edition, Bethesda, Maryland. American Association of Blood Banks, 2002.
2. Canadian Blood Services. Circular of Information for the use of human blood and blood components, 2004.
3. Canadian Standards Association. CSA Standard Z902-04 Blood and Blood Components.
4. CDC Guidelines, MMWR-2002.
5. Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. Transfus Med Rev 2003; 17: 120-162.
6. Standards for Hospital Transfusion Services (Version 1; September 2004). Canadian Society for Transfusion Medicine, Ottawa, Canada.
7. Bodnaruk ZM, Wong CJ, Thomas MJ. Meeting the clinical challenge of care of Jehovah's Witnesses. Transfus Med Rev 2004; 18: 105-116.
8. The product monograph for each product should be consulted for further information.

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Jeannie Callum and Peter Pinkerton

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Transfusion Reactions Advisory Panel: M A Blajchman, Chair, R M Barr, G Clarke, J DiTomasso, J Freedman, N Heddle, S Kleinman, R Koen, D H Lee, A Lima, S McMillan. Edited and produced by Helen Stevenson, Savattuq Inc., for Sunnybrook & Women's College Health Sciences Centre, Toronto, 2006.

A. Reporting

- **Attention: All transfusion reactions (mild to life-threatening) and transfusion-related errors must be reported to the hospital's transfusion service (blood bank).**

What

- The transfusion service will investigate, assess and report the event to the Transfusion Transmitted Injuries Surveillance System (TTISS) at Public Health Agency of Canada*.
- Reactions relating to the quality of the product must be reported directly to CBS/Héma-Québec.

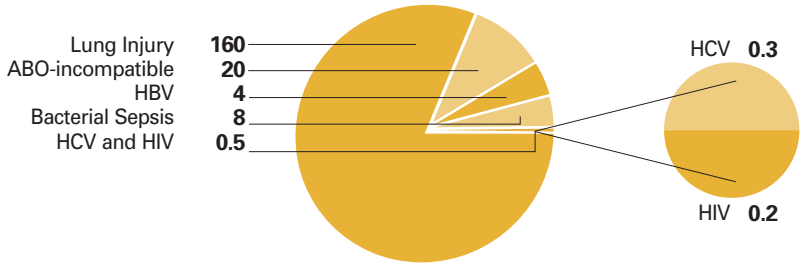
How

- CBS/Héma-Québec and Public Health Agency of Canada* reporting forms are available from all hospital transfusion services.
  - Contact your transfusion service for more information
  - It is the transfusion service's responsibility to submit them to CBS/Héma-Québec and Public Health Agency of Canada

*www.phac-aspc.gc.ca (click on Infectious Diseases; Blood Safety)

Estimated Number of Serious Adverse Events for Red Blood Cells Expected in Canada Each Year

- 800,000 units of RBC are transfused in Canada (except Quebec) each year.
- Most adverse events are not recognized or reported as such.



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B. Reaction by Symptom

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Fever

Management Algorithm

Fever (and/or Chills/Rigors)

> 1°C increase in temperature **AND** temperature > 38°C during transfusion or within 4 hours of the end of the infusion

↓

Immediate Management:

1. Stop transfusion & maintain IV access
2. Take patient's vital signs
3. Re-check identification of patient & blood product
4. Notify physician
5. Notify Transfusion Services, even if transfusion restarted or completed

↓

Clerical error or serious symptoms?

Temperature ≥ 39°C, hypotension/shock, tachycardia, rigors/chills, anxiety, dyspnea, back/chest pain, hemoglobinuria/oliguria, bleeding from IV sites, nausea/vomiting

No

↓

Administer acetaminophen 325 mg

↓

Continue transfusion **cautiously** under observation; likely a febrile non-hemolytic transfusion reaction

↓

Stop the transfusion if patient develops any of the above symptoms

Yes

↓

DO NOT RESTART TRANSFUSION

↓

SUSPECT

1. Hemolytic transfusion reaction; OR

2. Bacterial contamination

- Collect blood bank samples to re-check ABO group
- Clamp tubing, send unit to Transfusion Services along with attached IV solutions for bacterial cultures
- Arrange for untransfused portion of the transfused unit to be cultured
- Send blood cultures taken from a different IV site
- For more detail, refer to sections on pages 85-90

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Bacterial Sepsis or Contamination

Etiology

Blood components may be contaminated by:

1. Skin commensals from the donor (each venipuncture may result in a small skin plug that is retained in the donation bag)
2. Unrecognized bacteremia in the donor
3. Contamination from the environment or from handling the product

Organisms

- Serious morbidity and mortality occur most frequently with gram-negative bacteria, but are also reported with gram-positive skin bacteria
- A number of bacteria have been implicated, including:

Gram-negative	Gram-positive
■ Klebsiella pneumoniae	■ Staphylococcus aureus
■ Serratia marcescens	■ Staphylococcus epidermidis
■ Pseudomonas species	■ Bacillus cereus
■ Yersinia enterocolitica	

Incidence

	Bacterial contamination	Symptomatic septic reactions	Fatal bacterial sepsis
5 units of platelets	1 in 1,000	1 in 10,000	1 in 40,000
1 unit of RBC	1 in 50,000	1 in 100,000	1 in 500,000

- Bacterial sepsis accounts for at least 10% of transfusion-associated fatalities
- Bacterial sepsis occurs most frequently with platelets due to their storage at 20-24ºC for preservation of function
- These figures were established prior to measures for bacterial detection and may now be over-estimates

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Clinical Presentation

- Clinical features of transfusion-associated sepsis may include:
  - Rigors, fever, tachycardia, hypotension, nausea and vomiting, dyspnea, disseminated intravascular coagulation
- It is usually possible to culture the offending organism from both the patient and the transfused product.
- There may be no immediate clinical signs of bacterial infection after transfusion of bacterially contaminated platelets, if the bacterial load is small.

Management

- If transfusion-transmitted bacterial infection is suspected:
  - **Stop the transfusion!**
  - **Notify Transfusion Services**
    - Hospital transfusion service (blood bank) will notify the supplier so that
      - other products from the same donor(s) can be quarantined, cultured, and discarded **AND**
      - any recipients of other products can be identified and followed up
  - **Return residual of blood product(s) and tubing for culture (clamped) to Transfusion Services**
  - **Collect peripheral blood samples for blood culture from a different site**
  - Provide aggressive supportive therapy as appropriate, including broad-spectrum antibiotics
    - DO NOT WAIT FOR RESULTS OF BLOOD CULTURES PRIOR TO STARTING ANTIBIOTIC THERAPY
  - **Arrange for gram stain on unit(s) suspected of being contaminated**

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Prevention

- Culturing of apheresis platelets was introduced in 2004 by the blood collecting agencies (Canadian Blood Services and Héma-Québec).
- Routine culture of platelets is expected to be completely implemented in Canada by 2006-2007.
- All buffy coat derived platelet pools will be cultured prior to issue to hospitals.
- Some hospital transfusion services have implemented bacterial detection measures for random donor platelets.
- The first 40 mL of blood collected is diverted and sequestered in a pouch to reduce risk of transmitting organisms from skin (can be used for infectious agent testing).

Acute Hemolytic Transfusion Reaction

Etiology

- Acute hemolytic transfusion reactions may be associated with:
  - ABO-incompatibility
  - Other blood group alloantibodies
  - Rare cases when group O platelets with high titers of anti-A and/or anti-B are transfused to a non-group O recipient

- **ABO-incompatibility**
  - ABO-incompatibility is due to a clerical error or other error in patient identification
    - Most common cause of morbidity from RBC transfusion
  - HALF of all errors are due to administering properly labelled blood to the wrong patient
  - Other errors are the result of improper labelling of samples or testing errors

- **RBC alloantibodies (non-ABO)**
  - Result from patient immunization from a prior pregnancy or transfusion
  - Causes of reactions include:
    - Red cell alloantibodies in the patient's plasma below the level detected by the antibody screen
    - Clerical error during patient antibody screening
      - Failure to detect RBC antibody at detectable levels (laboratory error)
    - Uncrossmatched blood transfused to a patient who is alloimmunized

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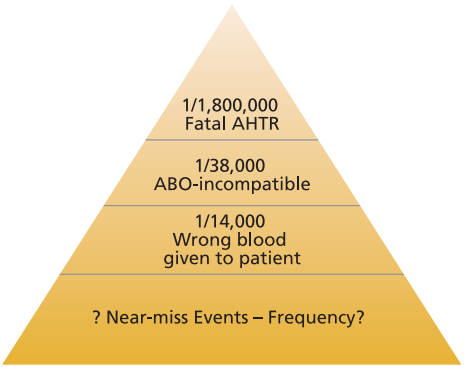
Incidence

- 1 in 38,000 RBC transfusions are ABO-incompatible due to transfusing the wrong blood to a patient.
- Less than 10% of ABO-incompatible transfusions result in a fatal outcome.
- Over 50% of patients have no morbidity from an ABO-incompatible transfusion.
- Risk of death correlates with the amount of incompatible blood transfused.
- 13% of major morbidities from RBC transfusions are the result of an acute hemolytic reaction from non-ABO group antigens.



Clinical Presentation

- Most common clinical presentation:
  - **Fever and chills**
  - **Hemoglobinuria**
  - Less common: pain, hypotension, nausea/vomiting, dyspnea, renal failure, DIC
- Fever may be the only presenting sign of an acute hemolytic transfusion reaction.

Management

- Stop the transfusion!
- Check if there is clerical error. Check identity of patient vs patient identity on blood product label.
- Notify Transfusion Services.
- Send samples to hospital transfusion service (blood bank) to re-check ABO group.
- Return residual of blood product(s) and tubing (clamped) to the hospital transfusion service.
- Provide supportive care.
- Maintain good urine output.
- Avoid fluid overload.
- Manage DIC and hemorrhage as clinically indicated.

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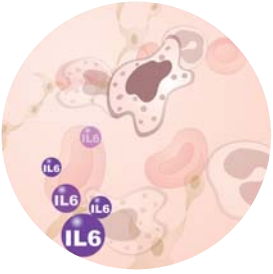
Prevention

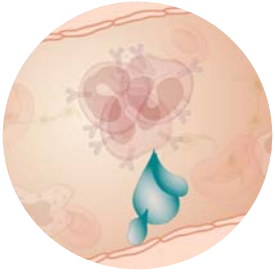
- **Pay meticulous attention to identifying the patient and labelling the tubes at sample collection (to ensure that patient is assigned to the correct blood group).**
- **Pay meticulous attention to verifying the patient's identity, by checking their wristband, before transfusing.**
  - Confirm the patient's identity (for patients that are conscious) verbally in case the patient's armband might be incorrect (armband errors do occur).

Febrile Non-Hemolytic Transfusion Reaction (FNHTR)

Etiology

- Attributable to:
  - Soluble factors (e.g. cytokines) in the plasma of the component transfused
  - Recipient antibodies, reactive to antigens expressed on cells in the component, usually white blood cells





Incidence

	Incidence
RBC	1 in 300
Platelet pool	1 in 10

Clinical Presentation

- Fever usually occurs during or up to several hours after transfusion.
  - May be associated with chills, rigors, nausea, vomiting and hypotension
- Fever is not always present (i.e. chills, nausea, etc. alone).

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Management

- Acetaminophen
- Meperidine (Demerol®) 25-50 mg IV may be effective for severe rigors if the patient has no contraindications to meperidine.

Prevention

- Pre-medication with acetaminophen and diphenhydramine has not been shown to be effective in preventing FNHTR in one randomized controlled trial.
- In patients with significant and recurrent FNHTR, the following measures have been used but efficacy is unproven:
  - Acetaminophen, corticosteroids, meperidine (Demerol®), fresh components, plasma-depleted components, washed red blood cells (washing platelets results in 50% loss of platelet function)
- Antihistamines are not effective.

Dyspnea

(Anaphylaxis is described under **Allergic Reactions/Anaphylaxis**)

Management Algorithm

Dyspnea

↓

Immediate Management:

1. **Stop transfusion** & maintain IV access with 0.9% saline
2. Take patient's vital signs
3. Re-check identification of patient & blood product
4. Notify physician
5. Notify Transfusion Services
6. Return clamped blood unit & tubing attached

↓

Consider:

- **TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**
- **TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)**
- **ANAPHYLAXIS**

- If TRALI is suspected, notify Transfusion Services so that special donor and recipient testing can be performed
- Order STAT chest X-ray
- Oxygen, diuresis, and supportive care as required

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Transfusion-Related Acute Lung Injury (TRALI)

Definition of Acute Lung Injury (ALI)

- Acute onset
- Hypoxemia
  - PaO_2/FiO_2 < 300mm Hg OR
  - Oxygen saturation is < 90% on room air OR
  - Other clinical evidence
- Bilateral lung infiltration on the chest radiograph
- No evidence of circulatory overload

Risk Factors for Acute Lung Injury

Predisposing factors for ALI include:

- Direct Lung Injury
  - Aspiration
  - Pneumonia
  - Toxic inhalation
  - Lung contusion
  - Near drowning
- Indirect Lung Injury
  - Severe sepsis
  - Shock
  - Multiple trauma
  - Burn injury
  - Acute pancreatitis
  - Cardiopulmonary bypass
  - Drug overdose

Definition of TRALI

- In patients with no evidence of ALI prior to transfusion, TRALI is diagnosed if:
  - New ALI is present
  - It occurs during, or within 6 hours of completion of, transfusion
  - There are no other risk factors for ALI

Definition of Possible TRALI

- In patients with no ALI prior to transfusion, possible TRALI is diagnosed if:
  - New ALI is present
  - It occurs during, or within 6 hours of completion of, transfusion
  - There are one or more risk factors for ALI

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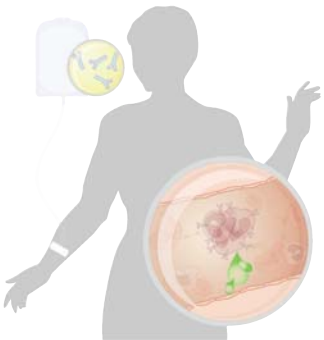
Etiology

- Presently not fully defined. Two postulated mechanisms have been implicated:
  1. Passive transfer of HLA or granulocyte antibodies from donor to blood product recipient; or, less commonly, HLA or granulocyte antibodies in the recipient (antibodies detected in donor or recipient in 75% of cases)
     - Antibodies are most common in multiparous female donors as a consequence of prior pregnancies
  2. Biologically active lipids in transfused component



Incidence

- True incidence of this syndrome is unknown; two separate hospital-based reports estimate TRALI at 1 in 1,200 to 5,000 plasma-containing transfusions, respectively.
- TRALI is known to be under-diagnosed and under-reported.

Presentation

- Dyspnea, hypoxemia, fever and hypotension.
- Chest X-ray reveals interstitial and alveolar infiltrates (pulmonary edema), without elevated pulmonary pressures.
- Usually occurs with transfusion of RBCs, platelets and plasma, but rarely with other blood products (including cryoprecipitate and IVIG).
- Almost always within the first 1-2 hours after the start of transfusion but can be delayed for up to 6 hours.
- Usually resolves in 24-72 hours.
- 72% of reported cases required mechanical ventilation and death occurs in 5-10% of patients experiencing a TRALI reaction.
  - TRALI is currently thought to be the most common cause of transfusion-associated fatalities.
- Milder forms of TRALI are thought to exist and may present as transient hypoxia.
- Acute transient leukopenia may be observed after a TRALI reaction.

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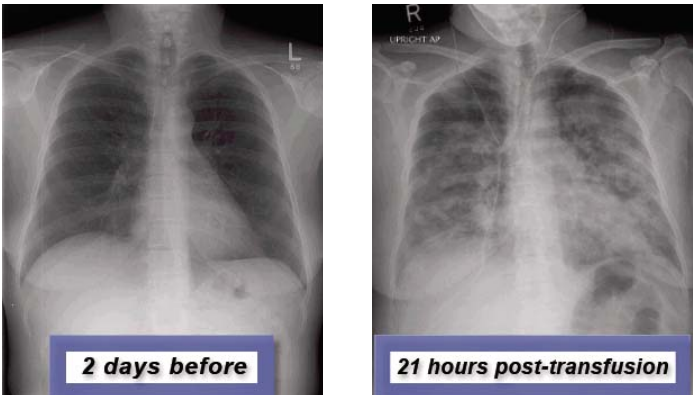
Chest X-ray of a patient before and during an episode of transfusion-related acute lung injury (TRALI)



Management

- Supportive care, including mechanical ventilation when clinically indicated.
- Diuretics and steroids are not believed to be useful in treating TRALI.
- Accurate reporting to hospital transfusion service is critical to identify implicated donors and prevent TRALI in other recipients.
- Patient and donor testing should be arranged through the hospital transfusion service (testing performed through Canadian Blood Services).

Prevention

- Deferral of donors confirmed to be implicated in an episode of TRALI, and with either antibodies or implicated in multiple episodes.
- Adherence to evidence-based transfusion guidelines.

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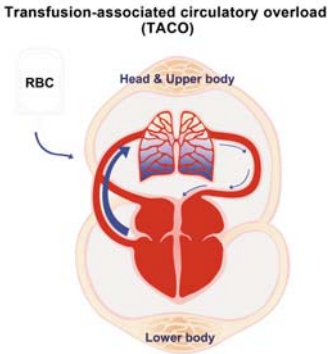
Transfusion-Associated Circulatory Overload (TACO)

Etiology

- Circulatory overload results from:
  1. Impaired cardiac function **AND/OR** 2. Excessively rapid rate of transfusion



Incidence

- Current estimate of the frequency of TACO is 1 in 700 transfusion recipients.
- In perioperative surgery setting in older orthopedic patients, incidence is much higher (1 in 100 patients).
- Patients over 60 years of age, infants, and patients with severe euvolemic anemia (hemoglobin < 50 g/L) are particularly susceptible.

Clinical Presentation

- Clinical presentation includes: dyspnea, orthopnea, cyanosis, tachycardia, increased venous pressure, and hypertension.

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Management

- Interrupt the transfusion.
- Administer oxygen and diuretics as needed.
- Consider restarting transfusion at a reduced infusion rate if clinical status allows and product still viable.
- Chest X-ray.

Prevention

- Pre-transfusion assessment is important to identify patients at risk and management should be adjusted accordingly.
- Preventative measures include:
  - Transfuse over longer periods (maximum 4 hours)
  - Pre-emptive diuretics
  - Components can be split into smaller aliquots to further reduce the speed of infusion without wasting product or increasing donor exposure
- In patients at risk, avoid transfusing more than one unit at a time.

