bloody easy 3

Blood Transfusions, Blood Alternatives and Transfusion Reactions

A Guide to Transfusion Medicine

Third Edition

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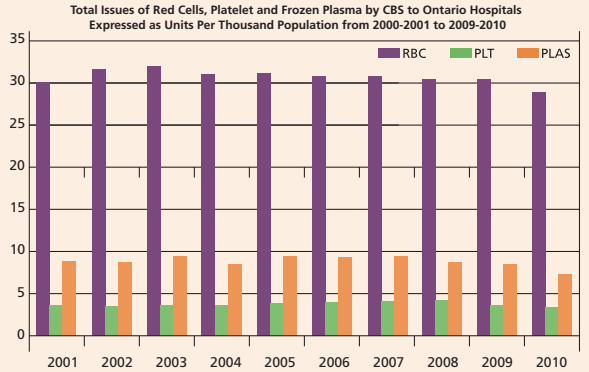
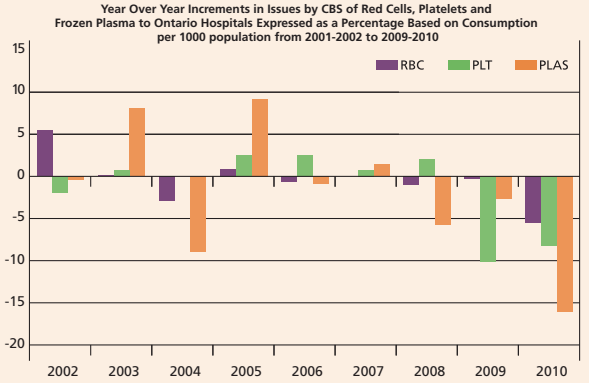
Preface to Third Edition

Since 2001 the Ontario Ministry of Health and Long-Term Care (MOHLTC) has provided funding and oversight for a variety of initiatives directed at promoting rational evidence-based use of blood components, derivatives and alternatives, and reduction of transfusion errors. These initiatives have included deploying 27 transfusion practitioners in 25 large hospitals that together use a majority of blood products in the Province, supporting the publication of this *Guide to Transfusion Medicine* and the development of various allied online educational products for physicians, nurses, technologists and patients. In 2007 the Provincial Blood Programs Coordinating Office established the Ontario Regional Blood Coordinating Network (ORBCoN) to promote measures for sound blood management; these include the updating and publication of Bloody Easy and its on-line derivatives. Details of ORBCoN's mandate and activities can be found at www.transfusionontario.org

Changes in Consumption of Blood Components in Ontario 2001-2010





Consumption of labile blood components (red cells, platelets and frozen plasma) has shown a downward trend starting in 2007-2008 and accelerating in 2008-2009 and 2009-2010.

Adapted from the WHO 1998 recommendations for the clinical use of blood: [1]

1. Transfusion is only one part of patient management.
2. Prescribing decisions should be based on national guidelines on the clinical use of blood, taking into account the needs of each individual patient.
3. Blood loss should be minimized (and blood conservation strategies considered*) to reduce a patient's need for transfusion.
4. A patient with acute blood loss should receive effective resuscitation (IV replacement fluids, oxygen, etc.) while assessing the need for transfusion.
5. A patient's hemoglobin value, although important, should not be the sole deciding factor in starting transfusion of red cells. The decision to transfuse should be supported by the need to relieve clinical signs and symptoms and to prevent morbidity and mortality.
6. The clinician should be aware of the risks of transfusion-transmissible infection (and non-infectious risks*) in the blood and blood products that are available for each individual patient.
7. Transfusion should be prescribed for a patient ONLY when the benefits outweigh the risks.
8. The clinician should clearly record the reason for the transfusion.
9. A trained health care professional should monitor the transfused patient and respond immediately if any adverse effects occur.
10. Informed consent for transfusion should be obtained prior to transfusion.*

* Additional recommendations by the Blood Products Advisory Panel for the 1st and 2nd Editions (see Appendix C, page 138).

Important Notes

- This booklet is an educational tool to assist in providing care to patients.
- The recommendations do not replace the need to consult an expert in transfusion medicine.
- These recommendations should not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion.

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CONTENTS

A Overview

Who regulates

- Health Canada regulates blood collection, testing, processing, and distribution.
- The agency has published standards relating to hospital transfusion practices.
  - The second edition of these standards is available from the Canadian Standards Association (Can/CSA-Z902-10).

Health Canada Santé Canada

National Standard

- Canadian Society for Transfusion Medicine – Standards for Hospital Transfusion Services Version 3, February 2011 www.transfusion.ca.

CSTM SCMT

Who collects

- Canadian Blood Services (CBS), in all provinces and territories except Québec.
- Héma-Québec (HQ) in Québec.