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Urticaria & Other Allergic Reactions/Anaphylaxis

Management Algorithm

Allergic Reaction

A transfusion reaction that may be associated with urticaria, facial edema, airway edema, lower respiratory tract symptoms, hypotension, or shock

↓

Immediate Management:

1. **Interrupt the transfusion** & maintain IV access with 0.9% saline
2. Take the patient's vital signs
3. Re-check name of patient & name on blood product
4. Notify patient's physician
5. Notify Transfusion Services even if transfusion restarted or already completed

↓

Clerical error, anaphylaxis or serious symptoms?

1. Hypotension
2. Dyspnea/cough
3. Tachycardia
4. Generalized flushing or anxiety
5. Nausea/vomiting
6. Widespread rash > $^{2}/_{3}$rds body

No

↓

Consistent with minor allergic reaction

↓

Give diphenhydramine 25-50 mg IV/po

↓

Continue transfusion cautiously

↓

Stop transfusion if patient develops any of the above symptoms

Yes

↓

DO NOT RESTART TRANSFUSION

- Notify the patient's physician **STAT**
- Notify Transfusion Services immediately

↓

SUSPECT ANAPHYLACTIC REACTION OR SEVERE ALLERGIC REACTION

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Anaphylaxis

Etiology

- Vast majority of anaphylactic reactions are unexplained.
- The following mechanisms have been implicated in anaphylaxis/anaphylactoid reactions:
  - Anti-IgA in an IgA deficient recipient
  - Antibodies to polymorphic forms of serum proteins (IgG, albumin, haptoglobin, a-1-antitrypsin, transferrin, C3, C4, etc.)
  - Transfusing an allergen to a sensitized patient (eg. penicillin, ASA, etc. consumed by donor)
  - Passive transfer of IgE (to drugs, food)
- 1 in 500 blood donors are IgA deficient, and 1 in 1,200 blood donors have anti-IgA, but most are NOT at risk of an anaphylactic transfusion reaction (reasons are not clear at this time).
- Haptoglobin deficiency is not uncommon in Asian patients (1 in 1,000) and has been associated with anaphylactic reactions.

Incidence

- Transfusion-associated anaphylactic shock is rare.

Clinical Presentation

- Reactions usually begin within 1 to 45 minutes after the start of the infusion.
- Cutaneous reactions (urticaria) are present in the majority of anaphylactic and anaphylactoid reactions.
  - When hypotension and hypoxia follow transfusion, examine skin for urticaria (e.g. under drapes in operating room)
- Anaphylactic/anaphylactoid reactions are associated with upper or lower airway obstruction (symptoms may include hoarseness, stridor, wheezing, chest pain, dyspnea, anxiety, feeling of impeding doom), hypotension, gastrointestinal symptoms (nausea, vomiting), rarely death (about 3% of cases).
- Potentially life-threatening.

Treatment

- Stop the transfusion! Do not restart.
- If severe urticarial reaction involving > $^{2}/_{3}$rds body surface area: Stop the transfusion and do not restart. Administer 25-50 mg diphenhydramine.
- Anaphylaxis – promptly administer epinephrine, corticosteroids, diphenhydramine, vasopressors, and supportive care as required.
- Provide ventilatory support as indicated clinically.

Note: Epinephrine should be readily available whenever transfusion is carried out.

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Prevention of Recurrent Anaphylaxis

- Pre-medication with intravenous steroids and diphenhydramine.
- If a patient is found to be IgA-deficient with anti-IgA, the following products are recommended:
  - RBC-washed (3L normal saline in 6 wash cycles)
  - Plasma products: IgA-deficient plasma from IgA-deficient donors, available from Canadian Blood Services and Héma-Québec

Minor Allergic Reaction – Urticaria

Etiology

- Unclear, but relates to factors in the plasma portion of the component.

Incidence

- 1 in 100 mild urticarial reactions with plasma-containing components.

Clinical Presentation

- One urticarial lesion to widespread urticarial lesions.
- May be associated with pruritis, erythema, flushing, or mild upper respiratory symptoms (cough, wheezing), nausea, vomiting, abdominal cramps, or diarrhea.

Management

- Interrupt the transfusion.
- Give diphenhydramine 25-50 mg po or IV depending on severity of the reaction.
- Restart the infusion slowly only if:
  1. The urticarial rash involves < $^{2}/_{3}$rds of the body surface area; and,
  2. There are no associated symptoms suggesting a severe allergic reaction.

Prevention

- If the urticarial reactions are recurrent, the following precautionary measures may be used although their efficacy is unknown:
  - Pre-medication with diphenhydramine or corticosteroids
  - Plasma depletion of RBCs or platelets
  - Washed RBCs or platelets

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Hypotension

Management Algorithm

Hypotension

> 30 mmHg drop in systolic or diastolic blood pressure

↓

Immediate Management:

1. **Stop the transfusion**
2. Provide supportive care, including IV fluids
3. Consider differential diagnosis

↓

Consider:

1. Acute hemolytic transfusion reaction
2. Bacterial sepsis
3. Severe febrile non-hemolytic transfusion reaction
4. Bradykinin mediated hypotension
5. Transfusion-related acute lung injury

No	**Yes**
Unrelated to transfusion	
↓	
Possibly resume transfusion after reassessing	Do not restart transfusion. Refer to appropriate sections.

Bradykinin Mediated Hypotension

Etiology

- Bradykinin is believed to play a major role in generating hypotension.
- Angiotensin-converting enzyme is the main enzyme responsible for degradation of bradykinin.
  - Some individuals have a genetic polymorphism resulting in a decrease in bradykinin degradation

Incidence

- Unknown

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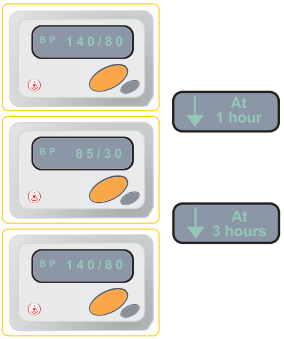
Clinical Presentation

- Majority of hypotensive reactions occur with platelet transfusions.
- Of reported cases, over half of the patients were on ACE inhibitors.
- Other symptoms may be present, including dyspnea, urticaria, nausea, and vomiting.
- May be difficult to differentiate from TRALI.
- Rarely associated with significant morbidity or mortality.



Treatment

- Detect early: Monitor the patient for the first 15 minutes and vital signs at 15 minutes.
- Stop the transfusion and do not restart.
- Provide supportive care, including intravenous fluids.
- Consider TRALI and allergic reactions in the differential diagnosis.

Prevention

- In cases where ACE inhibitors were implicated, consider (where possible) an alternative anti-hypertensive prior to additional transfusions.

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Hemolysis after Transfusion

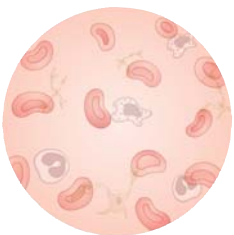
Hemolysis Not Related to RBC Alloantibodies

- Hemolysis may also occur in the following settings and should be considered in the differential diagnosis of hemolysis after transfusion:
  - Medical device-related (e.g. cell saver, blood warmer)
  - Overheating of RBCs due to improper storage (e.g. RBC placed on radiator)
  - Freezing of RBCs (e.g. transport of blood directly on ice or storage in freezer)
  - Transfusion of RBCs under pressure through a small bore needle
  - Transfusion of outdated RBCs
  - Use of hypotonic IV solutions with RBC transfusions
  - Non-transfusion-related causes

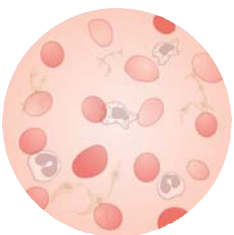
Delayed Hemolytic Transfusion Reactions

Etiology

- Results from the formation of antibodies in the recipient (to transfused red cell alloantigens or from RBC antigen exposure during a prior pregnancy) and below the level of detection on the initial antibody screen testing.
- Commonly implicated antigens are (in order of frequency): E, Jk^a, c, Fy^a, K.
- Delayed hemolysis may occur with transfusion-transmitted malaria and babesiosis.



Normal Blood Film



Spherocytes

Incidence

- 1 in 6715 units of RBCs transfused are associated with a delayed hemolytic transfusion reaction.

Clinical Presentation

- 3 days to 2 weeks after transfusion, the patient presents with hemolytic anemia (low hemoglobin, high bilirubin, reticulocytosis, spherocytosis, high LDH, positive antibody screen, and a positive direct anti-globulin test (formerly Coombs' Test)).

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Complications

- Most are benign, but life-threatening hemolysis with severe anemia and renal failure may occur.

Treatment

- Transfuse compatible blood ('antigen negative'; i.e. if the offending antibody is anti-Jk^a, then the transfusion service will provide units that do not carry the Jk^a antigen).

Prevention

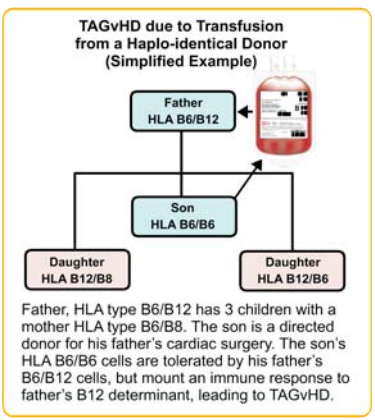
- Avoid RBC transfusions.
- Use of antibody screening methods with maximal sensitivity.

Cytopenias after Transfusion

Transfusion-Associated Graft vs Host Disease (TA-GvHD)

Etiology

- TA-GvHD has been reported in immunocompromised patients or in immunocompetent individuals transfused a haploidentical product (the risk of an HLA-haploidentical donor in North America is estimated at 1 in 17,700 to 39,000).
  - A donor who is homozygous for an HLA type (haploidentical), whose blood product is transfused to a recipient who is heterozygous for the same HLA type and a different HLA type places the recipient at risk.
  - The donor's lymphocytes mount a reaction against the different HLA determinants on the recipient's cells



Father, HLA type B6/B12 has 3 children with a mother HLA type B6/B8. The son is a directed donor for his father's cardiac surgery. The son's HLA B6/B6 cells are tolerated by his father's B6/B12 cells, but mount an immune response to father's B12 determinant, leading to TAGvHD.

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Incidence

- Unknown; there were 13 cases reported in the UK SHOT program over 7 years. Incidence reduced following universal leukoreduction.

- SHOT is Serious Hazards of Transfusion Group **www.shotuk.org**

Patients at risk, requiring irradiated products

- Patients with congenital immunodeficiency states
- Intrauterine transfusions
- Neonatal exchange transfusions
- Pre-term infants (rarely reported)
- Patients with hematologic malignancies, including lymphoma
- Patients undergoing bone marrow transplants or stem cell transplants
- Solid organ transplant recipients
- Patients with solid tumours undergoing aggressive or myeloablative chemotherapy
- Recipients of directed transfusions from family members
- Patients treated with purine analogs (eg. fludarabine)

Clinical Presentation

- Fever, rash, liver dysfunction, and diarrhea commencing 10 days post-transfusion, followed by pancytopenia 16 days post-transfusion (median).
- Overwhelming infections are the most common cause of death.
- Mortality is > 90%.
- Diagnosis can be made by skin biopsy, liver biopsy, or bone marrow examination.
- HLA-typing essential to confirm the diagnosis.

Treatment

- Largely ineffective.
- Survival (which is rare) is attributed to immunosuppressive therapy.

Prevention

- For patients at risk (see above), it is critical to give irradiated blood products **and** especially where the donor is related to the recipient.
- Irradiate all HLA-matched platelet products.

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Post-Transfusion Purpura (PTP)

Etiology

- Transfusion of platelet antigen-positive RBCs, plasma, or platelets to a patient who is lacking the same platelet antigen.
  - 75% of cases occur in an HPA-1b (Human Platelet Antigen-1b) homozygous patient who is transfused HPA-1a positive blood products
  - 3% of the North American population are HPA-1b homozygotes, but only 28% appear able to form anti-HPA-1a
- Autologous platelet destruction occurs but the mechanism is unclear.

Incidence

- Unknown; 300 cases have been reported in the medical literature.

Clinical Presentation

- There are 5 times as many female transfusion recipients with PTP as males, as a consequence of sensitization in previous pregnancy.
- Occurs post-transfusion by a median of nine days (range 1 to 24).
- Platelet count is less than 10 x 10^9/L in 80% of cases.
- Mortality is 8% and the majority of deaths are from intracranial hemorrhage.
- Transfusions are frequently associated with fever, chills, rigors, and bronchospasm.
- Differentiation from straightforward platelet alloimmunization is problematic.
  - *PTP should be considered when a platelet refractory patient fails to respond to HLA-matched platelets*

Treatment

- Test patient plasma for platelet-specific antibodies (performed at CBS and Héma-Québec).
- Thrombocytopenia lasts approximately 2 weeks.
- First-line therapy is IVIG at a dose of 1 g/kg daily for 2 days; the platelet count is expected to increase 4 days after the start of therapy.

Prevention

- Patients with PTP should receive antigen-negative RBC and platelet transfusions (washed RBCs do not appear to be safe in this population).

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Warning

- Affected patients (and their relatives) are at risk of neonatal alloimmune thrombocytopenia (NAIT). The family should be tested and counselled regarding both PTP and NAIT.
  - NAIT occurs when a woman has anti-platelet antibodies (usually anti-HPA-1a) and is carrying an antigen-positive fetus; the infant is frequently born with severe thrombocytopenia, and sometimes, intracranial hemorrhage

Transfusion-Related Alloimmune Thrombocytopenia

- Uncommon cause of thrombocytopenia
- Due to platelet specific donor alloantibodies to patient platelet antigens

Transfusion-Related Alloimmune Neutropenia

- Rare cause of neutropenia

Virus, Prion, and Parasite Infection

(Bacterial contamination is described under Fever)

Viruses

Risks

- Donating blood in the 'window period' – the interval between the time of infectivity and the appearance of detectable disease markers such as specific antibodies or viral nucleic acid sequences.
- **Figures in chart below are risk per donor exposure: (i.e. 1 unit of RBC)**
- Current 'window period' estimates are:
  - 11 days for HIV
  - 10 days for HCV
  - 59 days for HBV

HIV Virus

HIV	1 in 4.7 million
Hepatitis C virus (HCV)	1 in 3.1 million
Hepatitis B virus (HBV)	1 in 82,000
Human T-cell lymphotropic virus	1 in 3 million
West Nile Virus (WNV)	< 1 in 1 million

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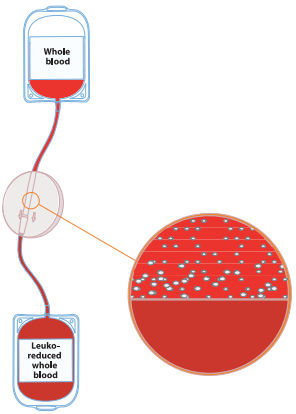
- Outcomes of **transfusion-related transmission of HIV, HCV, HBV and HTLV:**

Virus	Outcome
HIV	50% risk of developing AIDS within 7 years, with older recipients showing shorter latency periods.
HCV	50-70% of recipients develop chronic hepatitis, about 30 to 50% of which proceed to cirrhosis, usually indolent, and an uncertain proportion of these develop hepatocellular carcinoma.
HBV	60% of HBV-infected individuals develop evidence of hepatitis (incubation period of 11-12 wks). The vast majority of cases resolve by developing immunity. In less than 5% of cases, HBsAg persists beyond 6 months, indicating chronic infection with the likelihood of chronic liver disease. Rarely, hepatitis B presents as acute fulminant hepatitis.
HTLV	Long-term consequences of transfusion-transmitted HTLV remain unclear, but the virus is associated with the development of HTLV-associated lymphoma and myelopathy in the endemic form.

Cytomegalovirus (CMV):

- 40% of Canadian blood donors have antibodies to and harbour CMV in their white cells, but without clinical consequences.
- Transmission is vertical from mother to child, or by body fluids, sexual activity, transfusion, or transplantation.
- CMV-seronegative units are available from CBS and HQ for restricted use only. The most commonly recommended indications for CMV-seronegative products are:
  1. CMV-seronegative pregnant women
  2. Intrauterine transfusions
  3. CMV-seronegative allogeneic bone marrow transplant recipients
- Leukoreduction removes most, but not all CMV from blood components.
- The incremental benefit of providing CMV-seronegative components, in addition to leukoreduction, in the prevention of CMV transmission is unknown.



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West Nile Virus (WNV)

- No known cases in Canada since nucleic acid testing of donations began in July 2003.
- In the USA in 2003, there were 6 confirmed cases of transfusion-transmitted West Nile Virus from 6 million donations.
- 1 case in the USA in 2004.
- Facts about transfusion-transmitted West Nile Virus:
  - The virus can be transmitted through RBCs, platelets, plasma, and cryoprecipitate, but not through manufactured blood products (e.g. albumin, IVIG, clotting factor concentrates)
  - The onset of symptoms post-transfusion has ranged from 3 to 13 days (median 7 days)
  - Symptomatic recipients were primarily immunocompromised patients; however, postpartum and post-operative patients have been affected

Prions

- Variant Creutzfeldt-Jakob Disease (vCJD).
  - 2 suspected cases of transfusion-associated transmission of the agent of vCJD have been reported in the U.K.
  - At present, high risk blood donors (resident in the U.K. or France for more than 3 months, or in Europe for more than 5 years) are deferred in Canada

Mad Cow Disease

Trypanosoma cruzi

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Other Transfusion-Transmissible Agents

- Other rare infectious agents confirmed to be transmitted by blood components that may cause symptomatic infection are:
  - **Viral** – Parvovirus B19, Hepatitis A virus, Tick-borne encephalitis, Colorado Tick Fever, Human herpes virus 8
  - **Protozoal** – Malaria, *Trypanosoma cruzi* (Chagas Disease), Toxoplasmosis, Leishmaniasis, Babesiosis
  - **Helminthic** – Filariasis
  - **Spirochetal** – *Treponema pallidum* (Syphilis), *Borrelia burgdorferi* (Lyme disease)
  - **Rickettsial** – *R. rickettsii* (Rocky Mountain Spotted Fever), *R. burnetii* (Q fever), Ehrlichia (Ehrlichiosis)
- It is extremely important to report cases of the above infections in transfusion recipients and recent blood donors.
- The following agents are transfusion-transmissible but have not been established as causing disease in man: TT virus, SEN-V, and Simian foamy virus.