Canadian Blood Services
it's in you to give

HÉMA-QUÉBEC

Donor screening

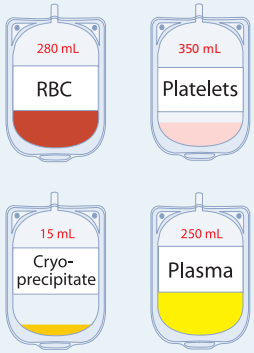
- Donors screened using:
  - donor questionnaire
  - donor vital signs (temperature, heart rate, blood pressure)
  - donor hemoglobin
- Donor units tested for:

Donor Units Tested For:	Specific Agents	Tests Used
Blood groups	ABO and Rhesus (Rh) D Red cell alloantibodies	Blood group serology
Viruses	HIV 1 and 2 Hepatitis B Hepatitis C HTLV I and II West Nile Virus	Antibody and nucleic acid testing Surface antigen, core antibody and nucleic acid testing Antibody and nucleic acid testing Antibody Nucleic acid testing
Bacteria	Syphilis Bacterial contamination	Serology Bacterial culture (Platelets only)
Parasites	Chagas Disease (at risk donors only)	Antibody

- All donors are unpaid volunteer donors.
- Plasma for fractionation is screened for parvovirus B19 by nucleic acid testing.

Whole blood processing

- Collect 500 mL whole blood.
- Divert the first 40 mL to reduce risk of bacterial contamination from donor skin; the 40 mL are used for donor unit testing.
- Blood is centrifuged and separated into 3 parts:
  - Red Blood Cells
  - Plasma
  - Buffy coat
- The Buffy coat units from four donors are combined with one plasma unit and further processed to separate the platelets.
- The red blood cell and platelet components are leukoreduced.
- Certain groups of patients need irradiated blood components to prevent transfusion-associated graft vs host disease (TA-GvHD).
- CBS and HQ provide irradiated products on demand.
  - Refer to TA-GvHD (page 63) for list of patient groups that need irradiated blood



HÉMA-QUÉBEC

HQ provides buffy coat platelets from 5 units of buffy coat.

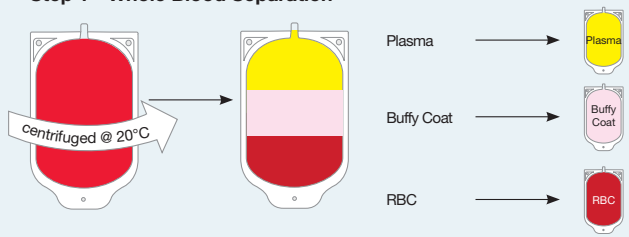
B Red Blood Cells and Components: Storage Conditions and Volumes

Component	Volume	Storage Limit	Storage Temp.
Red blood cells	280 mL	42 days	1-6°C
Buffy coat derived platelets (from 4 units)	350 mL	5 days	20-24°C
Apheresis platelets	300 mL	5 days	20-24°C
Frozen plasma	250 mL	1 year	-18°C or colder
Apheresis plasma	500 mL	1 year	-18°C or colder
Cryoprecipitate	15 mL	1 year	-18°C or colder
Autologous red blood cells	280 mL	42 days	1-6°C
Autologous frozen plasma*	250 mL	1 year	-18°C or colder
Directed red blood cells	280 mL	42 days	1-6°C
Directed frozen plasma*	250 mL	1 year	-18°C or colder

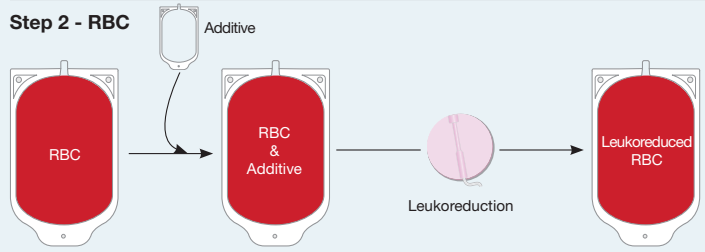
* Only on request and referral by patient's physician.

Process for Preparing Blood Components from Donated Units

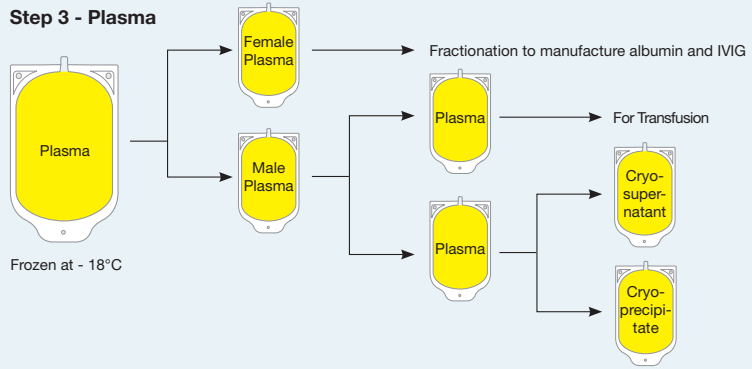
Step 1 - Whole Blood Separation



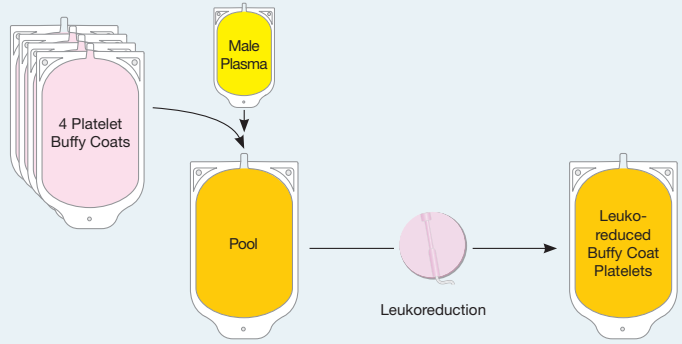
Step 2 - RBC



Step 3 - Plasma



Step 4 - Buffy Coat Platelet



C Informed Consent

When
- Discuss the option of a transfusion early enough to allow for a blood alternative(s) to be considered.

What [2]
- Include in your discussion:
  - Description of blood or blood product
  - Benefits
  - Risks
  - Alternatives
- Give your patient the opportunity to ask questions.

ATTENTION

Refer to pages 34-36 for risk charts, to assist discussion of risks with patients.

Of note
- Confirm that you discussed consent with the patient, by noting it in the patient's chart.
- Complete the informed consent documentation as required at your hospital.
- If transfusion is required, clearly document the reason in the patient's chart.
- In the special case of Jehovah's Witnesses, helpful advice may be obtained from their Hospital Information Services 24 hours a day at 1-800-265-0327 (see Appendix B, page 137).

Pediatrics
- For minors, the parent or legal guardian must give informed consent.
- Teenagers should give informed consent themselves. The age at which teenagers can give informed consent varies from province to province. Refer to provincial legislation.

D Directed Blood Donations

What
- Directed blood donations are units donated for a specific transfusion recipient.

Who
- Currently in Canada (other than Québec), directed blood donations are available only for the following recipients:
  - To minor child from parent
  - Patients with rare red blood cell types
  - HLA-alloimmunized, thrombocytopenic patients requiring HLA-matched platelet transfusions
  - Infants with neonatal allo-immune thrombocytopenia
- In Québec, all recipients may have access to directed blood donations, on recommendation of their physician.

Canadian Blood Services
it's in you to give

HÉMA-QUÉBEC

Where
- Directed blood donations are collected by CBS and HQ.

Of note
- Directed blood donations transfused to family members must be irradiated to prevent TA-GvHD.
- Presently, there are no data to support the concept that directed donors are safer than volunteer donors.
- Directed blood donation programs are logistically complicated to administer and financially more expensive than volunteer donor programs.

A When and How to Order Tests

1. Transfusion **MIGHT** occur during admission

2. Surgery with < 10% risk of transfusion (most minor surgeries do **NOT** require even a group or screen)

Group & Screen

1. Transfusion **PLANNED**

2. Surgery with > 10% risk of transfusion

Group & Screen & Crossmatch

GROUP

ABO group

Rh (D) group

SCREEN

Antibody Screen

CROSSMATCH

Antiglobulin Crossmatch **OR**

Immediate Spin Crossmatch **OR**

Computer Crossmatch

ATTENTION

Uncrossmatched blood is rarely required; consider if clinical status precludes waiting for antibody screen and crossmatch (45 mins).

Pediatrics

- For infants less than 4 months of age, initial testing must include ABO and Rh (D) group and an antibody screen, using either a sample from the infant or mother.
- If an unexpected RBC alloantibody is detected in the infant's or mother's specimen, it is required that the infant receive RBC units lacking the corresponding antigen(s) or units compatible by antiglobulin crossmatch.
- This regimen should continue until the maternal antibody is no longer detected in the infant's sample.

B Routine Transfusion Medicine Tests

Test	Time (min)	Information
ABO group	5	Patient RBCs tested for A and B antigen.
Rh (D) group	5	Patient RBCs tested for D antigen.
Antibody Screen	45	Screens for RBC alloantibodies formed as a result of prior transfusion or pregnancy.
Antiglobulin Crossmatch	45	Mandatory for patients with RBC alloantibodies. Involves incubation of donor RBCs, recipient plasma/serum, and anti-IgG.
Immediate Spin Crossmatch	5	Testing involves mixing of donor RBCs and recipient plasma/serum. Used to verify ABO compatibility only.
Computer Crossmatch	2	Computer selects appropriate unit (donor units must have been re-tested to confirm ABO group and recipient sample must be tested twice).