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Complications of Massive Transfusion

Definition

- More than 10 units of RBCs, or, transfusing more than one blood volume in a 24-hour period.
- Massive transfusion is an independent risk factor for developing multi-organ failure.

Complications

- The complications described below are dependent on the following factors:
  - Number of units transfused
  - Rapidity of transfusion
  - Patient factors

1. Dilutional coagulopathy

- 50% of massively transfused patients develop an INR > 2.0 and about 33% have thrombocytopenia with a platelet count < 50 x 10^9/L.
- Number of RBCs transfused does not accurately predict the need for a platelet and FP transfusion; use laboratory values to determine when these products should be transfused.
- Use laboratory monitoring where possible to guide the use of blood products. Avoid use of empirical 'formulae'.

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2. Hypothermia

- Rapid infusion of cold blood can result in cardiac arrhythmias.
- Prevention is critical – if massive transfusion is likely, use an approved and properly maintained blood warmer.
- Mortality after massive transfusion is inversely related to core temperature (data from 1987):
  - < 34°C – 40%
  - < 33°C – 69%
  - < 32°C – 100%
- Risk of clinically important hypothermia is significantly increased by infusion of 5 or more units of blood.
- Consequences of hypothermia:
  - Platelet dysfunction
  - Reduced clearance of citrate
  - Decreased cardiac output
  - Hypotension
  - Arrhythmias (especially if cold blood is transfused rapidly through a central line)
  - ECG changes: prolonged PR, QRS, QT; T-wave inversion; J (Osborne) waves

3. Hypocalcemia/Hypomagnesemia/Citrate toxicity

- Citrate is the anticoagulant used in blood components.
- It is usually rapidly metabolized by the liver.
  - A normothermic adult not in shock can tolerate upwards of 20 units per hour without calcium supplementation
- With massive transfusion, the capacity of the liver to degrade citrate may be overwhelmed.
- Citrate binds ionic calcium and magnesium, causing functional hypocalcemia, hypomagnesemia, and also metabolic alkalosis (from bicarbonate, a metabolite of citrate).
- Clinical symptoms include: hypotension, narrow pulse pressure, elevated pulmonary artery pressure, tetany, paresthesia, arrhythmias.
- **If hypocalcemia develops OR patient develops signs or symptoms of hypocalcemia then administer:**
  - **1 gram (1 ampoule) of calcium chloride IV** at maximum rate of 100 mg/minute

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4. Metabolic acidosis

- Rare; from acid pH of blood products.
- Usually, metabolic alkalosis is due to bicarbonate production from citrate metabolism.
- Can be aggravated by the lactic acidosis in patients with tissue hypoxia.

5. Hyperkalemia

- Release of potassium from stored RBCs increases with storage time and after irradiation.
- After 28-days storage in citrate, a unit of RBCs contains approximately 6 mmol of potassium per unit.

Note: For discussion of the changes in electrolytes and acid-base balance with massive transfusion, see Wilson et al.

Tips during massive transfusion/bleeding

- **Monitor core temperature.**
- **Prompt use of measures to prevent hypothermia, including use of a blood warmer** for all IV fluids and blood components.
- **Watch for dilutional coagulopathy.**
  - While patient is actively bleeding:
    Transfuse to keep platelet count > $50x10^9$/L (with head injury > $100x10^9$/L), INR < 1.5, and fibrinogen > 1.0 g/L with blood components
- **Watch for hypocalcemia.**
- **Use SQ40 Pall® filter** with blood tubing to minimize the number of times the blood tubing has to be changed.
  - Change blood tubing q4-q24h with SQ40 filter
  - Change blood tubing q2-4 units of RBCs if SQ40 Pall® not used

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Dale Towns

Acute hemorrhage is often classified into four categories (I–IV) depending on the fraction of the normal circulating blood volume lost:

- Class I <15%
- Class II 15–30%
- Class III 31–40%
- Class IV >40%

Class I hemorrhage may require no fluid therapy. Class II hemorrhage may be treated with crystalloid and/or colloid infusion, with RBCs only rarely required. Class III hemorrhage may be treated with crystalloid first, but RBCs should be readily available if there is inadequate response to crystalloid therapy. Class IV hemorrhage requires transfusion of RBCs in addition to maintenance of intravascular volume with crystalloid and/or colloid.

With slow blood loss occurring over hours, provided normovolemia is maintained, up to 50% of red cell mass may be lost without the requirement for RBC transfusion. A large Canadian randomized trial showed that among 838 critically ill patients, a hemoglobin transfusion threshold of 100 g/L (average achieved 107 g/L) provided no better outcomes than a threshold of 70 g/L (average achieved 85 g/L). The applicability of this result to patients with cardiac disease, however, is uncertain. Such patients have less tolerance for red cell loss. As well, in actively bleeding patients with coagulopathy, hemostatic function may be improved at higher hemoglobin levels.

Clinical assessment of the urgency for RBC transfusion will determine whether the patient receives unmatched emergency group O RBCs, group-specific RBCs, or a fully crossmatched RBC unit. In all cases, a pre-transfusion sample of appropriately identified and labelled blood should be obtained and sent to the blood bank for typing and initiation of compatibility testing. Risks of ABO transfusion errors are potentially high, particularly in urgent clinical situations involving multiple-trauma patients. Particular care and attention must accompany patient identification procedures in this setting.

Group O unmatched RBCs can be used if the patient's blood group is unknown and transfusion is immediately required. In this scenario, group O Rh-positive RBCs can be transfused to males who have no prior history of transfusion with Rh-positive blood. Group O Rh-negative RBCs should be reserved for females of child-bearing age, children, and others suspected or known to be alloimmunized to the D antigen.

Type-specific unmatched blood can usually be provided within 10 minutes; however, completion of an antibody screen and crossmatch often takes 30–60 minutes. Transfusing physicians should familiarize themselves with the policies and procedures of the hospital blood bank in providing blood for emergency use.

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Crystalloid, Colloid, Pentastarch (Pentaspan®), Albumin

If only volume replacement is required, crystalloid solutions may be used for initial therapy. However, with larger volumes, colloid solutions may be preferred, as they will maintain plasma oncotic pressure and cause less peripheral edema. A recent study has shown neither fluid type to be superior.

Pentastarch is an artificial colloid plasma expander available as a 10% solution in 0.9% normal saline. It has been in use in Canada since 1993. Its cost compares favourably with albumin, and it is not a human-derived product. It is available in 250 mL and 500 mL plastic bags, which may allow for more rapid infusion than albumin. It is not a substitute for red blood cells or coagulation factors. Pentastarch is renally excreted and should not be used in patients with renal disease and coexisting anuria or oliguria. It should be used with caution in patients who are at risk of volume overload. Hypersensitivity, though rare, can occur. The total infusion should not exceed 2000 mL in 24 hours (28 mL/kg body weight). Coagulation mechanisms may be altered if the recommended infusion volume is exceeded.

Albumin is available in 50 mL or 500 mL (as a 25% solution) and 250 mL or 500 mL (as a 5% solution) glass bottles. Unless clotting factors are required, albumin may be preferred to frozen plasma because of the decreased infectious risks associated with its use.

Massive Transfusion

Massive transfusion—generally defined as the replacement of a patient's blood volume in 24 hours or less—can result in several adverse effects. Awareness, diagnosis, and correction of these complications are essential.

1) Hypothermia

RBCs are stored at 1–6°C. Massive transfusion may produce clinically significant hypothermia (body temp. < 35°C), which reduces platelet and coagulation function, decreases citrate metabolism, increases hemoglobin-oxygen affinity (decreasing oxygen release to the tissues), and decreases myocardial function. Blood warming devices (to temperatures NOT greater than 37°C) are vital for the management of massive transfusion. With pressurized infusion systems, avoidance of air embolization is imperative. Other measures to warm the patient should also be employed.

2) Impaired hemostasis

Massive transfusion can lead to hemostatic problems due to either dilution or the loss of clotting factors and platelets. With red blood cell replacement for gradual losses of up to one blood volume, clotting factor levels may be reduced to 25% of normal and PT INR and aPTT may be mildly prolonged without clinical coagulopathy. As a result, in modern practice using RBC replacement of blood loss, plasma transfusion is often required before platelets. Rapid blood loss may warrant earlier transfusion of plasma or platelets. Adverse effects on coagulation are compounded by hypothermia. Disseminated intravascular coagulopathy (DIC) occurs in 5%–30% of massively transfused trauma patients.

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3) Citrate toxicity

Blood components are anticoagulated with sodium citrate. When transfused, the citrate may bind with circulating calcium and magnesium. Although a relative hypocalcemia may transiently occur as a result of calcium chelation, it is unlikely to cause significant coagulopathy. Massive transfusion may, however, impair the body's ability to metabolize citrate. Resulting hypocalcemia may lead to cardiac arrhythmias, reduced ventricular function, and increased neuromuscular excitability. This problem is more common with rapid infusion devices. Metabolic alkalosis may develop secondary to the accumulation of bicarbonate, the metabolic by-product of citrate.

4) 2,3-diphosphoglycerate (2,3-DPG) and altered hemoglobin function

The level of 2,3-DPG in stored RBCs decreases to < 10% of normal after two weeks storage. Although the level is restored by 24 hours post-transfusion, effects of decreased 2,3-DPG may be present immediately post-transfusion. The primary effect is a left shift of the hemoglobin-oxygen dissociation curve, which increases the RBC affinity for oxygen. While not a concern for most patients, the elderly and those with cardiovascular disease may be more susceptible to the reduced oxygen availability, and therefore may benefit from a higher hematocrit.

5) Microaggregates

Microaggregates of platelets, leucocytes, and fibrin found in RBCs may not be removed by a standard (170 um) blood filter. Although microaggregate filters < 40 um intended to remove aggregates < 170 um are available, their use has not been shown to improve patient outcome. Furthermore, they may impair the capability for rapid transfusion of RBCs.

6) Potassium

Potassium leaks from RBCs during storage, and may reach levels of up to 80 mmol/L in a unit of RBCs. Infrequently, hyperkalemia due to massive transfusion produces cardiac arrhythmias or myocardial depression. This may be treated with sodium bicarbonate, calcium and potassium-lowering measures. Hypokalemia, possibly due to alkalosis and catecholamine effects, may also complicate massive transfusion.

7) Volume status and myocardial function

Massively transfused patients, particularly those with ongoing hemorrhage, are vulnerable to extremes of intravascular volume (hypovolemia to hypervolemia) and myocardial depression. Physical examination may be inadequate, and invasive monitoring (central venous pressure, pulmonary artery catheter, echocardiography) may be important to guide management.

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Follow-up Testing and Adjunctive Therapy

Laboratory measurements of hemoglobin, hematocrit, platelet count, PT INR, aPTT, fibrinogen and D-dimer help guide decisions about ongoing transfusion requirements. However, transfusion should be withheld when coagulation tests are abnormal but clinical coagulopathy is absent. Frozen plasma, cryoprecipitate, and platelets should not be administered in a fixed ratio to the number of red cell units transfused; rather, clinical and laboratory monitoring of blood counts and coagulation status should guide therapy. Recombinant activated human factor VII (recombinant factor VIIa) has been anecdotally reported to be successful for intractable bleeding. However, protocols for appropriate use are still being established, as is the evidence based on properly designed clinical trials. Acid-base status, calcium, magnesium, potassium, and albumin should also be monitored during massive transfusion.

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Kathryn Webert and Heather Hume

Prevention of Hemolytic Disease of the Fetus and Newborn

Serological Testing in Pregnancy

It is recommended that all pregnant women undergo testing for ABO/D grouping and screening for unexpected red cell antibodies as early as possible in pregnancy. Ideally this occurs at the initial visit in the first trimester of pregnancy. For first pregnancies, the D antigen status should be confirmed on two separate occasions if there is no previous record of D status. The purpose of the antibody screen is to determine whether or not D-negative women have made anti-D, as well as to identify women with other red cell antibodies capable of causing hemolytic disease of the fetus/newborn (HDFN). D-negative women should be tested again for unexpected red cell antibodies at 26 to 28 weeks prior to the administration of Rh immune globulin (RhIg) prophylaxis, but the administration of RhIg (see next section) should not be withheld pending these results. Women who have a history of clinically significant red cell antibodies, blood transfusions or traumatic deliveries may require additional antibody testing regardless of D status. These recommendations are summarized in Table 1.

Table 1: Recommended schedule for serological testing in pregnancy

Test	Timing
ABO determination	
■ All pregnancies	■ Initial visit
■ Other	■ Pre-transfusion testing
Rh status	
■ All pregnancies	■ Initial visit
■ First pregnancy	■ At 26–28 weeks (unless known to be Rh positive on 2 separate occasions)
■ Other	■ Pre-transfusion testing
Antibody screen	
■ All pregnancies	■ Initial visit
■ D- pregnancies	■ Before RhIg administration
■ D+ pregnancies	■ Third trimester if transfused or history of unexpected antibodies
■ Other	■ Pre-transfusion testing
Antibody identification	When initially detected

Adapted with permission from: Judd WJ, for the Scientific Section Coordinating Committee of the AABB. Practice guidelines for prenatal and perinatal immunohematology, revisited. Transfusion 2001; 41:1445-1452.

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Weak D Phenotype

Some D-positive RBCs have weak expression of the D antigen. This phenotype is known as "weak D." Women with this phenotype are genetically D-positive and are at extremely low risk of producing anti-D (in fact, will produce anti-D only if the weakened expression of the D antigen is also associated with an anomaly of the D antigen termed partial D). The issue of whether or not weak D testing should be performed routinely for prenatal patients is controversial and experts differ in their opinions. Most recently published guidelines/opinions recommend that weak D testing NOT be performed given the increased sensitivity of current anti-D reagents and the (albeit small) risk of anti-D formation in patients with partial D antigen variants. Current AABB and CSTM standards do not require weak D testing for perinatal patients. CBS perinatal testing laboratories either do not routinely perform weak D testing or are in the process of eliminating weak D testing for D-negative prenatal patients. When weak D testing is not performed these women are considered to be D-negative and are eligible for Rh immune globulin prophylaxis. This may protect partial D-positive women from development of anti-D. One additional clinical implication of this policy is the likelihood of false positive reactions in screening tests for fetal-maternal hemorrhage (the rosette test). Alternate methods for fetal maternal hemorrhage screening may be required for these women.

Rh Immune Globulin

Rh immune globulin (RhIg) consists primarily of IgG anti-D that is concentrated from pools of human plasma containing anti-D. Recommended doses of RhIg are shown in Table 2. These doses are based on the fact that 20 µg of RhIg neutralizes 1 mL of D-positive RBCs or 2 mL of D-positive blood. The mechanism of action of RhIg has not been clearly elucidated; however, its benefits are well documented. When RhIg is administered within 72 hours of a full-term delivery of a D-positive infant by a D-negative mother, the incidence of alloimmunization is decreased from 12–13% to 1–2%. When RhIg is also administered at 28 weeks, the incidence of alloimmunization is further decreased to 0.1%.

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Table 2: Recommended doses of Rh immune globulin for D-negative women without anti-D during pregnancy[+]

Indication	Dose of RhIg (WinRho)
Pregnancy (28 weeks gestation)[#]	300 µg (1,500 IU) IV or IM
Postpartum, if newborn is D-positive, including weak D-positive	120 µg (600 IU) IV or IM[*] or 300 µg (1,500 IU) IV or IM[‡]
Threatened abortion (at any time)	300 µg (1,500 IU) IV or IM
Abortion before 34 weeks (including very early pregnancy loss)	300 µg (1,500 IU) IV or IM
Amniocentesis and chorionic villus sampling before 34 weeks gestation[#]	300 µg (1,500 IU) IV or IM
Abortion, amniocentesis, or any other manipulation after 34 weeks gestation[#]	120 µg (600 IU) IV or IM
Other indications[†]	300 µg (1,500 IU) IV or IM

[+]Where paternity is certain, D blood typing of the baby's father may be offered to a D-negative woman to avoid unnecessary blood product administration.

[#]Dose should be repeated every 12 weeks after the initial dose is given.

[*]Testing should be performed to quantitate fetomaternal hemorrhage. Additional RhIg will be required if fetomaternal transplacental hemorrhage greater than 12 mL of fetal blood (6 mL of fetal RBCs) is documented.

[‡]Additional RhIg will be required if fetomaternal transplacental hemorrhage greater than 30 mL of fetal blood (15 mL of fetal red cells) is documented.

[†]Other indications include any incident that might result in fetal cells entering the maternal circulation at any time in the pregnancy. These conditions include but are not limited to: versions, abdominal trauma, ectopic pregnancy and stillbirth.

Adapted from: Win-Rh$_o$ SDF [Rh$_o$(D) Immune Globulin (Human) for Injection] package insert. Cangene Corporation, Winnipeg, Canada. August 2001 and Fung Kee Fung K, Eason E, Crane J, et al. for the Maternal-Fetal Medicine Committee, Genetics Committee. Prevention of Rh Alloimmunization, SOGC Clinical Practice Guideline. J Obstet Gynaecol Can 2003; 25: 765-773.

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Management of Non-sensitized D-Negative Women

Rhlg (300 µg) should be given routinely to all D-negative non-sensitized women at 28 weeks gestation. Alternatively, 120 µg may be given both at 28 weeks and at 34 weeks. Rhlg should also be given to all D-negative women without antibodies after any incident that might result in fetal cells entering the maternal circulation at any time in the pregnancy. These conditions include, but are not limited to, abortion, threatened abortion, amniocentesis, chorionic villus sampling, versions, abdominal trauma, ectopic pregnancy and fetal death *in utero*.

At delivery, all D-negative women should receive Rhlg 120 or 300 µg within 72 hours of delivery of a D-positive infant. It is generally recommended that all women be investigated for the presence of a fetomaternal hemorrhage and, if present, the size of the bleed should be quantitated (see below). This is particularly important if the lower dose of Rhlg is administered. If Rhlg is not given within 72 hours of delivery, it should be given as soon as the need is recognized, up to 28 days after delivery. If the antepartum dose of Rhlg is given prior to 28 weeks gestation, then consideration should be given to repeating Rhlg prior to birth if the period without exposure to Rhlg prophylaxis exceeds 12 weeks.

Where paternity is certain, D blood grouping of the baby's father may be offered to a D-negative woman to eliminate unnecessary blood product administration (should the baby's father also prove to be D-negative).