Note: For centres using immediate spin or computer crossmatch, crossmatching red cell units in advance of transfusion/surgery is rarely required unless antibody screen is positive.

C Checking Identity of Patient

You must accurately identify the patient at the following times:

1. When collecting a blood sample
   - Accurately label each specimen **before** leaving the patient's bedside.

2. **Before** beginning the transfusion
   - Verify the patient's identity, by checking the name and date of birth on their wristband against the identification on the blood component label before transfusing, and, where possible, also by verbal confirmation.

ATTENTION

Check the patient's wristband before transfusing!

Failure to check is the major cause of acute hemolytic transfusion reactions.

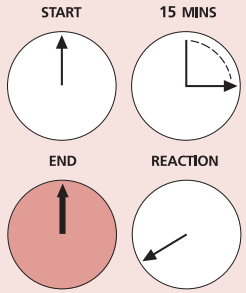
D Monitoring & Infusion Practices

How
- RBCs must be transfused through a blood administration filter (170-260 microns).
- RBCs are compatible **ONLY** with normal saline.
- 16-18 gauge needle required for fast flow rates.
- 20-22 gauge needle appropriate for patients with small veins.

When
- Start within 30 minutes of removing RBCs from refrigeration.

Storage
- Only store RBCs in a temperature-controlled refrigerator with continuous temperature monitoring by the transfusion service.
- Freezing or heating blood may cause hemolysis, and may harm the patient.

Monitor patient
- Check patient's vital signs; vital signs should be assessed:
  - prior to starting
  - 15 minutes after starting
  - at end of transfusion
  - during any transfusion reactions.
- Transfuse slowly (**50 mL/hr**) for the **first 15 minutes**, where appropriate.
- Monitor the patient closely for the first 15 minutes.



ATTENTION
Monitor patient closely for first 15 minutes.

Pediatrics[3,4]
For pediatric patients, transfuse slowly (1 ml/kg/h, up to 50 ml) for the first 15 minutes. Usual administration rate is 5 ml/kg/h, up to 150 ml/h.

Transfuse
- In **non-urgent/non-bleeding/inpatient settings** red blood cells should be transfused during **daytime hours** (for patient safety) and transfused **one unit at a time**.
- Assess patient prior to ordering another unit.
- Each unit is usually infused over 2 hours, but always within 4 hours of issue from blood bank.
- Consider a slower rate for patients at risk of circulatory overload.
- In massive transfusion, blood should only be warmed using an approved blood warming device.

ATTENTION
Transfuse one unit at a time.

ATTENTION
Infuse each unit over 2 hours, maximum 4 hours.

E Ordering RBCs

- If the patient is not adequately volume resuscitated, the hemoglobin value may be spuriously high OR, in the setting of over hydration, spuriously low.
- A falsely low hemoglobin value may result if test samples are taken near a site of IV infusion.
- Certain patients require irradiated or CMV-seronegative products. Refer to page 63 (irradiated products) and page 67 (CMV-seronegative products).

ATTENTION
Record the order in the correct patient's chart.

Pediatrics
Dosage:
- A transfusion of 15 ml/kg of RBC stored in an additive solution is expected to raise the hemoglobin level by approximately 20 g/L.[5]

F Indications for RBCs

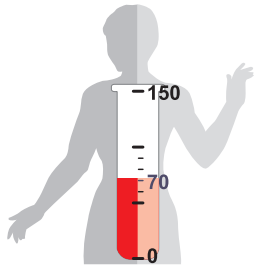
Acute blood loss

- Maintain **hemoglobin > 70 g/L during active bleeding**.[6]
  - Consider rate of bleeding, hemodynamic factors, evidence of tissue ischemia, institutional speed of blood delivery/ laboratory testing in decision about transfusion.
  - Ensure prompt blood availability when hemoglobin is < 80 g/L
- Consider maintaining a **higher hemoglobin level for patients with**:[7]
  - Impaired pulmonary function
  - Increased oxygen consumption (fever, chills)
  - Unstable or acute coronary syndromes[8,9,10]
  - Coronary artery disease[9]
  - Uncontrolled/unpredictable bleeding.
- Consider that patients with **hemoglobin >100 g/L** are **unlikely to benefit from transfusion**.

Anemia in critical care and coronary care

- Recommend a transfusion when the patient's hemoglobin is less than 70 g/L.[9]
- In a patient with an acute coronary syndrome, there is controversy over where to maintain the hemoglobin level.[8,9,10]
  - There are insufficient data to recommend maintaining the hemoglobin above some arbitrary level
  - Consider transfusing if there are clear signs of inadequate tissue oxygen delivery in a patient with a low hemoglobin and an acute coronary syndrome
- Unnecessary phlebotomy for laboratory testing is a major contributor to anemia in a critically ill patient.
- Except for patients with unstable coronary artery syndromes, a restrictive transfusion policy (trigger Hb 70 g/L) has proved at least as effective as a liberal transfusion policy for critically ill patients.[9,11]

ACUTE BLOOD LOSS & ANEMIA IN CRITICAL CARE



ATTENTION

Minimize blood work as it contributes to need for transfusion in critical care.

- Recombinant erythropoietin does not reduce RBC transfusion requirements in critically ill patients and its use is associated with an increased rate of thrombotic events.[12]

Pediatrics

Anemia in pediatric critical care

- In children whose condition is stable in the ICU, a transfusion is not usually required unless the patient's hemoglobin is less than 70 g/L.
- A restrictive transfusion strategy (trigger Hb 70 g/L) was proven to be as safe as a liberal transfusion strategy (95 g/L).[11]
  - This recommendation may not be applicable to neonates under 28 days old, children with severe hypoxemia, hemodynamic instability, active blood loss or cyanotic heart disease as these groups were excluded from this clinical trial.

Anemia in neonatal critical care

- Several guidelines for small-volume RBC transfusions for newborns have been published in the last decade.[13,14,15,16]
- Two recent randomized controlled trials came to differing conclusions regarding whether a restrictive strategy was as safe as a liberal strategy.[17,18]
- Attention must be drawn to phlebotomy for laboratory testing since it is a significant cause of anemia in neonates.[19]
- Due to the conflicting evidence from randomized control trials in this patient population, an accepted standard approach for the transfusion of neonates cannot be recommended.

Perioperative patients

- Manage patients undergoing elective surgery preoperatively, intraoperatively, and postoperatively with strategies to minimize the need for RBCs.[6] (see pages 74-75)
- Administer RBCs one unit at a time in non-urgent settings.[7,20]
- Assess patient prior to transfusing additional units (clinical exam and hemoglobin level).[7]
- For orthopedic patients with cardiovascular disease, post operative transfusion for symptomatic anemia or hemoglobin of less than 80 g/L does not increase adverse outcomes or delay recovery compared to a transfusion trigger of 100 g/L.[21]
- Follow guidelines for perioperative patient:[7]

ATTENTION

RBCs:
One unit at a time.

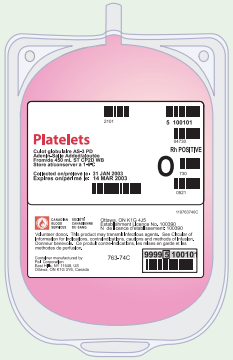
Hemoglobin	Recommendation
> 100 g/L	Likely inappropriate except in exceptional circumstances
70-100 g/L	Likely to be appropriate if there are signs or symptoms of impaired oxygen delivery
< 70 g/L	Likely to be appropriate
< 60 g/L	Transfusion highly recommended[22] ◆ Young patients with low risk of ischemic cardiovascular disease can sometimes tolerate greater degrees of anemia

Chronic anemia[23,24]

- Administer transfusions only when alternatives do not exist or have failed.[6]
- Administer RBCs at intervals to maintain the hemoglobin just above the lowest concentration that is not associated with symptoms of anemia.[6]
- Assess patients that are expected to have long-term transfusion dependent survival for iron overload.
- Chelation therapy should be considered in patients who are iron-overloaded, transfusion dependent, and who have a life expectancy of more than one year.
- Iron overload is typically present after 20 units of RBCs (patients with a significant component of ineffective erythropoiesis and upregulation of iron absorption may become iron overloaded more quickly).
- Monitor serum ferritin and transferrin saturation: tissue iron overload is likely if ferritin > 1000 ug/L and transferrin saturation > 75%.
- Either desferrioxamine or deferasirox are appropriate as first line therapy, with target ferritin between 500 and 1000 ug/L, and appropriate monitoring for drug toxicity (including annual eye and ocular examinations).

A Basics

- **Platelets come in 3 forms:**
  - Pool of 4 units of buffy coat derived platelets (pools of 5 in Québec)
  - Single donor (collected by apheresis)
  - HLA-matched single donor (for patients with HLA-alloimmunization and refractory to random donor platelets)
- In non-bleeding patients, the risk of spontaneous hemorrhage is low when platelet count is greater than 10 x 10^9/L.
- In Canada, all platelet products are tested for bacterial contamination which lowers but does not eliminate the risk of sepsis.
- The commonly held belief that platelet transfusions are contraindicated in immune mediated thrombocytopenia (i.e., HIT, ITP, PTP) is not supported by substantial evidence.[25]

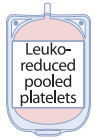


B Monitoring & Infusion Practices

How

- Buffy coat derived pooled platelets from multiple donors or single donor apheresis platelets are supplied.
- Platelets must be transfused through a blood administration filter (170-260 microns).
- Fresh blood administration filter preferred.
- Platelets are compatible **ONLY** with normal saline.