Fetal-Maternal Hemorrhage Screening and Therapy

Although cost-effectiveness has not been demonstrated, it is generally recommended that following delivery maternal blood should be tested for the presence of fetal RBCs and, if present, the quantity of the fetomaternal hemorrhage should be determined. If the quantity of hemorrhage exceeds the capacity of the Rhlg to provide protection, additional Rhlg should be administered. Given that one 120 µg dose of Rhlg protects against 6 mL of D-positive RBCs or 12 mL of whole blood, a bleed estimated to be larger than this will require administration of additional Rhlg. The additional Rhlg should be administered within 72 hours of delivery. However, if the need for additional Rhlg is discovered longer than 72 hours after delivery but within 28 days of delivery, it is still recommended that additional doses be given as soon as possible.

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Management of Women with RBC Antibodies

All women (whether D-negative or D-positive) with a positive red cell antibody screen should have the specificity of the antibody determined upon its discovery. If the antibody is a potential cause of HDFN, the father should be tested to determine if he expresses the corresponding antigen(s). Whenever there is a risk of HDFN, an experienced obstetrician and hematologist/hematopathologist should be consulted early in the pregnancy regarding the treatment plan, and the mother should be referred for investigation and management when indicated. Invasive testing, because of the risk to the fetus, should be performed only for pregnancies where the fetus is at risk for HDFN. Consideration should be given to delivering the infant where neonatal intensive care facilities are available. RBC antibodies associated with HDFN are listed in Table 3.

Table 3: Common red cell (RBC) antibodies that may be associated with the hemolytic disease of the fetus or newborn (HDFN)*, according to blood group system and antigen specificity

Indication	System	Antigens
RBC antibodies that may be associated with severe HDFN	■ Rhesus ■ Kell ■ Duffy ■ Kidd	■ D, C, c, E ■ K, k ■ Fy^a ■ Jk^a, Jk^b
RBC antibodies that may be associated with mild HDFN	■ ABO ■ Ii ■ Duffy ■ Lutheran	■ A, B ■ i ■ Fy^b ■ Lu^a, Lu^b
RBC antibodies not associated with HDFN	■ Lewis ■ Ii ■ P	■ Le^a, Le^b ■ I ■ P_1

* This list includes only the most common RBC antibodies; it is not exhaustive. For less common antibodies refer to: Issit PD, Anstee DJ. Applied blood group serology, 4th ed. Montgomery Scientific Publications, Durham NC, 1998.

Role of Transfusion Practice in the Prevention of HDFN

RBC alloimmunization that could lead to HDFN is a risk of allogeneic transfusion in female patients at or prior to child-bearing age. As for other complications, the most important way of avoiding this risk is to administer transfusions only when absolutely necessary. Where appropriate (e.g. elective surgery likely to require RBC transfusion in adolescent girls and women), autologous rather than allogeneic RBC transfusion should be used if possible. If a D-negative female patient is transfused with platelets that are either from a D-positive donor or a donor of unknown D status, then an appropriate dose RhIg should be administered. Finally, a woman of child-bearing age should not receive a directed donation from her spouse.

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Perinatal Thrombocytopenia

Neonatal Thrombocytopenia

Neonatal thrombocytopenia may be caused by decreased production of platelets, increased consumption of platelets, or because of dilution. Increased consumption is the most common etiology and may result from a variety of causes including sepsis, necrotizing enterocolitis, disseminated intravascular coagulation, placental insufficiency, congenital infection, asphyxia, or may be immune-mediated. In general, immune-mediated neonatal thrombocytopenia may be classified into two categories: (1) neonatal alloimmune thrombocytopenia (NAIT), and (2) thrombocytopenia secondary to maternal idiopathic thrombocytopenic purpura (ITP). Infants and children may have thrombocytopenia because of ITP.

Neonatal Alloimmune Thrombocytopenia

NAIT occurs when fetal platelets express a paternal antigen that is not found on maternal platelets. Fetal platelets may enter the maternal circulation during gestation or delivery. If the mother becomes alloimmunized, the maternal IgG alloantibody may cross the placenta and cause thrombocytopenia in the fetus. The thrombocytopenia is self-limiting and generally resolves within two to three weeks after delivery. The severity of NAIT is variable, ranging from mild thrombocytopenia to severe thrombocytopenia with clinical hemorrhage. The incidence of intracranial hemorrhage may be as high as 30% with approximately 50% of these occurring *in utero*.

Serologic investigations: Parents who have delivered an infant with NAIT should have testing performed, including platelet typing for platelet-specific antigen systems that have been associated with NAIT. The most common antigen, HPA-1a (PI^{A1}) causes approximately 90% of cases in the Caucasian population. The mother should also be investigated for platelet-specific antibodies.

Treatment of an affected infant: An infant with NAIT who requires platelet transfusions should receive antigen-negative platelets. If maternal platelets are used, the plasma should be removed and the platelets resuspended in plasma or saline. As this is a directed donation, irradiation of the platelets prior to transfusion is also critically important. Other treatments that may be effective include IVIG infusion and exchange transfusion.

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Treatment of subsequent pregnancies: During subsequent pregnancies, women who have previously delivered infants with NAIT should be followed by an obstetrician and hematologist experienced in the care of such patients. Fetal platelet counts may be followed by cordocentesis beginning at 20 weeks gestation. If the infant is found to be thrombocytopenic (or if in the opinion of the obstetrician/hematologist the risk of neonatal thrombocytopenia is significant), the mother may be treated with an infusion of IVIG (1 g/kg) weekly until delivery. Maternal platelets are often collected before delivery for use by the infant. Alternatively, apheresis collection of platelets from a donor known to lack the platelet antigen involved may be used.

Maternal ITP

Infants born to mothers with ITP may also have thrombocytopenia due to passive transfer of the maternal autoantibody across the placenta. Most infants have only mild thrombocytopenia and the risk of hemorrhage is very low, with the occurrence of intracranial hemorrhage being exceedingly rare.

Treatment: Infants with thrombocytopenia secondary to maternal ITP rarely require treatment. If platelet transfusions are required, there is no benefit to maternal platelets as all platelets tend to have a shortened survival. Other therapies that may be beneficial in severe cases include IVIG and corticosteroids.

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Kathryn Webert and Heather Hume

While the practice of transfusion of blood products to neonatal and pediatric recipients has much in common with the transfusion of blood products to adults, there are several important differences and special circumstances. This chapter will highlight the most common considerations that are unique to this group of patients.

Normal Values

The normal values of hemoglobin for neonates, infants and children are listed in Tables 1 and 2. In general, an infant's hemoglobin concentration at birth tends to be approximately 165 g/L increasing up to a mean of 184 g/L within 24 hours of birth. During the first three months of life, all infants have a normal or "physiologic" decrease in their hemoglobin down to approximately 115 g/L. This decrease is greater in preterm infants. By age 12, the hemoglobin levels of healthy children are the same as those for adults.

Table 1: Normal hemoglobin values for neonates

Age	Hemoglobin concentration (g/L) mean (-2 SD)		
	Preterm		Term
	1.0–1.5 kg	1.5–2.0 kg	
2 weeks	163 (117)	148 (118)	165 (125)
1 month	109 (87)	115 (82)	140 (100)
2 months	88 (71)	94 (80)	115 (90)
3 months	98 (89)	102 (93)	115 (95)

Preterm infant is defined as an infant less than 37 weeks gestational age. Normal values for preterm infants will depend on gestational age. Normal values may differ depending on the laboratory performing the investigations.

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Table 2: Normal hemoglobin values for infants and children

Age	Sex	Hemoglobin concentration (g/L) mean (- 2 SD)
0.5 to 2 years	Both	120 (105)
2 to 6 years	Both	125 (115)
6 to 12 years	Both	135 (115)
12 to 18 years	Female	140 (120)
12 to 18 years	Male	145 (130)
> 18 years	Female	140 (120)
> 18 years	Male	155 (135)

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At birth until six months of age, the concentrations of vitamin K-dependent factors (factors II, VII, IX, X) and the vitamin K-dependent inhibitors of coagulation (proteins C and S) are lower than adult levels (Table 3). By age six months, the concentrations of coagulation factors, contact factors and natural coagulation inhibitors have reached approximately those of adults

Table 3: Normal values for coagulation factor assays and screening tests in preterm infants (30–36 weeks) and infants

Coagulation test or factor assay	Preterm infant (mean ± 2SD)	Term infant (mean ± 2SD)	Time at which values attain adult norms
Fibrinogen (g/L)	2.43 + 0.93	2.83 (1.67–3.99)	Prenatally
Factor II (U/mL)	0.45 (0.20–0.77)	0.48 (0.26–0.70)	2–12 months
Factor V (U/mL)	0.88 (0.41–1.44)	0.72 (0.34–1.08)	Prenatally
Factor VII (U/mL)	0.67 (0.21–1.13)	0.66 (0.28–1.04)	2–12 months
Factor VIII (U/mL)	1.11 (0.50–2.13)	1.00 (0.50–1.78)	Prenatally
Factor IX (U/mL)	0.35 (0.19–0.65)	0.53 (0.15–0.91)	3–9 months
Factor X (U/mL)	0.41 (0.11–0.71)	0.40 (0.12–0.68)	2–12 months
Factor XI (U/mL)	0.30 (0.08–0.52)	0.38 (0.10–0.66)	1–2 months
Factor XII (U/mL)	0.38 (0.10–0.66)	0.53 (0.13–0.93)	9–14 days
Factor XIII (U/mL)	0.70 (0.32–1.08)	0.79 (0.27–1.31)	3 weeks
PT (s)†	10.6–16.2	13.0 (10.1–15.9)	1 week
aPTT(s)†	53.6 + 26.1	42.9 (31.3–54.5)	2–9 months
INR	0.61–1.7	1.00 (0.53–1.62)	1 week
TCT (s)†	24.8 (19.2–30.4)	23.5 (19.0–28.3)	Few days

Note: Assays quoted are biologic unless otherwise specified.

All values are given the mean with 95% confidence interval.

†Values vary between laboratories depending on the reagents used.

Abbreviations: Standard deviation (SD); prothrombin time (PT); international normalized ratio (INR); activated partial thromboplastin time (aPTT); thrombin clotting time (TCT).

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Pre-Transfusion Testing

The neonate, who for the purposes of transfusion medicine is considered to be an infant under four months of age, requires limited pre-transfusion testing when compared to that required for older infants, children and adults. For neonates the required testing includes ABO and Rh typing and an antibody screen. The determination of the ABO group of a neonate is based on red cell typing only. Serological ("reverse") typing is not performed because ABO antibodies initially present after birth are of maternal, and not neonatal, origin. However, if a non-group O neonate is to receive a non-group O red cell transfusion with blood that is not known to be compatible with the maternal ABO group, then the neonate's serum or plasma must be tested for maternal anti-A or anti-B, and the choice of blood must take into consideration both the neonate's ABO group and the maternal antibodies present in the neonate's circulation. Because of this complexity in the choice of ABO blood group for neonatal RBC transfusions, many transfusion services routinely use only group O RBCs for neonates.

The antibody screen is performed to detect unexpected red cell antibodies and may be performed using either a neonatal or a maternal blood specimen. Initially, the origin of antibodies, if present, will be maternal and not neonatal. Because of the infant's immature immune system, if the initial screen is negative, it is not necessary to repeat this in the course of the initial hospitalization up to four months of age. Furthermore, if the antibody screen is negative, it is not necessary to perform a crossmatch for this group of patients, and this test may be omitted in an effort to decrease iatrogenic blood loss.

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RBC Transfusion

Neonatal Recipients

Indications for RBC Transfusions

The indications for transfusion in neonates vary compared to children and adults for several reasons, including the infant's small blood volume, physiologic anemia of infancy, decreased production of endogenous erythropoietin, and the infant's inability to tolerate minimal physiologic stress. The indications for transfusion in neonates have been well studied; nevertheless, the indications remain somewhat controversial for several reasons. These reasons include:

- the difficulties determining when a neonate may benefit from a transfusion because of the varying hemoglobin levels and hemoglobin type (HbF versus HbA);
- the difficulties in assessing the neonate for clinical indications for transfusion;
- the lack of consensus of how significant symptoms are defined; and
- the suggestion that the hemoglobin or hematocrit concentration may not accurately reflect the RBC mass in preterm and/or ill newborns.

The Premature Infants in Need of Transfusion (PINT) study has recently been completed and showed that a restrictive transfusion policy was safe in infants weighing less than one kilogram.

Various publications exist that provide guidelines for RBC utilization in neonates. In general, it is recommended that neonates be transfused if they have:

- acute blood loss of >10% blood volume;
- hemoglobin less than 80 g/L in a stable newborn with symptoms of anemia (apnea, bradycardia, tachycardia, decreased vigor, poor weight gain); or
- hemoglobin less than 120 g/L in an infant with respiratory distress syndrome or congenital heart disease (Tables 4 and 5).

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Table 4: Guidelines for transfusion of RBCs in patients under four months of age

1. Hemoglobin <70 g/L with low reticulocyte count and symptoms of anemia*
2. Hemoglobin <100 g/L in an infant:
   - on <35% hood O_2
   - on O_2 by nasal cannula
   - on continuous positive airway pressure and/or intermittent mandatory ventilation with mechanical ventilation with mean airway pressure <6 cm H_2O
   - with *significant* apnea or bradycardia†
   - with *significant* tachycardia or tachypnea‡
   - with low weight gain#
3. Hemoglobin <120 g/L in an infant:
   - on >35% hood O_2
   - on continuous positive airway pressure/intermittent mandatory ventilation with mean airway pressure ≥ 6–8cm H_2O
4. Hemoglobin <150 g/L in an infant:
   - on ECMO
   - with congenital cyanotic heart disease

*Tachycardia, tachypnea, poor feeding.

†More than 6 episodes in 12 hours or 2 episodes in 24 hours requiring bag and mask ventilation while receiving therapeutic doses of methylxanthine.

‡Heart rate >180 beats per minute for 24 hours; respiratory rate >80 breaths per minute for 24 hours.

#Gain of <10 g per day observed over 4 days while receiving ≥100 kcal per kg per day.

Adapted from: Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. Transfusion 2002; 42:1398-1413.

Note: There are conflicting data on the usefulness of clinical signs in the assessment of the need for RBC transfusion in a premature infant.

Table 5: Canadian Pediatric Society recommendations for RBC Transfusions in Neonates

1. Hypovolemic shock associated with acute blood loss
2. Hematocrit 30% to 35% in extreme illness conditions for which RBC transfusions may improve oxygen delivery to vital organs
3. Hematocrit between 20% and 30% and the infant is severely ill and/or on mechanical ventilation with compromised oxygen delivery
4. Hematocrit falling (20% or less) and signs or symptoms attributable to the anemia

Adapted with permission from Paediatrics & Child Health, Vol. 7 No. 8 (October 2002), Canadian Paediatric Society Position Statement (FN 2002-02). For the full text of this statement, please visit http://www.cps.ca/english/statements/FN/fn02-02.htm

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The usual dose of RBC, depending on the product used and the volume the infant can tolerate is 10 to 20 mL per kg of recipient body weight. In general, a transfusion of RBCs in CPDA-1, of 10 mL/kg or a transfusion of RBCs in AS-3 (or any other additive solution), of 15 mL/kg can be expected to raise the baby's Hb concentration by about 20 g/L. The larger volume required for RBCs stored in additive solution is due to the differences in hematocrit of the two products: RBCs stored in CPDA-1 have a hematocrit of approximately 0.75 L/L while RBCs stored in additive solutions have a hematocrit of approximately 0.55 L/L. If supernatant fluid is removed from the RBC unit then the amount transfused should be decreased accordingly.

Age of Blood

It has been suggested that all neonates should receive relatively fresh RBCs (stored for less than five days). This has been suggested for two reasons: (1) because of the increased amount of plasma potassium in RBCs stored for longer than five days; and (2) because of the decreased levels of RBC 2,3 DPG with extended storage. These concerns are valid for infants receiving large-volume transfusions (>20 mL per kg) as the potassium content of stored blood when administered rapidly may be lethal for a neonatal patient. In contrast, infants receiving smaller volume transfusions (<20 mL per kg) over three or four hours, in most cases, do not require fresh RBCs. In fact, several studies have demonstrated the safety of assigning a fresh (less than five days old) RBC unit to a neonatal patient and using aliquots of this same unit up to its normal expiry date for subsequent small-volume RBC transfusions. This strategy is beneficial as it contributes to decreased donor exposure for the infant.

Additive Solutions

Various additive solutions for the storage of RBCs are available for use, including AS-3, AS-1 and SAG-M. Table 6 lists the components of these solutions. In Canada, AS-3 is the additive solution most commonly used for the storage of RBCs and CP2D is the anticoagulant solution (Nutricel® system). When additive solutions first began to be used in the late 1980s, concerns were raised about the safety of transfusing RBCs stored in these solutions into neonatal patients because of the high concentrations of certain components (e.g. adenine, dextrose or mannitol). However, in general, RBCs stored in AS-3 or other additive solutions are considered safe for neonatal patients without renal failure who are receiving small-volume transfusions (i.e. less than 20 mL per kg in three to four hours). Although there are only a few small clinical studies, several years of experience have confirmed this. For neonates receiving massive transfusions, it is suggested that they receive blood products that have been collected into CPDA-1 or that have had the additive solution removed and the RBCs resuspended in an appropriate medium such as saline.

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Table 6: Composition of additive solutions for red cell concentrates

	CPDA	CPD/SAG-M	CPD/AS-1	CP2D/AS-3
Volume (mL)	63	100	100	100
NaCl (mg)	–	877	900	410
Dextrose (mg)	2000	900	2200	1100
Adenine (mg)	17.3	16.9	27	30
Mannitol (mg)	–	525	750	–
Trisodium citrate (mg)	1660	–	–	588
Citric acid (mg)	206	–	–	42
Sodium phosphate (monobasic) (mg)	140	–	–	276

Comparison assumes the 450 mL collection volume currently used at CBS.

Use of Erythropoietin

There have been many controlled trials that have evaluated the use of recombinant human erythropoietin (rHuEPO) in premature infants for the treatment and prevention of anemia of prematurity. Because of varying results of the trials due to patient population and dosing schedules, there remains controversy about whether or not preterm neonates with anemia of prematurity might benefit from administration of rHuEPO. A meta-analysis concluded that it is premature to make firm recommendations for the use of rHuEPO in patients with the anemia of prematurity. Some studies have indicated that erythropoietin administration might decrease the number of transfusions low birth weight infants receive. However, it is likely that donor exposure may be kept just as low through the use of a dedicated donor unit used until its expiration date of 35 or 42 days. This should be combined with careful attention to the amount of blood withdrawn for laboratory testing and adherence to evidence-based transfusion guidelines. The use of erythropoietin in neonates requires further study and its ultimate role will likely be determined by factors including transfusion indications, ability to decrease transfusion requirements, ability to decrease donor exposure, potential erythropoietin toxicities, and cost-effectiveness.