INFUSION



Pool of 4 buffy coat derived platelet units

=

Single Apheresis Donor

≅ 30 x 10^{10} Platelets

What

- ABO/Rh-identical platelets are preferred, but ABO/Rh non-identical platelets may be transfused when ABO/Rh-identical platelets are not available.
- Rh negative women of childbearing potential require Rh-immunoglobulin when Rh positive platelets are transfused to avoid formation of anti-D antibody.
  - Each platelet pool contains up to 0.5 mL of red cells[26]
  - Each 120 ug of Rh-immunoglobulin covers 12 mL whole blood (6 mL RBC) and lasts approximately 21 days

Storage

- Platelets must be stored at 20-24˚C (room temperature) with constant mixing to preserve platelet function.
- Do not refrigerate. Inadvertently "chilled" platelets will be rapidly cleared by hepatic macrophages.

ATTENTION

Do NOT put platelets in the refrigerator.

Pediatrics

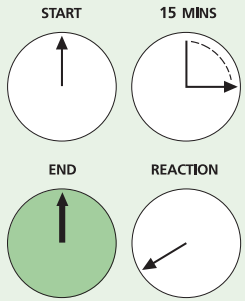
Dose: [13,14]

- Children over *10* kg: 1 U/10kg, up to an equivalent of 1 pool of platelets OR 10 ml/kg up to a maximum of 1 pool of platelets.
- Neonates 10 ml/kg

Ⓑ Monitoring & Infusion Practices (cont'd)

Monitor patient

- Check patient's vital signs; vital signs should be assessed prior to starting, 15 minutes after starting, at end of the transfusion and if there are any transfusion reactions.
- Transfuse slowly (**50 mL/hr**) for the **first 15 minutes**, where possible.
- Monitor the patient closely for the first 15 minutes.
- Each dose of platelets should increase the patient's platelet count at 1 hour by at least 15-25 x 10^9/L.[27]



ATTENTION

Monitor patient closely for first 15 minutes.

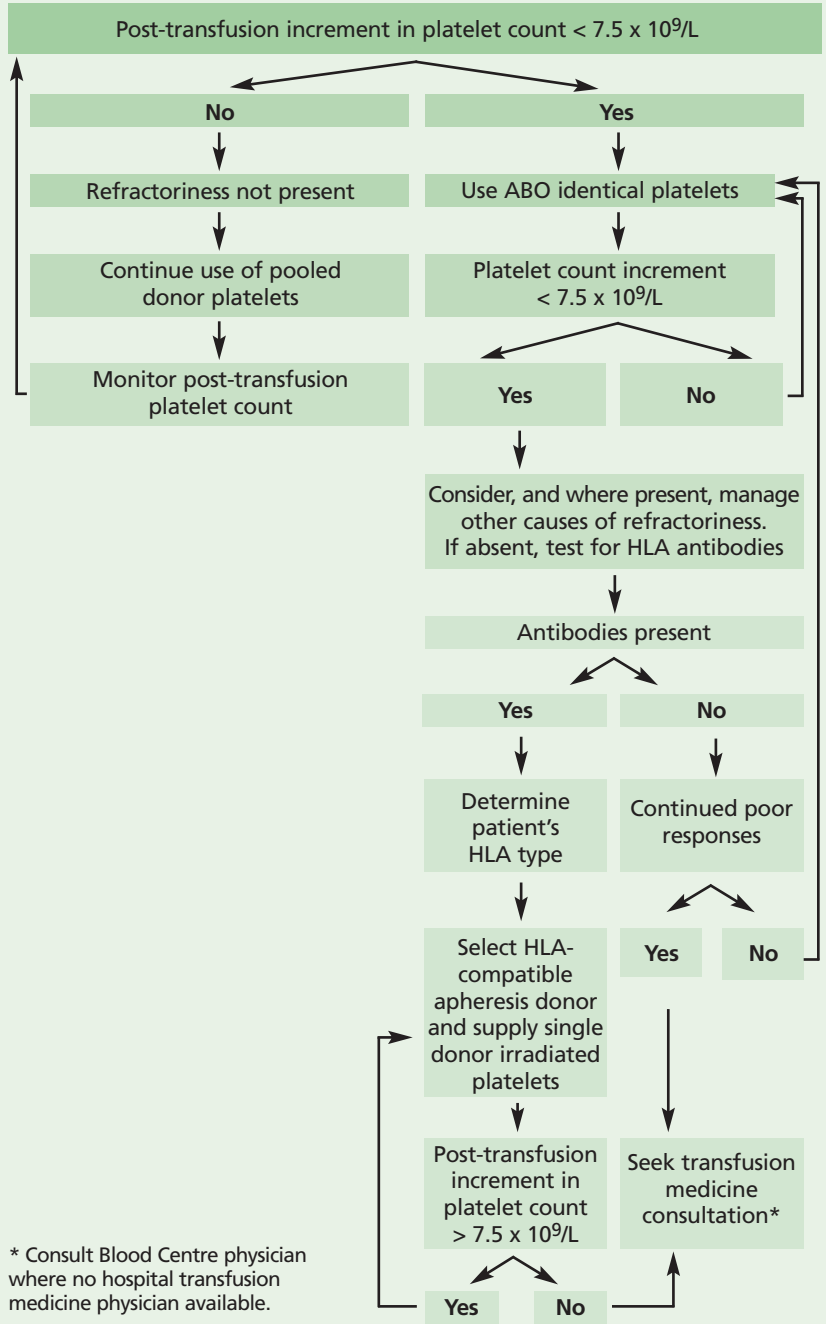
Transfuse

- Recommended **infusion time is 60 minutes** per dose (maximum infusion time 4 hours).

Follow-up

- Obtain **post-transfusion platelet counts** (10-60 min.) after all transfusions to ensure adequate replacement and recognition of platelet refractoriness.[28]
  - A platelet increment of < 7.5 x 10^9/L suggest refractoriness and requires investigation.[27]
- If increments in platelet count are NOT adequate, special measures are required. Refer to the algorithm on page 25.

PLATELET REFRACTORINESS MANAGEMENT ALGORITHM[27,29]



* Consult Blood Centre physician where no hospital transfusion medicine physician available.

Indications & Infusion Recommendations

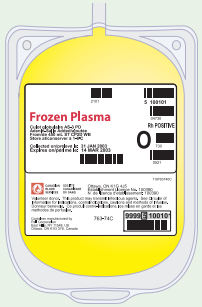
PLT (x 10^9/L)	Clinical Setting	Suggest
< 10	Non-immune thrombocytopenia	Transfuse 1 pool of platelets[28]
< 10	Non-immune thrombocytopenia & HLA-alloimmunized	Transfuse 1 unit of HLA-matched apheresis platelets[28]
< 20	Non-immune thrombocytopenia and fever > 38.5˚C or coagulopathy	Transfuse 1 pool of platelets[28]
< 20	Procedures not associated with significant blood loss	Transfuse 1 pool of platelets[28]
20-50	Procedures not associated with significant blood loss	1 pool of platelets on hold, transfuse only if significant bleeding[22]
< 50	Epidural anesthesia and lumbar puncture	Transfuse 1 pool immediately before procedure[30]
< 50	Procedures associated with blood loss or major surgery (> 500 ml expected blood loss)	Transfuse 1 pool immediately before procedure[22,31]
< 50	Immune thrombocytopenia	Transfuse platelets only with serious bleeding[32]
< 100	Pre-neurosurgery or head trauma	Transfuse 1 pool of platelets[33,34]
Any	Platelet dysfunction and marked bleeding (e.g., post cardiopulmonary bypass, aspirin, antiplatelet agents)	Transfuse 1 pool of platelets[22]

Pediatrics – Neonates[13]

PLT (x 10^9/L)	Clinical Setting	Suggest
< 30	Any neonate	10 ml/kg
< 50	Stable premature neonate with active bleeding or planned invasive procedure	10 ml/kg
< 100	Sick preterm neonate with active bleeding, planned invasive procedure, or DIC	10 ml/kg

Note: These guidelines are based on experts opinions and are not evidence driven since there are no clinical trials in this patient population.

A Basics[35,36]



- Frozen plasma (FP) can be derived from two sources:
  - Random donor plasma (250 mL)
  - Apheresis donors (250 or 500 mL)
    - plasma collected alone or in conjunction with platelets
    - large apheresis units (500 mL) are equivalent to 2 units of random donor plasma

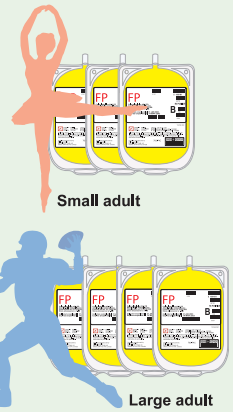
Notes:

- 'Frozen plasma' (FP) is frozen within 24 hours of collection and 'Apheresis Fresh Frozen Plasma' (FFPA) is frozen within 8 hours.
- FP is produced from whole blood donations with longer "hold" as part of the buffy-coat production method.
- The factor VIII is slightly lower in FP but this is not clinically significant. All other coagulation factor levels are the same in FP and FFPA, and the 2 products can be used interchangeably.
- FP and FFPA contain 400-900 mg fibrinogen per 250 mL equivalent (4 units of FP contain approximately 2.5 g of fibrinogen).

B Monitoring & Infusion Practices

How

- Frozen plasma must be transfused through a blood administration filter (170-260 microns).
- FP is compatible **ONLY** with normal saline.