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Pediatric Recipients

The principles used to guide the decision to transfuse RBCs to infants older than four months of age and children are essentially the same as for adults (Table 7 and Chapter 2: Blood Components). In general, young children have lower hemoglobin concentrations than adults, with a child of six months of age having an average hemoglobin of 95–115 g/L and a child of two years of age having a hemoglobin of 115–125 g/L. The physiologic responses of children to anemia have not been well studied, but are thought to be similar to adults.

Table 7: Guidelines for transfusion of RBCs in patients more than four months of age

1. Emergency surgical procedure in patient with significant preoperative anemia.
2. Preoperative anemia when other corrective therapy is not available.
3. Intraoperative blood loss ≥ 15% total blood volume.
4. Hct < 24%:
   - in perioperative period, with signs and symptoms of anemia
   - while on chemotherapy/ radiotherapy
   - chronic congenital or acquired symptomatic anemia.
5. Acute blood loss with hypovolemia not responsive to other therapy.
6. Hct < 40% with:
   - severe pulmonary disease
   - ECMO.
7. Sickle cell disease with
   - cerebrovascular accident
   - acute chest syndrome
   - recurrent priapism
   - preoperatively when general anesthesia is planned.
8. Chronic transfusion programs for disorders of RBC production (such as ß-thalassemia major and Diamond-Blackfan syndrome unresponsive to therapy).

Adapted with permission from: Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. Transfusion 2002; 42:1398-1413.

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However, young infants may be less able to tolerate rapid blood loss, because of their limited ability to respond to hypovolemia by increasing myocardial contractility. This is complicated by the fact that the severity of acute blood loss may be underestimated in children (as well as in older children and young adults). On the other hand, children rarely have underlying cardiovascular or respiratory diseases and so often tolerate low levels of hemoglobin well, particularly if the anemia develops slowly.

In general, there is no single value of hemoglobin concentration that indicates that a transfusion is required, and clinical evaluation is of critical importance. The major indication for RBC transfusions is the prevention or alleviation of symptoms or signs of inadequate tissue oxygen delivery. RBCs are generally dosed based on the child's weight (i.e. 10 mL/kg for RBC in CPDA-1 and 15 mL/kg for RBCs in AS-3 or other additive solutions).

Limiting Donor Exposure

Limiting donor exposure is considered prudent to decrease both the infectious and non-infectious risks of transfusion. Various strategies may be used to limit the number of donor exposures, of which the most important is to administer transfusions only when absolutely necessary. For neonates who do require RBC transfusions, it is generally agreed that the best way to decrease donor exposure is by the use of a dedicated donor unit with multiple satellite packs or with the use of a sterile docking device. Because of the small amount of blood required by a neonate for each transfusion, repeated transfusions may be given to the same patient from a single unit. Using this technique, the RBC transfusion requirements of most preterm infants can be provided using one or, at most, two RBC units.

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Directed Donation

Directed donation refers to selection by the recipient—or in the case of pediatric patients by the recipient's parent(s)—of the donor of his/her blood components. When directed donations are used to limit the number of donors to whom a recipient is exposed, it can be argued that this is an appropriate safety measure. However, directed donations are frequently requested by the parents of pediatric patients (or other patients) in situations in which the number of donor exposures will not be affected. While directed donations from parent to child are permitted by Canadian Blood Services, there is currently no evidence that directed donations are either safer or less safe than donations from regular, anonymous allogeneic donors. The overall frequency of positive transmissible disease (TD) markers is higher in directed donors, including parental donors, as there are relatively more first-time donors among directed donors than regular CBS donors and first-time donors (either directed or non-directed) do have higher rates of positive TD markers.

Designated Donor Programs

Pediatric patients who will require repeated RBC transfusions on a regular and predictable schedule over a prolonged period of time may benefit from participation in a designated donor program. Such a program involves the use of a limited number of donors (usually three to five) for preparation of RBC units for the designated patient. Such donors may include the parents as directed donors, but will usually also include or consist entirely of regular allogeneic donors. In the latter case, if for some reason the unit is not used for the designated recipient, it may be placed in the general inventory. Designated donor programs have been shown to effectively limit the number of donor exposures for appropriately chosen pediatric recipients.

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Platelet Transfusions

Neonatal Recipients

As for adults, platelet transfusions are indicated to prevent or decrease bleeding associated with quantitative or qualitative platelet disorders. The decision to transfuse platelets to an infant or child should be made with consideration to the etiology and natural history of the thrombocytopenia. Guidelines for platelet transfusions for infants and children are essentially the same as those for adults (Chapter 2: Blood Components).

It is reasonable to assume that neonates may require platelets at a higher platelet threshold because of their increased bleeding tendency and, in particular, their higher risk of intracranial hemorrhage. Furthermore, preterm infants or infants with other co-morbidities may have an increased risk of bleeding. Although adequate data are lacking, various guidelines based on expert opinion have been published to indicate when platelets should be transfused to neonates. An example is shown in Table 8. In general, a transfusion trigger of 20 x 10^9/L may be used for stable term infants with a slightly higher trigger (i.e. 30 to 50 x 10^9/L) used for preterm infants. Infants who are bleeding or who have a consumptive coagulopathy may require a higher platelet transfusion threshold to be used.

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Table 8: Guidelines for platelet transfusion support of neonates

Platelet transfusion thresholds for bleeding prophylaxis:

1. Stable premature neonates with platelet counts < 30 x 10^9/L.
2. Stable term neonates with platelet counts < 20 x 10^9/L.
3. Sick premature neonates* with platelet counts < 50 x 10^9/L.
4. Preparation for an invasive procedure (eg, lumbar puncture) or minor surgery in neonates with platelet counts < 50 x 10^9/L, and for major surgery in neonates with platelet counts < 100 x 10^9/L.

Platelet transfusion threshold in neonates with clinically significant bleeding:

1. Neonates with platelet counts < 50 x 10^9/L.
2. Neonates with conditions that enhance the risk of bleeding (e.g. disseminated intravascular coagulation or other significant coagulopathy) and platelet counts < 100 x 10^9/L.
3. Neonates with documented significant platelet functional disorders (e.g. Glanzmann's thrombasthenia) irrespective of the circulating platelet count.

*The term *sick premature neonates* includes those infants with a history of perinatal asphyxia, extremely low birth weight (< 1000g), and the need for ventilatory assistance with an inspired oxygen content greater than 40%; those who are clinically unstable or who show signs of sepsis; and those who require numerous invasive interventions (e.g.,placement of indwelling catheters).

Adapted with permission from: Blanchette VS, Rand M, Carcao MD, Hume H. Platelet transfusion therapy in infants and children. In: Kickler TS, Herman JH (eds). Current issues in platelet transfusion therapy and platelet alloimmunity. AABB Press, Bethesda, MD, 1999.

Each unit of platelets can be expected to increase the platelet count by 10 to 15 x 10^9/L/m^2. Platelets are generally given in doses of 5 to 10 mL per kg, which should be expected to increase the platelet count of a full-term infant by 50 to 100 x 10^9/L. Ideally, type-compatible platelets should be given. If the plasma in the platelet product is not compatible with recipient RBCs, the platelet product should be plasma-reduced to avoid the risk of hemolytic transfusion reaction.

Childhood ITP

Children with ITP should be transfused with platelets only if severe bleeding is present as the transfused platelets will have a shortened survival.

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Plasma Transfusions

Although studies are limited, it is generally agreed that children should be transfused plasma products based on the same principles as those used for adults (Chapter 2: Blood Components). Infants under six months of age have decreased levels of vitamin K-dependent coagulation factors and inhibitors of coagulation (factors II, VII, IX, X, protein C, protein S). Therefore, these factors may be depleted more rapidly, so that it may be reasonable to transfuse plasma to infants younger than six months of age earlier than one would for older children and adults.

The primary indication for transfusion of plasma in a neonate or young child is the correction of bleeding due to multiple acquired coagulation factor deficiencies. Where feasible, the decision to transfuse plasma should be guided by the clinical situation and by appropriate laboratory testing. The use of plasma is not recommended when the sole purpose of the transfusion is to treat hypovolemia. Additionally, plasma transfusion should be avoided when a safer product can be used to obtain the same therapeutic goal. For example, virus-inactivated recombinant factor concentrates are preferable for the treatment of any isolated coagulant factor deficiency.

Plasma is normally given at a dose of 10 to 15 mL per kg. This dose can be expected to increase factor activity by 20% in an infant without ongoing consumption of coagulation factors.

Massive Transfusion in Neonates

Massive blood transfusion is defined as the replacement of greater than one blood volume in 24 hours. The blood volume of a full-term infant is approximately 85 mL per kg and that of a preterm infant is approximately 100 mL per kg. In the neonate, massive transfusion generally occurs in the following situations:

- cardiopulmonary bypass (CPB);
- extra-corporeal membrane oxygenation (ECMO); and
- exchange transfusion.

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Cardiopulmonary Bypass (CPB)

Infants and children may undergo CPB during surgical correction of congenital cardiac abnormalities. These children are generally exposed to large numbers of blood products in the perioperative period. The infant is heparinized during the surgery with heparin levels adjusted according to the activated clotting time (ACT). During the surgery, a volume of blood that is two to three times the patient's blood volume is passed through the circuit. The prime needed for CPB is generally one or two units of reconstituted whole blood (i.e. RBC and FFP). During the passage through the circuit, platelets and neutrophils may become activated and coagulation factors may be consumed. Following the surgery, component support (RBC, platelets, cryoprecipitate) should be provided as indicated.

Extra-Corporeal Membrane Oxygenation (ECMO)

ECMO is a type of cardiopulmonary bypass with a membrane oxygenator that is used to temporarily support infants with respiratory or cardiac failure. Infants tend to require ECMO for an average of five days but rarely it may be used for as long as 28 days. When the infant is placed on ECMO, two units of group-specific (or group O) RBC are used as the priming volume. It is suggested that these units be crossmatched against the infant's specimen to detect passive antibodies that may be of clinical significance. One unit of group-specific packed RBCs should be available at all times in case of circuit failure and the need to re-prime the system.

To prevent clotting in the circuit, infants are heparinized while on ECMO. In addition, qualitative and quantitative platelet dysfunction occurs. Therefore, the infant's risk of hemorrhagic complications is high and it is generally recommended that platelet transfusions be given to maintain the platelet count greater than 100 x 10^9/L or greater than 150 x 10^9/L in neonates who have had an intracranial hemorrhage.

Use of Gamma Irradiated Blood Products

Gamma irradiation of cellular blood products is used to reduce the risk of TA-GvHD. The minimum central dose required to prevent TA-GvHD is 25 Gy (2,500 rads) with no less than 15 Gy to any area of the bag. Irradiation guidelines mandate a maximum 28-day storage limit for RBCs following irradiation; total storage time cannot exceed that for the nonirradiated component. Irradiation followed by storage is associated with higher concentrations of potassium in the supernatant fluid than that of nonirradiated components with the same storage period. While this is not of concern for most patients, RBC units for neonatal and young pediatric patients should be irradiated at or close to the time of issue or have the supernatant fluid removed, particularly for large-volume transfusions. Generally accepted indications for the gamma irradiation of blood products for neonates and children are listed in Table 9. (Refer also to Chapter 15: CMV Seronegative, Irradiated and Washed Blood Components.)

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Table 9: Indications for the use of gamma irradiated cellular blood components in pediatric patients

- Intrauterine transfusion
- Neonatal exchange transfusion*
- Neonatal ECMO
- Low birth weight infants (<1250g)*
- Granulocyte transfusion
- Patients with congenital immunodeficiency syndromes
- Hematopoietic or solid organ transplant recipients
- Patients with Hodgkin's disease
- Other patients undergoing chemo- or radiotherapy*
- Transfusions from a biologic relative
- HLA-matched blood components

*Not all guidelines include transfusions in these situations.

Use of Cytomegalovirus (CMV) Seronegative Blood Products

The transmission of cytomegalovirus (CMV) by transfusion of RBCs or platelet components can be decreased effectively and to about the same extent (residual risk of about 2–4%) by the exclusive use of either CMV seronegative components or leukoreduced components. In 1998–1999 Canadian Blood Services implemented universal leukoreduction of RBC and platelet units, thus eliminating the requirement for using CMV seronegative components in many situations in which these components were previously used. It is not known if there is any additional benefit of providing CMV seronegative components in the setting of universal leukoreduction. In January 2000, Canadian Blood Services and Héma-Québec convened a consensus development conference to address this issue. The majority opinion of that panel was that CMV seronegative components should continue to be used for all intrauterine transfusions, and for CMV seronegative patients in the following situations: pregnancy, hematopoietic stem cell transplant from a CMV seronegative donor, and possibly HIV-infected persons and organ transplant recipients with a CMV seronegative donor. The panel did not recommend the routine use of CMV seronegative components (in addition to leukoreduction) for autologous hematopoietic stem cell recipients or for neonates, regardless of CMV serostatus.

For granulocyte concentrates, obviously the only method of providing a CMV low-risk product is through the use of a CMV seronegative donor.

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Nadine Shehata

Background

Therapeutic plasma exchange, or therapeutic apheresis, is regularly used to treat patients with a variety of disorders and has become a relatively common treatment modality. The rationale and techniques for apheresis, as well as the care of the apheresis patient, will be discussed in this chapter.

Therapeutic apheresis may be used as primary therapy or as an adjunct to other therapies. The potential benefits or indications for therapeutic apheresis include:

- removal of antibody;
- removal of antigen;
- removal of immune complexes;
- removal of toxins;
- infusion of a deficient substance; and/or
- removal of an excess of normal constituents.

The process of apheresis involves the removal of blood from an individual and the separation of that blood into components. A specified portion of the whole blood is retained and the remainder of the blood is returned to the individual. Apheresis procedures can preferentially remove plasma, leukocytes, platelets or other plasma constituents such as low-density lipoproteins. The two main techniques for the separation of blood components during apheresis are centrifugation (either intermittent flow centrifugation or continuous flow centrifugation) and membrane filtration.

Intermittent flow centrifugation involves the processing of small volumes of blood in cycles (a cycle consists of blood being drawn, processed, and re-infused). The advantages of using an intermittent flow instrument include portability of the machine and use of single venous access; however, the procedure time is longer and larger fluctuations in extracorporeal blood volume occur than with continuous flow centrifugation.

Continuous flow centrifugation involves the simultaneous removal, processing and re-infusion of blood. Continuous flow instruments have the advantage of faster procedures, but require two sites of vascular access.

Membrane filtration devices allow for the removal of plasma components selectively by altering pore sizes of membranes, but do not allow for the collection of cellular products.

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The Care of the Therapeutic Apheresis Patient

The care of apheresis patients requires supervision by a physician. Any patient requiring apheresis needs a medical history, physical examination and laboratory investigations. The latter include:

- a complete blood count;
- electrolytes;
- calcium;
- albumin; and
- coagulation studies.

Additional studies, depending on the indication for apheresis, may also be necessary. Unstable patients require supervision in an intensive care unit.

Vascular Access

Vascular access is required for therapeutic apheresis procedures. Ideally the access maintains a flow rate that allows a completed exchange to occur in less than three hours. Vascular access may involve peripheral or central veins. Access through peripheral veins is the preferred route as it is associated with fewer infections, thrombotic complications and hemorrhage. Central access is also associated with complications related to insertion (hemorrhage and/or pneumothorax) and prolonged access (infection and/or thrombosis) with the central route. Central access requires double lumen catheters that may have limited flow rates.

Technical problems with apheresis catheters such as leakage and inadequate flow rates can often be resolved by replacing the catheter and/or repositioning it, or clearing a blockage by using a fibrinolytic agent. Scarring and thrombosis as a result of repeated peripheral access may be reduced by rotating access sites.

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Replacement Solutions

As 1 to 1.5 plasma volumes are typically removed with each exchange, replacement of the intravascular volume is necessary. The solutions used to replace intravascular volume and maintain oncotic pressure include

- crystalloids;
- 5% serum albumin solution;
- fresh frozen plasma; and
- cryosupernatant plasma.

The use of each of these solutions has associated advantages and disadvantages.

Crystalloids such as normal saline require replacing the volume with two to three times that removed because of the lower oncotic pressure of saline.

Albumin (5%) can be used in a one-to-one replacement ratio, but may be associated with prolongation of the aPTT, hypofibrinogenemia and thrombocytopenia. Usually the changes in coagulation parameters are not associated with clinically significant bleeding and normalise within 24 to 72 hours.

Fresh frozen plasma is the only solution that replaces coagulation factors; however, as a biological product it cannot be considered free of risk of infection. Plasma also has the potential to sensitize against red cell and human leucocyte antigens (HLA). The substantial amount of citrate contained in fresh frozen plasma can lead to citrate toxicity and hypocalcemia at rapid infusion rates or with the use of large volumes.

Cryosupernatant plasma is frequently used as a replacement fluid for patients with thrombotic thrombocytopenic purpura. As cryosupernatant is devoid of the largest plasma von Willebrand's factor multimers thought to be pathogenic in thrombotic thrombocytopenic purpura, it may offer advantages over fresh frozen plasma in the treatment of these patients.

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Clinical Indications for Apheresis

Therapeutic apheresis is a modality used for patients with various disorders. Yet, few absolute clinical indications exist for this procedure. The clinical disorders where therapeutic apheresis is standard or effective therapy are listed in Table 1. Therapeutic apheresis has been used for patients with various other clinical diseases such as cryoglobulinemia, coagulation factor inhibitors, thrombocytosis and leucocytosis. The procedure may confer a benefit for patients with these disorders; however, its efficacy has not been established. Guillain-Barré syndrome, myasthenia gravis, thrombotic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, and Waldenström's macroglobulinemia account for 81.1% of apheresis procedures in Canada.

Table 1: Clinical indications for therapeutic apheresis

- Guillain-Barré syndrome
- Familial hypercholesterolemia
- Myasthenia gravis
- Paraprotein associated neuropathy
- Chronic inflammatory demyelinating polyneuropathy
- Multiple myeloma
- Thrombotic thrombocytopenic purpura
- Waldenström's macroglobulinemia
- Goodpasture's syndrome

The frequency for using a therapeutic apheresis procedure is dependent on the disease and the response of the patient. Apheresis may be performed as often as daily in the initial therapy for patients with thrombotic thrombocytopenic purpura, or as infrequently as once to twice per week for patients with chronic inflammatory demyelinating polyneuropathy. Standard schedules for apheresis have not been developed for the majority of clinical disorders.

Adverse Events

Adverse events occur in approximately 12% of patients. The majority of adverse reactions are mild (55.4%) or moderate (35.4%). The most common reactions are fever, chills, and urticaria, and most severe events are related to catheter placement. Adverse events may occur because of citrate toxicity, as citrate is an anticoagulant used during the apheresis procedure and is the anticoagulant used in plasma. Symptoms of citrate toxicity include paresthesias, nausea, vomiting, chills, twitching, tetany, syncope, and cardiac arrythmias. In renal patients, infusion of citrate can lead to metabolic alkalosis. Adverse events and the frequency of these events are listed in Table 2.

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Table 2: Reactions associated with therapeutic apheresis

Reaction	Frequency
Fever, chills, urticaria	29.5%
Muscle cramps, paresthesias	19.7%
Hypotension	18%
Nausea, vomiting, abdominal pain	12%
Headache	9.6%
Chest pain	1.8%
Arrhythmia/dyspnea, bronchospasm	0.9%
Convulsions/respiratory arrest	0.3%
Miscellaneous	6%

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The treatment of adverse events depends on the reaction. Mild symptoms of allergic reactions can be treated with antihistamines or corticosteroids. Pre-treatment with antihistamines is recommended for patients with allergies. Hypotension is treated by increasing the volume of the replacement fluid. The management of citrate toxicity is to use less citrate as an anticoagulant and to choose, if possible, non-citrated replacement fluids such as albumin. Calcium can be infused for the acute treatment of citrate toxicity if tetany, carpopedal spasm or EKG changes, such as prolongation of the QT interval, develop.

Patients with various clinical disorders are being treated with therapeutic apheresis. The care of a patient requiring therapeutic apheresis requires a multidisciplinary approach. Caution exercised during apheresis will limit the adverse effects experienced by patients. Most procedures are not associated with untoward events.

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Judith Hannon and Heather Hume

Blood Components at Low Risk for CMV Transmission

Cytomegalovirus (CMV) is a large, enveloped, double-stranded DNA herpes virus that is largely cell-associated *in vivo*. It may also be found free in the secretions of an infected individual. Seroprevalence is high, with 50% to 80% of the population, depending on the geographic area, testing positive for CMV antibody. CMV may remain latent in tissues and leukocytes for many years following an asymptomatic or mild infection. Only a small proportion of seropositive individuals are infectious. Community transmission occurs frequently in daycare and other institutional settings, and CMV may be transmitted from a seropositive mother to her infant through breast milk.

CMV may also be transmitted through solid organ or hematopoietic stem cell transplantation or transfusion of a CMV seropositive blood component to a CMV seronegative transfusion recipient. In an individual with normal immunologic function, transfusion-transmitted CMV (TT-CMV) is usually of no clinical consequence. However, in fetuses, low birth weight neonates, hematopoietic stem cell transplant recipients and, to a lesser extent, other immunosuppressed patients TT-CMV can lead to organ- or life-threatening CMV disease. In the 1980s and early 1990s, prior to the introduction of methods to prevent/control CMV infection (including the use of blood components at low risk for CMV transmission*), infection rates between 30–60% were reported in CMV negative hematopoietic stem cell transplant recipients. CMV-related pneumonia was the commonest presentation and was usually fatal.

As CMV is a cell-associated virus, the risk of TT-CMV is associated with cellular blood components. CMV serologic screening of blood donations prior to transfusion reduces the risk substantially. Removal of leukocytes either by use of WBC reduction filters or, in the case of single-donor platelets, as an integral part of the centrifugal apheresis process, to levels of WBCs $< 5 \times 10^6$/unit also attenuates the risk of CMV transmission. All allogeneic cellular blood components supplied by Canadian Blood Services can be considered at reduced or low risk for TT-CMV, as they are all leukoreduced pre-storage. However, neither leukoreduction nor the provision of CMV seronegative cellular components completely eliminates the risk of TT-CMV, at least in the setting of allogeneic hematopoietic stem cell transplantation, where each method has a residual risk of CMV transmission of approximately 2–3%. No data comparing the efficacy of screening for CMV antibody plus WBC reduction versus either method alone are available.

*See below, as well as current CMV monitoring techniques and early treatment with antiviral medications.

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With the introduction of universal pre-storage leukoreduction of cellular blood components in Canada in 1998/1999, the question of the necessity of continuing to perform CMV antibody testing arose. A Canadian Consensus Conference (Toronto, January 2000) was held to address this question. The majority view of the conference panel recommended continued CMV serologic screening of blood products in Canada following implementation of universal leukoreduction for patient groups at highest risk for TT-CMV. A summary of the panel's recommendations is shown in Table 1.

Table 1: Recommendations for the provision of CMV seronegative blood components in the setting of universal pre-storage leukoreduction*

CMV seronegative cellular blood components are recommended for:

- Intrauterine transfusions
- CMV seronegative pregnant women (prior to the onset of labour)
- CMV seronegative recipients of allogeneic hematopoietic stem cell transplant

CMV seronegative cellular blood components are possibly recommended for:

- CMV seronegative solid organ transplant recipients
- CMV seronegative patients with conditions likely to require an allogeneic hematopoietic stem cell transplantation
- CMV seronegative patients with HIV infection

CMV seronegative cellular blood components are not recommended for:

- Autologous hematopoietic stem cell recipients
- Neonates**

*Reference: Prevention of posttransfusion CMV in the era of universal WBC reduction: A consensus statement. Transfusion 2001; 41: 560-569

**Worldwide recommendations for neonates vary: AABB Bulletin #97-2 indicates that either CMV seronegative or leukoreduced (LR) components may be used, with LR components possibly being preferable; while UK guidelines recommend that CMV serologic testing in addition to LR be used for all neonates and infants up to the age of one year.

According to the Canadian Standards Association Z902-04 for blood and blood components, standard 11.6, each transfusion service must have a written policy indicating which recipients or categories of recipients are to receive cellular blood components selected or processed to reduce the risk of CMV transmission.

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Irradiated Blood Components

Cellular blood products are irradiated to prevent transfusion-associated graft-vs-host disease (TA-GvHD). TA-GvHD may occur following transfusion of viable, immunocompetent T-lymphocytes in a cellular blood component to a transfusion recipient whose immune system fails to recognize and/or eliminate the transfused lymphocytes. Donor lymphocytes engraft, proliferate and mount an immunologic attack against recipient tissues. This may occur in two situations: in immunocompromised hosts who are unable to prevent donor lymphocyte engraftment, or when the transfusion recipient's immune system does not recognize the donor lymphocytes as foreign—as may occur in transfusions from family members or when HLA-matched platelets are used.

Although rare, TA-GvHD is a serious transfusion complication with a mortality rate over 80–90%. Symptoms include fever, maculopapular or erythematous rash, diarrhea, hepatitis and progressive bone marrow failure. Onset is often delayed for one to two weeks post-transfusion, therefore a high level of suspicion is important. Diagnosis is based on characteristic pathologic changes on skin biopsy and/or demonstration of donor lymphocytes in recipient tissues using molecular, cytogenetic or tissue typing techniques. Death results from infection or bleeding as a result of severe bone marrow hypoplasia. Treatment is supportive.

Prevention is the key to reducing mortality related to TA-GvHD. Irradiation using a ^{137}Cs or ^{60}Co source is the only effective technique for the prevention of TA-GvHD. Irradiation decreases the number of viable lymphocytes in the blood product by direct damage to nuclear DNA and/or by the generation of free radicals that cause cell damage. Leukoreduction by filtration may reduce the risk by decreasing the number of lymphocytes in the blood component; however, TA-GvHD has been reported following the transfusion of leukoreduced blood components, demonstrating that leukoreduction is clearly insufficient to prevent TA-GvHD. The minimum lymphocyte dose capable of causing TA-GvHD is unknown. It likely depends on the immunocompetence of the transfusion recipient and the degree of HLA similarity between the blood donor and the transfusion recipient.

Cellular blood components must be irradiated prior to transfusion to patients in specified risk groups. Blood components that are frozen without cryoprotective agents (i.e. FFP/FP, cryoprecipitate and cryosupernatant plasma) and fractionated plasma products have not been associated with TA-GvHD and do not require irradiation.

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Table 2: Cellular blood components requiring irradiation

Components to be irradiated prior to transfusion to patients at risk for TA-GvHD

- Whole blood
- Red cell concentrates (including washed and frozen deglycerolized)
- Platelets (prepared from whole blood or collected by apheresis)
- Granulocyte concentrates*

Components to be irradiated prior to the transfusion of any patient**

- Directed donations from a blood relative
- HLA-matched platelets or platelets known to be HLA homozygous

*Canadian Blood Services does not provide granulocyte concentrates

**Plasma that has never been frozen would also require irradiation; however, this product is not supplied by Canadian Blood Services.

Table 3: Patients at risk for TA-GvHD

Patient groups with a well defined risk for TA-GvHD

- Fetuses undergoing intrauterine transfusion
- Newborns who have previously undergone intrauterine transfusions
- Patients with congenital cellular immunodeficiency; e.g. patients with SCID, Di George syndrome, purine nucleoside phosphorylase deficiency, reticular dysgenesis, and cell-mediated immune deficiency of unspecified etiology
- Selected patients with acquired immunodeficiency in particular: patients with Hodgkin's disease or patients treated with purine antagonists such as fludarabine
- Hematopoietic stem cell transplant recipients

Patient groups with an identified but not clearly defined risk for TA-GvHD

- Preterm infants
- Patients with hematologic malignancies other than those listed above
- Patients with solid tumours
- Patients undergoing solid organ transplantation

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Irradiation of cellular blood components is considered essential for patients with a well-defined risk for TA-GvHD; however, this requirement is debatable for patients with an identified but not clearly defined risk (Table 3). Irradiation of cellular blood components is not considered necessary for patients with HIV infection or humoral immune deficiency disorders such as hypogammaglobulinemia.

The recommended radiation dose is 25 cGy to the central point of the blood pack with a minimum dose of 15 cGy to other parts, and a maximum dose of 50 cGy. Time for component irradiation is dependent on the radiation intensity of the source. Commercially available indicator labels should be applied to the blood component to verify that an adequate radiation dose has been delivered.

Increased extracellular potassium and hemolysis with decreased RBC recovery occur as a result of radiation-induced RBC membrane damage. Therefore for neonatal patients and young children, irradiation of RBC components should occur immediately prior to issue. If this is not possible, removal of supernatant or washing of RBCs will also reduce the risk of hyperkalemia for patients at high risk of complications (e.g. pediatric cardiac surgery) or those receiving high-volume (e.g. intrauterine or exchange) transfusions. As a result of damage to the RBC membrane, the expiry of irradiated RBC components is reduced to 28 days (not to exceed normal product expiry). As radiation effect on platelet function and survival is minimal, outdate of platelet components is not decreased following irradiation.

Washed Blood Components

Cellular blood components may be modified by washing to remove substances (antibodies, serum proteins such as IgA, additive solutions, increased levels of electrolytes—in particular potassium, other cellular metabolites or cytokines) that may be harmful for some transfusion recipients.

Washed Red Blood Cell Components

RBC washing is a component modification applied to a standard RBC component. The RBCs are washed several times with a compatible solution, most commonly sterile 0.9% sodium chloride injection (USP), and then resuspended. Washing may be performed manually or by using an automated procedure using blood processing equipment. At present both processes involve non-sterile opening of the RBC component. The procedure markedly reduces the levels of plasma proteins, antibodies and electrolytes in the product; however, RBC recovery is decreased by up to 20–25% due to RBC loss during washing. Generally, washing adds at least two hours to the time required for preparation of RBC for transfusion.

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Procedures for storage and administration of washed RBC products are the same as those for unwashed RBCs, with the exception of a reduced expiry time of 24 hours after washing due to the increased risk of bacterial contamination during processing. Viability of washed RBCs is also compromised since the anticoagulant-preservative solution is removed during washing.

Washing alone is inadequate for removal of white blood cells or for elimination of the risk of viral transmission. All RBC products currently collected by Canadian Blood Services are leukocyte-reduced by filtration prior to storage (or washing or freezing). Washed RBCs therefore meet the standard for leukocyte reduction of $< 5 \times 10^6$ WBC/unit. Currently CBS prepares washed RBCs using an open automated technique. The product name is red blood cells washed, LR.

Risks associated with RBC transfusion also apply to the washed product, and the risk of bacterial contamination is slightly increased due to washing in an open system. The incidence of febrile and allergic reactions is reduced due to the removal of white blood cells and plasma from the product. Because of the 24-hour storage limit for washed RBC units, these units may not be readily available for sites remote from a blood centre.

Local policies regarding provision of washed RBCs may vary, but red blood cells washed, LR may be provided for neonatal exchange transfusion or massive transfusion in neonatal/pediatric patients, in order to minimize the amount of additive solution or potassium in the transfused product. The washed RBCs can be resuspended in albumin, 0.9% sodium chloride injection (USP), or ABO type compatible frozen plasma, LR, as appropriate, prior to transfusion. Red blood cells washed, LR are also indicated for patients with repeated febrile or allergic transfusion reactions not ameliorated by pre-transfusion medications, for patients with anti-IgA when RBCs from an IgA deficient donor are unavailable, and for patients with a history of anaphylactic transfusion reactions of unknown etiology.

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Washed Platelet Components

Platelet components may also be washed to remove plasma/supernatant substances such as antibodies or serum proteins that may be harmful to some transfusion recipients. Platelets prepared from whole blood donations or harvested by apheresis may be washed using normal saline, or saline buffered with ACD-A or citrate.

This procedure may be indicated in the clinical setting of neonatal alloimmune thrombocytopenia where maternal platelets are collected and washed to remove anti-HPA-1a (anti $P1^{A1}$). If an HPA-1a negative allogeneic volunteer apheresis donor is available, this approach may be preferred over providing a maternal platelet transfusion in this clinical situation, as the platelet unit will not need to be washed (providing the donor does not have anti-HPA-1a). Washed platelets are also used for IgA deficient patients with documented anti-IgA when platelets from an IgA deficient donor are unavailable, and for patients with a history of anaphylaxis of unknown etiology associated with previous blood transfusions.

Canadian Blood Services does not currently provide washed platelet components; therefore, hospitals wishing to use these products must prepare them in the hospital blood bank. There may be a considerable reduction in platelet recovery (up to 33% platelet loss) as a result of platelet activation during washing. Platelet survival of those recovered is normal. Due to the high platelet loss associated with washing, plasma volume reduction is considered a more suitable option for those situations in which complete removal of plasma is not required.

As there is an increased risk of bacterial contamination and possible metabolic damage to platelets, washed platelet products must be administered within four hours of entering the platelet unit. Since the washing procedure itself takes at least two hours, the timing of the washing procedure with respect to the timing of the transfusion requirement must be carefully coordinated between the blood bank and the hospital ward.

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Peter Lesley

Eligibility

Autologous donation is the donation of blood by a patient for his/her own future use. In particular, autologous donation prior to elective surgery is common. Informed consent must be obtained in writing prior to initiating the donation series. There are no age limits for autologous donors. However, the decision to accept the autologous donation is at the discretion of the medical director of the blood centre, or hospital autologous collection program, after evaluation of the donor's health status to determine if it is appropriate and safe to collect his/her blood. There are no specific weight requirements but donors must have a minimum weight of 25 kg (55 lb). Before their first donation, donors must have a minimum hemoglobin of 110 g/L and a minimum hematocrit of 33%. At subsequent donations the minimum hemoglobin required is 105 g/L with a hematocrit of 32%. Most autologous donors donate at their local CBS blood centre or in hospitals where such programs exist.

A donor with some medical conditions would be excluded from autologous collections at CBS blood centres. (A case-by-case assessment would be made in conjunction with the hospital or treating physician and/or the CBS medical director for the consideration of autologous collection at the hospital.)

Absolute contraindications for autologous donation include:

- idiopathic hypertrophic sub-aortic stenosis;
- aortic stenosis;
- left main coronary artery disease;
- unstable angina;
- cardiac failure;
- myocardial infarction within six weeks of a donation date; and
- atrio ventricular block.

Product/Donor Testing

Each unit in every series of autologous collections for every donor is tested for the same infectious disease markers as for allogeneic collections. Tests are done for hepatitis B and C, HIV, HTLV and syphilis as well as West Nile virus. Any unit testing confirmatory positive for infectious markers (except for syphilis) will be destroyed and the donor will be deferred from continuing the autologous collections. Units testing confirmatory positive for syphilis are still safe for autologous use. Units that are false positive or indeterminate after transmissible disease testing is completed are acceptable for use. Donors with a history of hepatitis and or jaundice after the eleventh birthday are acceptable for entry into the program but may be referred to their physician for testing prior to autologous donation.

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Indications

Autologous collection should be considered only if the chance of requiring a transfusion exceeds 10%. Low risk surgeries that rarely require blood are excluded from eligibility for autologous collection. These include:

- hysterectomies;
- routine pregnancy (vaginal or caesarean delivery);
- transurethral prostatectomy;
- cervical spine fusion;
- intervertebral discectomy;
- mastectomy;
- reduction mammoplasty;
- cholecystectomy; and
- tonsillectomy.

Usually, the number of autologous units collected is the same as the number of units that would be ordered for an allogeneic crossmatch for that type of surgical procedure. The maximum surgical blood-ordering schedule can be used to determine the number of autologous units to request for collection. Alternatively, the clinician could use a case-by-case assessment to determine the number of units to be ordered for any one patient. The major indications for autologous collections are hip and knee surgery, scoliosis surgery, major vascular (including cardiac) surgery, and radical prostatectomy.

Process of Donation

Units are normally drawn one week apart for a total maximum of four units. The first unit and series of collection should begin as far in advance of the surgery date as is possible to allow maximal time for donor red cell mass reconstitution. The last unit must not be drawn from the donor within 72 hours of the date of the anticipated surgery, and ideally one full week before surgery. Units are currently collected in CPDA-1 and are stored as whole blood. This preservative solution allows for a 35-day shelf life, hence the first collection must be within 35 days of the planned surgical date. Following implementation of buffy coat production, autologous red blood cells will be collected in CPD and will have added SAGM solution. This preservative solution will allow a shelf life of 42 days. Autologous plasma will be available only upon special request prior to donation. Autologous whole blood will not be available.

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Product Safety and Potential Adverse Effects

Autologous units should be transfused using the same indications as if the units were allogeneic units. The risk of transmission of emerging infections and known transmissible diseases are eliminated due to the autologous nature of the units collected, but the risk of bacterial contamination remains the same as (or even greater than) it would for allogeneic transfusion. While the units are carefully marked for autologous use only with specialized tags, clerical errors are still a factor and an autologous donor could receive an allogeneic unit by mistake. The risks of receiving the wrong unit with significant serologic (ABO) incompatibility are the same as for allogeneic transfusion.

Directed Donations

A directed donation is an allogeneic donation where the patient who requires a blood transfusion personally selects an individual or individuals to provide the necessary blood product(s) (usually RBCs). For patients who are not yet of legal age, the selection of the donor(s) is done by the parents.

Since 1996 directed donation programs have been offered in Canada. CBS provides directed donations from a parent (biological or adoptive) or legal guardian to their minor child (aged 17 or younger) only. The request for a directed donation must be made by the transfusing physician after blood group compatibility has been confirmed, and a decision noted as to whether CMV seronegative blood is required.

Directed donors must meet all criteria that are required of regular allogeneic donors with the following exceptions:

- The interval between repeat donations (if required) may be less than 56 days.
- Women may donate within six months postpartum with verification from a physician that they are in good health.
- Women may donate while breast feeding and in the three-month period after cessation of breast feeding.
- Hemoglobin levels must be a minimum of 110 g/L and hematocrit a minimum of 33% at the first donation (for subsequent donations, minimum hemoglobin of 105 g/L and hematocrit minimum of 32%).

Donations are recommended to be at least one week apart for a maximum of four donations in any one series with the last not less than 72 hours prior to anticipated transfusion (ideally, one week before, to allow time for completion of testing).

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An extensive review of American and Canadian literature clearly shows that the risk of transfusion-transmitted disease is NOT less with a directed donation compared with that of regular allogeneic transfusions. In fact, the risk may be higher, because directed donors are frequently first-time donors. First-time donors have been shown to have an increased frequency of infectious disease markers compared to repeat blood donors. Furthermore, graft-vs-host disease may complicate a transfusion from a biological relative. This risk is mitigated by appropriate gamma irradiation of the blood component(s) prior to transfusion. The irradiation process alters the storage life of the red cell component and affects RBC membrane permeability with significantly increased extracellular potassium concentration.

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Man-Chiu Poon

General Principles

Abnormal bleeding may result from defects in platelets, coagulation factors and/or blood vessels. Screening tests for coagulation factor abnormalities include the aPTT and PT (INR). Thrombocytopenia is the most common platelet defect. Qualitative platelet defects may also occur and may or may not be associated with thrombocytopenia. In patients with platelet defects, bleeding time and/or closure times in the platelet function analyzer (PFA-100™) may be prolonged. Vascular defects may be reflected by mild prolongation of bleeding time and some may be accompanied by joint hyperflexibility or skin laxity. Effective treatment of hemostatic disorders requires accurate diagnosis and sophisticated special coagulation testing that may include coagulation factor assays, inhibitor assays, and platelet function tests. An algorithmic approach to diagnosis is beyond the scope of this review.

Congenital Coagulation Disorders

General Principles

Congenital coagulation disorders are relatively rare and their management can be complex. Management of these patients is best coordinated with the regional comprehensive hemophilia/bleeding disorders programs and hematologists expert in the management of these disorders. In Canada, practically all patients with hemophilia are registered with one of the 24 Hemophilia/Bleeding Disorders Programs located across the country. While the mainstay of therapy for bleeding is to increase the coagulation factor level with concentrates or pharmaceuticals, appropriate use of adjunctive agents including antifibrinolytics (tranexamic acid or epsilon amino caproic acid), fibrin glue, gel foam and microporous polysaccharide particles are often effective for minor bleeds. These adjunctive agents, together with clotting factor concentrates in more severe bleeding, can result in earlier hemostasis and less overall use of factor concentrates. Conservative measures, including local pressure, as well as rest, ice, immobilization and elevation (RICE), should be applied where appropriate. Antifibrinolytic agents should be avoided when using concentrates with thrombogenic potential, such as FEIBA or prothrombin complex concentrates, and in patients with bleeding from the upper urinary tract. Antifibrinolytics are generally safe when used with rFVIIa.

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Hemophilia

Hemophilia can be due to a deficiency of either factor VIII (hemophilia A, classic hemophilia) or factor IX (hemophilia B, Christmas disease) with an incidence of about 1:10,000 births. Hemophilia A is more common, comprising 80–85% of cases. The management of bleeding depends on the type and severity of hemophilia as well as the site and severity of bleeding.

Desmopressin: In mild hemophilia A patients (baseline FVIII activity >5%), minor bleeding or minor procedures can often be successfully managed with desmopressin (0.3 µg/kg up to 20 µg IV or subcutaneously). Preferably the patient should have had prior testing to assure an adequate response. Closely spaced repetitive dosing may result in tachyphylaxis, so that supplementation by factor concentrates is required for prolonged treatment. Patients on desmopressin may develop fluid retention and hyponatremia. This is particularly problematic in neonates and the elderly. Attention to restricting fluid intake and monitoring sodium levels are important with this therapy.

The approach to factor VIII or factor IX replacement therapy is outlined in Table 1. The initial desired factor level for different types of bleeding and maintenance therapy for severe bleeding are described. A general formula for dosage calculation in IU/kg suitable for these concentrates (applicable also to other clotting factor concentrates) with known *in vivo* recoveries is in the footnote to Table 1. In general, if the dosing interval is identical to the T1/2 (half-life) of the clotting factor, the maintenance dose required to reach the original peak factor concentration is half the loading dose. Pharmacokinetic studies to measure the recovery and T1/2 are desirable for patients starting a new product to guide dose and dose interval. This is particularly important in children who may have a larger plasma volume and require larger doses to achieve the same factor levels as an adult patient.

Continuous infusion following a loading dose for severe bleeding and for surgery (Table 1) has an advantage in that the *in vivo* factor level is more constant, without peaks and troughs that result from bolus injections. Continuous infusion may result in less overall use of concentrate. Infusion pumps capable of delivering small volumes are required, as the concentrates should not be diluted beyond manufacturer recommended dilutions.

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Table 1: Management of bleeding episodes in patients with hemophilia A and B using clotting factor replacement therapy

Indication	Recommended initial factor level (see legend for dosage calculation)*	Comments
Mild hemorrhage ■ Early joint or muscle bleed ■ Severe epistaxis ■ Persistent hematuria ■ Gingival or dental bleed unresponsive to antifibrinolytics	20–30% activity (0.2–0.3 U/mL)	■ If repeat dosage is necessary because of persistent bleeding, use half initial dose q8–12h for FVIII and q12–24h for FIX**
Major hemorrhage ■ Advanced joint or muscle bleed ■ Prophylaxis following severe physical trauma without bleeding	40–50% activity (0.4–0.5 U/mL)	■ If repeat dosage is necessary because of persistent bleeding, use half initial dose q8–12h for FVIII and q12–24h for FIX**
Life-or-limb-threatening hemorrhage ■ Intracranial bleed ■ Hematoma of neck, tongue or pharynx ■ Surgery (except dental) ■ Bleeding from major trauma ■ Gastrointestinal bleeding	70–100% activity (0.7–1.0 U/mL)	■ Maintenance treatment with half the initial dose (q8–12h for FVIII, and q12–24 for FIX) for 5d to several weeks may be required.** ■ Alternatively, continuous infusion (2–3 U/kg/h for FVIII, 4–5 U/kg/h for FIX, with subsequent dosages adjusted according to the plasma clotting factor level) following the initial bolus
Dental Extraction	40–50% activity (0.4–0.5 U/mL) plus oral antifibrinolytics (e.g. tranexamic acid 25 mg/kg q8h) or local antifibrinolytics (e.g. 10mL 5% tranexamic acid mouthwash rinse 4x/d) for 7–10 days.	■ Some studies suggest dental extraction can be safely performed with plasma clotting factor level as low as 10% if both oral and local antifibrinolytics agents are also given for 7–10 days

*Formula for dosage calculation: Dosage in IU/kg = (desired % factor activity – baseline % factor activity) ÷ *in vivo* recovery in % activity rise per IU/kg body weight infused.

Activity *Recovery* per IU/kg infused for rFVIII and pdFVIII, ~2%; pdFIX, ~1%; rFIX, ~0.8% for adults and 0.65% for children ≤ 15 year old (see Table 1, Chapter 5 – Coagulation Factor Concentrates)

Thus, using the dosage calculation formula, raising factor level from 10% (baseline) to 100% (desired) will require for rFVIII or pdFVIII: 45 IU/kg; for pdFIX: 90 IU/kg; for rFIX, 112.5 IU/kg (adult) or 138 IU/kg (children)

**The maintenance dose to reach the original peak factor concentration is half the original loading dose if the dosing interval is identical to the $T_{1/2}$ for the clotting factor for the particular patient.

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Reference Resources: Association of Hemophilia Clinic Directors of Canada (AHCDC) Clinical Practice Guidelines: Hemophilia and von Willebrand's Disease. 1. Diagnosis, comprehensive care and assessment; 2. Management (**www.ahcdc.ca** ➜ publications and guidelines).

Hemophilia with Inhibitors and Acquired FVIII Inhibitors

Twenty to thirty percent of hemophilia A patients and one to three percent of hemophilia B patients develop inhibitors to the clotting factor protein for which they are deficient. This renders treatment with clotting factor concentrates difficult. Management of bleeding in these patients **must** be in consultation with a centre experienced in the management of inhibitor patients. All serious bleeds should be managed in these centres.

Hemophilia A with factor VIII inhibitors: Patients with low responding inhibitor levels (titer usually ≤ 5 Bethesda units (BU)) that do not rise above 5 BU with exposure to FVIII, or patients with a high responding inhibitor (titer usually >5 BU) that rises above 5 BU with exposure to FVIII, but with low inhibitor titers, may be treated with human factor concentrate at a sufficiently high dose to neutralize the inhibitors and leave excess factor activity available to stop the bleeding. Doses of 100 IU/kg can be initiated with monitoring of clinical response and clotting factor levels to allow for adjustment of dosage. Patients with an inhibitor level of >5–10 BU are unlikely to respond to FVIII concentrates. Alternative agents include rFVIIa (Niastase®) (~90 µg/kg q 2–3 hours) and FEIBA (50–100 FEIBA U/kg q 8–12 hours, limit ≤ 200 U/kg/24 hours). See reference resource at end of Inhibitor section for management algorithm. Antifibrinolytics can be used concurrently with human FVIII, porcine FVIII, and rFVIIa, but should be avoided with FEIBA. Switching between rFVIIa and FEIBA should allow for a time gap of 3–6 hours for rFVIIa ➜ FEIBA and 6–12 hours for FEIBA ➜ rFVIIa, in order to decrease the thrombogenic potential of this combination. There are anecdotal reports of successful use of the two agents together.

Factor VIII products and FEIBA (which may contain inactive FVIII molecules) should be avoided in hemophilia A inhibitor patients waiting for inhibitor titer to drop below 10 BU to start immune tolerance induction (ITI) therapy. This avoids an anamnestic response that may interfere with initiation of ITI. Despite this risk, such concentrates may be used for treatment of intercurrent bleeding during ITI. A discussion on ITI is beyond the scope of this review.

Refractory patients (with continuing severe bleeding) may require plasmapheresis or IgG column immunoadsorption (in selected centres only) to rapidly decrease inhibitor titer and allow effective use of FVIII containing concentrates.

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Hemophilia B with FIX inhibitors: The management principle is similar to that of hemophilia A with inhibitors. It is important to recognize that about 50% of hemophilia B patients with inhibitors may have severe allergic responses (including anaphylaxis) to factor IX containing concentrates and to FEIBA. In such patients, rFVIIa can be used.

Acquired factor VIII inhibitors: Management includes treatment of bleeding and concurrent immunosuppression (prednisone 1 mg/kg/d and/or cyclophosphamide 1.5 mg/kg/d) to eradicate the inhibitors.

Minor bleeding often can be managed successfully with desmopressin (0.3 µg/kg to 20 µg iv or sc) and other conservative measures. Severe bleeding requires the use of porcine factor VIII (50–100 IU/kg), rFVIIa (~90 µg/kg q2–3 hours) or FEIBA (50–100 IU/kg q8–12 hours, maximum 200 IU/kg/d). (See reference resource for management algorithm at end of Inhibitor section.)

Rapid reduction of inhibitor titers to facilitate response to hemostatic agents can sometimes be accomplished by adjunctive treatment with IVIG (40 mg/kg/day x 5 days), or by plasmapheresis. These measures by themselves do not result in the eradication of the inhibitors.

Reference resource: AHCDC Clinical Practice Guidelines: Suggestions for the Management of Hemophiliacs and Non-hemophiliacs with Factor VIII Inhibitors (**www.ahcdc.ca** ➜ publications and guidelines). Algorithms for management of bleeding in hemophilia patients with inhibitors and non-hemophilia patients with acquired inhibitors are presented.

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Von Willebrand's Disease (vWD)

Most patients with mild quantitative von Willebrand's factor (vWF) deficiency (type 1 vWD) and some patients with qualitative vWF defects (type 2A) respond to desmopressin (0.3 µg/kg up to 20 µg iv, sc, or intranasally at 150 µg for body weight < 50 kg and 2 x 150 µg for weight > 50 kg). This agent should be used for minor bleeding and minor procedures for these patients. Prior testing to establish desmopressin responsiveness is desirable. Patients with type 3 disease (virtual absence of vWF) and type 2M disease do not respond to desmopressin, and the use of this agent may result in thrombocytopenia in type 2B patients.

Replacement therapy for desmopressin non-responsive patients and for severe bleeding can be accomplished using factor VIII/vWF concentrates. Canadian treatment centres have most experience with Humate P®, but two other FVIII/vWF concentrates (Immunate® and Alphante®) have also been shown to be effective. While high molecular weight multimers of vWF are present in Humate P®, none of the concentrates have a multimer pattern identical to normal human plasma. This does not appear necessary for clinical hemostasis. Correction of bleeding time is not necessarily related to the hemostatic effectiveness of these concentrates. The usual dosage is 30–50 ristocetin cofactor (vWF:Rcof) units/kg for minor bleeding, and 50–80 vWF:Rcof units/kg for more severe bleeding. Types 2 and 3 patients should receive the higher dose within the range. The dose can be repeated every 12 hours. In patients refractory to FVIII/vWF concentrates, desmopressin or platelets may be used in addition. Although vWF is necessary for initial cessation of mucosal bleeding, adequate FVIII levels are more important for soft tissue and surgical bleeding and for maintenance of hemostasis. FVIII/vWF concentrate contains both FVIII and vWF at various ratios, depending on the product. When prolonged coverage with these concentrates is required, it is desirable to monitor the FVIII level and to maintain FVIII below 200% activity (2 U/mL) to decrease potential thrombogenic effects. This is particularly important in surgical and immobilized medical patients.

Rare Congenital Coagulation Disorders (each with an incidence of 1:500,000–1:2,000,000 in the population)

Patients with rare congenital coagulation factor deficiencies with bleeding diatheses include those with FII, FV, FVII, FX, FXI, fibrinogen and FXIII deficiencies. Management of bleeding in these patients is summarized in Table 2.

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Table 2: Management of a patient with a rare clotting factor deficiency

Deficiency	Plasma T1/2	*In-vivo* recovery	Desired levels	Treatment options	Comments
Fibrinogen	2–4d	50–70%	▪ 0.3–0.5 g/L for most bleeding ▪ 1 g/L for major surgery	▪ Fibrinogen concentrate 20–40 mg/kg ▪ Cryoprecipitate (200–300 mg/bag): 1 bag/5kg initially, then 1 bag/15 kg q24h	
FII	2–3d	50%	▪ 20–30% for most bleeding and surgery	▪ Plasma† 15–20 mL/kg, then 3mL/kg q12–24h ▪ PCC‡ – FII 20–30 IU/kg	
FV	15–36h	80%	▪ 10–15% for most bleeds ▪ 25–30% for surgery	▪ FFP* 20 mL/kg, then 5–10 mL/kg q12h	
FVII	2–6h	100%	▪ 15–25% for most bleeds ▪ 40–60% for surgery	▪ FVII concentrate 20–40 IU/kg q6–12h ▪ rFVIIa 15–30 microgram/kg q4–6h ▪ Plasma† 15–20mL/kg, then 4 mL/kg q6h	▪ Variable bleeding diathesis inconsistent with FVII level, but likely to bleed with FVII <3% ▪ FVII level can vary with thromboplastin used in assay
FX	24–40h	50–95%	▪ 10–40% for most bleeds	▪ Plasma† 15–20 mL/kg, then 3–6mL q12h ▪ PCC‡ – FX 20–30 IU/kg	

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Table 2: Management of a patient with a rare clotting factor deficiency (continued)

Deficiency	Plasma T1/2	*In-vivo* recovery	Desired levels	Treatment options	Comments
FXI	35–60h	90%	■ 20–30%	■ Plasma† 15–20 mL/kg then 3–6 mL q12h ■ FXI concentrate 15–25 IU/kg	■ Variable bleeding diathesis inconsistent with FXI level – correlated with family history of bleeding. When in doubt, patients with FXI activity <10% should receive replacement therapy before surgery ■ FXI concentrate dose >30 IU/kg may be associated with thromboembolism particularly in the elderly
FXIII	9–19d	50–100%	■ 2–5% for most bleeds and surgery	■ Plasma† 15–20 mL/kg ■ FXIII concentrate 20–30 IU/kg (50 IU/kg for severe bleeds) ■ Prophylaxis: FXIII concentrate: 20–30 IU/kg q4–6w	

† Plasma: stored plasma or fresh frozen plasma. If the desired level and hemostasis cannot be reached with plasma, may need plasmapheresis with plasma replacement.

* FFP: fresh frozen plasma. If the desired level and hemostasis could not be reached with plasma, may need plasmapheresis with plasma replacement.

‡ PCC: prothrombin complex concentrate. Thrombotic risk precaution – use minimal effective dose.

Congenital Platelet Disorders

There are many types of congenital platelet functional defects and a complete list of these is beyond the scope of this article. These disorders include Glanzmann's thrombasthenia (platelet membrane GPIIb/IIIa deficiency or abnormality) and Bernard-Soulier syndrome (platelet membrane GPIa/V/IX deficiency or abnormality).

Most minor bleeding in these patients can be managed with conservative measures, including pressure, antifibrinolytics, topical hemostatics including fibrin glue. Desmopressin may also be effective for minor/moderate bleeding, but response to this agent is variable.

Severe bleeding that is not responding to conservative treatments can be managed by platelet transfusions. In transfused patients who have developed antibodies to HLA and/or the missing platelet glycoproteins and who are refractory to platelet transfusion, some case series suggest that rFVIIa can be useful. Experience with Glanzmann's thrombasthenia suggests that rFVIIa (at a dose of approximately 90 µg/kg q2–2.5 hours for three doses or more, as appropriate), in conjunction with administration of antifibrinolytics, is effective in a high proportion of bleeding episodes and surgical procedures. **Limited experience suggests that the continuous infusion (CI) of rFVIIa may not be effective to stop ongoing bleeding, although CI appears effective in surgical prophylaxis.** Thrombotic complications have been reported with high dose continuous infusion for a prolonged period in surgical settings in persons with co-morbid risks for thrombosis.

Vascular Disorders

Patients with vascular disorders seldom have serious bleeding and most episodes can be managed with conservative measures. Desmopressin has been used successfully in some patients undergoing surgical procedures probably by improving platelet-endothelium interaction. There is no evidence that blood products are indicated.

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Acquired Coagulation Disorders

Liver Disease

With the exception of tissue factor, all clotting factors are synthesized in the liver with some (factors II, VII, IX, X) requiring vitamin K as a cofactor. In patients with liver disease the levels of clotting factors are often low. Exceptions are fibrinogen and FVIII, which are acute phase reactants with their levels increased in uncomplicated liver disease. Concomitant DIC should be considered if fibrinogen and FVIII levels are decreased.

The aPTT and PT (INR) are usually prolonged in liver disease and are usually sufficient for monitoring therapy without the need for assays of clotting factor levels. Patients with liver disease may also have thrombocytopenia because of splenomegaly from portal hypertension or from underlying viral infection. Bleeding from coagulopathy related to liver disease is generally mild and can usually be treated adequately with the infusion of plasma, which contains all the clotting factors synthesized in the liver. Bleeding from structural lesions such as varices and ulcers may be severe in these patients, and management must include attempts to achieve hemostasis at the bleeding site in addition to treating the coagulopathy.

Oral Anticoagulant Overdose

Vitamin K is required for the synthesis of functional factors II, VII, IX, and X (vitamin K dependent factors). Coumarin type drugs exert their anticoagulant action by competitively inhibiting vitamin K function. This results in a decrease in functional vitamin K dependent factors and an increase in PT (INR). Many drugs may interact with coumarin and may result in excessive anticoagulation with marked increases in PT (INR). When the PT (INR) is moderately increased without bleeding, cessation of the anticoagulant drug may be sufficient. This is with or without vitamin K administration to allow the vitamin K dependent factors to increase slowly according to the intrinsic synthetic rate. In situations where the immediate increase of the clotting factor is required, infusion of plasma is usually sufficient. As the vitamin K dependent factors are stable, stored plasma can be used at a dose of 5–8 mL/kg.

In patients with life-threatening bleeding (e.g. intracranial bleeding) and oral anticoagulant overdose, prothrombin complex concentrate can be used. Prothrombin complex concentrate may contain thrombogenic material and its use in patients with liver disease is discouraged. The diseased liver is less able to remove thrombogenic materials and the activated clotting enzymes generated. Additionally, there is a deficiency of naturally occurring anticoagulant proteins (antithrombin, proteins C and S) synthesized in the liver. Recent case series and anecdotal reports suggest that rFVIIa may be effective, but clinical trial data are lacking.

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Disseminated Intravascular Coagulation (DIC)

DIC can be triggered by a number of clinical situations, including massive tissue destruction, infection, obstetrical complications, and cancer, among others. Unregulated activation of the coagulation system will result in the activation and consumption of clotting factors and platelets. In addition, widespread secondary fibrinolytic activation will result in the destruction of clotting factors and generation of fibrin-fibrinogen degradation products that interfere with fibrin polymerization and platelet function. The result is a bleeding diathesis.

Depending on the balance between coagulation and fibrinolysis, patients may have bleeding or thrombotic complications. Removal of the stimulus that initiates DIC in a non-bleeding patient is often sufficient to reverse the process. When bleeding occurs, the patient can be stabilized by replacing the consumed factors. Therapy may include the use of fresh frozen plasma, cryoprecipitates (for FVIII and fibrinogen) and platelet transfusion (for severe thrombocytopenia). Transfusion therapy is an adjunct to treating the underlying clinical condition that initiates DIC. Replacement of clotting factors does not stop the DIC process.

Overwhelming bacterial sepsis with DIC and skin necrosis is associated with high morbidity and mortality. Phase III clinical trials suggest a survival benefit with the use of recombinant activated protein C treatment. Case series also show benefit with antithrombin and protein C (non-activated) therapy. However, a large phase III trial did NOT show survival benefit with the use of antithrombin. Controlled trial data on protein C use in this setting are not yet available.

Congenital Antithrombin and Protein C Deficiency

Antithrombin concentrate together with heparin has been used in patients with inherited antithrombin (AT) deficiency with heparin resistance, as prophylaxis for surgery, trauma, and thromboembolism during pregnancy as well as after delivery, with favourable results. There are, however, no randomized clinical trials to establish their efficacy.

Patients with homozygous protein C deficiency present with skin necrosis usually within the first two weeks of postnatal life. Replacement therapy with protein C concentrate at dose of 40–125 IU/kg (median 40 IU/kg) every 6–24 hours to maintain a trough protein C level of about 25% activity has been successful. Various IV doses daily to three times weekly and subcutaneous (sc) doses of 250–350 IU/kg q48 hours have been used for primary prophylaxis.

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The product monographs (package insert) should be consulted for further information about the various products discussed in this chapter.

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Alan Tinmouth

Platelets are the smallest of the blood cells, with a diameter of 2–3 µm and no nucleus. Their function is primarily hemostatic, but they are also involved in pathogenic thrombotic processes. Platelets circulate individually in the blood stream until, following an injury to a blood vessel, they are exposed to the subendothelial matrix and undergo morphologic changes. These activated platelets bind to the sites of injury and to each other to form a temporary hemostatic plug that stops bleeding and serves as a base for plasma coagulation factors to form a more permanent hemostatic plug. A normal platelet count is 150 to 400 x 10^9/L, and individuals with very low platelet counts (below 50 x 10^9/L) are prone to bleeding and bruising. Individuals with congenital or acquired disorders of platelet function are also at increased risk of bleeding.

The two types of platelet products, apheresis and whole blood derived platelets, are interchangeable in terms of effectiveness for most patients. Apheresis platelets offer the advantage of providing matched platelet products for specific indications. Apheresis platelets also decrease exposure to blood donors and, as a result, may be associated with lower rates of some adverse reactions. However, with a limited supply of apheresis platelets available, the only absolute indication for apheresis platelets is the provision of matched platelets for patients with (1) documented anti-platelet antibodies (either anti-HLA or anti-platelet antibodies) and (2) alloimmune platelet refractoriness or post-transfusion purpura.

Indications

The indications to transfuse platelets include:

- to prevent bleeding complications (prophylactic transfusions)
- to stop bleeding (therapeutic transfusions)

in patients with thrombocytopenia due to decreased production or abnormalities of platelet function. The effectiveness of platelet transfusions in patients with thrombocytopenia due to increased consumption (such as immune thrombocytopenic purpura, heparin-induced thrombocytopenia or thrombotic thrombocytopenic purpura), or sequestration secondary to splenomegaly may be limited; however they still may be considered in cases of serious or life-threatening bleeding. Increases in platelet counts and platelet survival in such patients are reduced compared to recipients in whom platelets are decreased because of diminished production. In the case of thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia (HIT), platelet transfusions may even increase the risk of thrombosis.

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Therapeutic Platelet Transfusions

The precise clinical circumstances in which platelet transfusions are beneficial in stopping bleeding have not been defined and, as a result, only general guidelines are available for therapeutic platelet transfusions. In patients with normal platelet function, a therapeutic platelet transfusion is only beneficial if there is severe thrombocytopenia. While there is not strong clinical evidence to determine when platelet transfusions are beneficial in patients with thrombocytopenia, there is a general consensus that, in patients with bleeding and a platelet count > 50 x 10^9/L, platelet transfusions are not likely to be beneficial. However, platelet transfusions for patients with platelet counts < 100 x 10^9/L may still be recommended in specific situations such as central nervous system bleeding or for neonates.

In patients with acquired or congenital platelet dysfunction, platelet transfusions may be required to control bleeding problems regardless of the patient's platelet count. Since patients with congenital platelet disorders may require intermittent platelet transfusions over the course of their lives, platelets should be judiciously transfused to reduce the risk of these patients becoming refractory to platelet transfusions. Alternative methods of achieving or maintaining hemostasis should be considered prior to transfusing platelets to such patients. Acquired disorders of platelet function include the use of certain drugs, renal failure, myeloproliferative disorders, myelodysplastic syndromes, and cardiopulmonary bypass.

Prophylactic Platelet Transfusions

Prophylactic platelet transfusions are given for either very low platelet counts, when there is a risk of spontaneous bleeding, or at higher platelet counts prior to invasive procedures. Based on cohort studies from the 1960s that demonstrate decreased bleeding complications in leukemia patients receiving regular platelet transfusions, prophylactic platelet transfusions have become standard treatment for patients with cancer-related thrombocytopenia. Prophylactic transfusions represent the majority of platelet transfusions and are given primarily for thrombocytopenia due to decreased bone marrow production.

Platelet thresholds: The minimum threshold for prophylactic platelet transfusions has not been precisely determined and depends on the clinical situation. For patients without bleeding and no additional risk factors for bleeding, transfusion of platelets is not indicated unless the platelet count is < 10 x 10^9/L. Two large randomized controlled trials and one prospective controlled cohort study demonstrated that lowering the prophylactic platelet transfusion from 20 x 10^9/L to 10 x 10^9/L would decrease platelet utilization by more than 20% without increasing major bleeding. Smaller studies have suggested that a transfusion threshold of 5 x 10^9/L may also be safe, but this has not been demonstrated in adequately powered randomized controlled clinical trials. The evidence to support specific thresholds for platelet transfusions in patients with other risk factors for bleeding is limited. For patients at increased risk of bleeding due to fever, antibiotics, anticoagulant use, or other factors, higher thresholds (e.g. 15 x 10^9/L) for prophylactic platelet transfusions may be appropriate.

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In patients with thrombocytopenia, prophylactic platelet transfusions prior to an invasive procedure or surgery may also reduce the risk of bleeding complications. However, the specific thresholds at which platelet transfusions are required are not known. Platelet transfusions are unlikely to be a benefit for platelet counts of 50 x 10^9/L or greater. For platelet counts below this level, platelet transfusions may be warranted depending on the clinical situation. In patients with platelet dysfunction or in other specific situations (e.g. neurosurgery), transfusion of platelets at higher platelet counts may be indicated.

Platelet dose: There is little evidence in the clinical literature to determine the appropriate dose for platelet transfusions. In adults, the standard dose of whole blood derived platelets is 4–6 pooled units or one apheresis unit. In children, a dose of one unit of whole blood derived platelets/10 kg is reasonable. Higher doses of platelets have been used historically, but there is no evidence to suggest that higher doses are more effective in preventing or treating bleeding. While higher doses result in higher post-transfusion platelet counts and increase the time until the next transfusion is required, recent studies suggest that the use of higher doses of platelets will increase total platelet utilization in patients requiring repeated platelet transfusions. Lower doses of platelets may reduce both total platelet utilization and donor exposure, but the hemostatic effectiveness of the lower dose as compared to standard dose transfusions still needs to be determined.

Platelet Administration

Platelets have A and B antigens on their cell surface but do not express the Rh antigens. Ideally, ABO identical platelet transfusions should be transfused, but non-identical ABO transfusions can be given if ABO-matched platelets are not available. ABO-mismatched platelets have similar recoveries following the initial transfusion, but platelet recovery may decrease with subsequent mismatched transfusions. Hemolysis due to anti-A and anti-B antibodies in the plasma of mismatched ABO platelet transfusions has been reported. Plasma reduction of platelet units can be considered to remove these antibodies, but is often unnecessary. Additionally, some studies have suggested that increased morbidity and mortality may be associated with mismatched platelet transfusions, but this has not been confirmed in other studies.

While platelets do not express Rh antigens, platelet products may contain small amounts of red blood cells. As a result, transfusing Rh-positive platelets to Rh-negative patients may result in the recipient producing anti-D antibodies, which may interfere with future transfusions or complicate pregnancies. As a result, Rh-negative patients should receive Rh-negative platelets when possible. Administration of anti-D immune globulin (WinRho) will prevent alloimmunization and should be considered in all Rh-negative patients, especially female children and women of child-bearing age who receive platelets from an Rh-positive donor. Other clinical factors, including recent chemotherapy which reduces the rate of alloimmunization, need to be considered prior to giving anti-D immune globulin.

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Adverse Reactions

Platelet transfusions are associated with both infectious and non-infectious adverse effects. With a few exceptions noted below, the risk of most adverse events is the same for either a unit of platelets or a unit of red blood cells (see Chapter 10: Adverse Reactions).

While each unit of platelets has the same risk of transmitting viral infections as a unit of red blood cells, bacterial infections are a particular concern with platelets because they are stored at room temperature. The rate of bacterial contamination of platelet units is estimated at 1:3000–5000. The source of the bacteria may be a bacteremia in the donor or bacterial contamination during collection. The rate of septic reactions due to contaminated platelet transfusions is not known, but this is probably under-recognized and under-reported. All apheresis units issued in Canada are cultured within 24 hours of collection, and units that are positive for bacterial growth result in initiation of a product recall, or, in the event that the unit has been transfused to a patient, physician notification takes place regarding bacterial contamination.

Platelet transfusions are associated with the unique complication of alloimmune refractoriness. In this condition, routine platelet transfusions no longer increase the recipient's platelet count. This occurs in patients who develop anti-human leukocyte antigen (HLA) antibodies or, less commonly, anti-platelet antibodies after a blood transfusion or a pregnancy. These antibodies can cause the immediate destruction of platelets that are transfused from randomly selected units. Adequate increments in the post-transfusion platelet count can then only be achieved by the selection and transfusion of matched (HLA or platelet antigen) apheresis platelet units. Alloimmune refractoriness can occur in up to 40% of patients receiving platelet transfusions, but in Canada this risk has been shown to be significantly reduced by the universal leukoreduction of all blood components. The risks of alloimmunization and platelet refractoriness are similar with both whole blood derived platelets and apheresis platelets since both products are leukoreduced.

While apheresis platelet transfusions will reduce total exposure to donors, apheresis platelets from an HLA-matched donor or a blood relative is associated with an increased risk of causing TA-GvHD. To prevent TA-GvHD, all HLA-matched blood products should be irradiated.

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Management of Special Situations

Platelet Refractoriness

A major complication in the management of thrombocytopenic patients is platelet refractoriness. Platelet refractoriness may be due to immune or non-immune causes. The causes of non-immune refractoriness include fever, infection, drugs, splenomegaly and disseminated intravascular coagulation. In patients with poor responses to platelet transfusions, measuring the post-transfusion platelet count after the platelet transfusion may allow for differentiation between immune and non-immune causes. The corrected count increment (CCI) or the percent platelet recovery (PPR) can be used to determine post-transfusion platelet count increments. These formulas account for both patient size and the number of platelets transfused.

$$PPR = \left[\frac{(\text{platelet increment}) \times (\text{weight in kg}) \times (75\ \text{mL/kg})}{(\text{platelet count of platelet product}) \times (\text{volume of platelet count})} \right] \times 100\%$$

$$CCI = \frac{(\text{platelet increment}) \times (\text{body surface area})}{(\#\ \text{of platelets transfused} \times 10^{11})}$$

In patients with poor response to platelet transfusion, the platelet response measured between 10–60 minutes after completion of two ABO-matched platelet transfusions may be used to determine if alloimmunization is the likely cause of the refractoriness. A CCI of $< 7.5 \times 10^9$/L or a PPR of < 30% are evidence of alloimmune refractoriness. Since the platelet count of whole blood derived platelets is not routinely measured, a one-hour post-transfusion platelet increment $< 5 \times 10^9$/L can be used instead of the CCI or PPR. Testing for HLA- or platelet-specific antibodies can be done using special tests, including lymphocytotoxic antibody assay and flow cytometry. HLA alloimmunization is the more frequent cause of alloimmune refractoriness. Isolated anti-platelet antibodies have only rarely been reported as a cause of platelet refractoriness.

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In refractory patients with identified anti-HLA- or anti-platelet-specific antibodies, matched apheresis platelet products may be useful to achieve adequate post-transfusion platelet count increments. Matched platelet products can be obtained from HLA-typed apheresis platelet donors. If the donors are well matched for HLA A and B antigens (no HLA A and B antigens expressed by the donor that are not expressed by or cross-reactive with the recipient's), then up to 70% of patients will have an adequate post-transfusion platelet count increment as measured by the CCI or PPR. Failures of HLA-matched apheresis platelets to produce an expected increment in the post-transfusion platelet count may be the result of anti-platelet antibodies. A platelet crossmatch can be used, in conjunction with or as an alternative to HLA matching, for patients with alloimmune refractoriness. While this would be useful for patients with anti-platelet antibodies, a large number of platelets may need to be screened during platelet crossmatch, and false negative results also occur. Management of refractory patients who do not respond to matched platelets is problematic. Despite poor platelet count increments and survival, patients may still derive hemostatic benefits from regular platelet transfusions. Some authors have recommended that lower dose transfusions be given three or four times per day.

Post-Transfusion Purpura

Patients who are negative for a specific platelet antigen may produce an antibody against these antigens after exposure through a blood transfusion or a pregnancy. This occurs most commonly in patients lacking the platelet antigen HPA-1a (also known as $P1^{A1}$), but this can also occur with other platelet-specific antigens. If patients are re-exposed to this platelet antigen, an amnestic response will occur in the following five to 10 days. This will lead to the destruction of the transfused platelets and the patient's own platelets. The mechanism of the autologous platelet destruction is not known, but proposed mechanisms include a cross-reactive antibody or by-stander platelet destruction. Patients with post-transfusion purpura should receive steroids and intravenous immunoglobulin or plasma exchange to speed platelet recovery. All future platelet transfusions should be from selected donors who are negative for the offending antigen.

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