Dose

- Small adult: 3 units (10-15 mL/kg).[37]
- Large adult: 4 units (10-15 mL/kg).[37]
- Pediatric: 10 to 20 mL/kg.

When

- The recommended infusion time is 30 to 120 minutes (maximum time 4 hours).

Storage

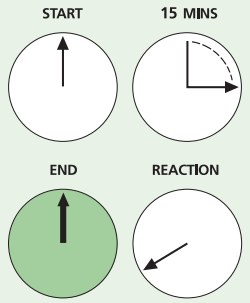
- Frozen plasma is kept *frozen* for up to one year.
- After issue, FP and FFPA should be administered within 4 hours.
  - The biological half-life of plasma coagulation proteins is different for each protein:[38]
    - 3-6 hours for factor VII
    - 8-12 hours for factor VIII
    - 2-3 days for factors II and IX

ATTENTION

The effective half-life of FP is measured in hours. Administer immediately before planned procedures.

Monitor patient

- Check patient's vital signs; vital signs should be assessed prior to starting, 15 minutes after starting, at end of transfusion and if there are any transfusion reactions.
- Transfuse slowly (**50 mL/hr**) for the **first 15 minutes**, where possible.
- Monitor the patient closely for the first 15 minutes.
- If clinically indicated, the PT/INR and PTT should be checked after infusion (10-60 minutes).



ATTENTION

Monitor patient closely for first 15 minutes.

Indications for Frozen Plasma

1. Bleeding or prior to an operative procedure in patients with INR, PT or PTT more than 1.5 times normal when no coagulation factor concentrates or other alternative therapy are available.[2]
   - Repeating INR/PT/PTT after infusion of FP may be beneficial to ensure that replacement is adequate[33]

ATTENTION

FP is NOT indicated or required when INR < 1.5 as coagulation factor levels are adequate for hemostasis.

Note: [39,40,41,42]

- If available, prothrombin complex concentrates (PCCs) should be used for urgent reversal of warfarin therapy or treatment of vitamin K deficiency in a bleeding patient OR a patient requiring an emergency invasive procedure. Vitamin K (2-10 mg i.v.) should also be given.
- For non-emergent reversal of warfarin or vitamin K deficiency, vitamin K should be used rather than PCCs.
  - For patients without bleeding and INR > 5 and < 9 due to warfarin, 1-2 mg of oral Vitamin K will bring INR within the therapeutic range. For an INR ≥ 9, use 5-10 mg of oral vitamin K
  - After intravenous administration, Vitamin K effect can be detected after 2 hours and the INR should be normalized after 12-24 hours
  - SC and IM NOT recommended due to variable absorption: intravenous formulation can be used orally for more rapid effect or if oral tablets are not readily available

ATTENTION

IV Vitamin K works faster than oral.

ATTENTION

FP is NOT indicated or effective for reversal of heparin, low molecular weight heparin, rivaroxaban or dabigatran.

Pediatrics [43]

Vitamin K dose:

- INR > 5 & < 9: 1 to 2 mg oral
- INR ≥ 9: 5 mg oral
- Significant bleed in infants and children: 5 mg IV OR 30 mcg/kg IV

2. Microvascular bleeding or massive transfusion AND patient's clinical status precludes waiting 30-45 minutes for INR/PT/PTT results.[2]

3. Thrombotic thrombocytopenic purpura.

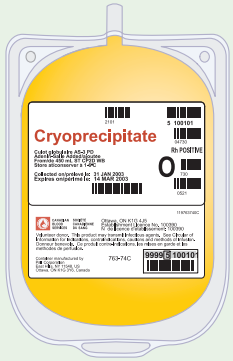
ATTENTION

1:1 replacement with FP and RBCs not required when patient is expected to need less than 10 PRBC units over 24 hours or time allows replacement based on laboratory testing.

Ⓐ Basics[22]

What

- Cryoprecipitate contains factor VIII (8), fibrinogen, and von Willebrand factor.
  - Each unit of cryoprecipitate contains 150 mg of fibrinogen



How

- Cryoprecipitate must be given through a blood administration filter (170-260 microns).
- Cryoprecipitate is compatible **ONLY** with normal saline.

Dose

- 1 unit per 10 kg of body weight (i.e. 8 to 12 units per dose).
  - Small adult: 8 units
  - Large adult: 12 units
- Each dose will increase the fibrinogen by 0.5 g/L.[22]
- Recommended infusion time is 10-30 minutes per dose (maximum infusion time 4 hours).
- Half-life of fibrinogen is about 7 days.

Ⓑ Indications

1. Treatment of **microvascular or massive bleeding** in patients with a **fibrinogen** concentration of **less than 0.8 to 1.0 g/L**; or, patient's clinical status highly suggestive of a **low fibrinogen concentration** in the setting of massive bleeding and clinical status precludes waiting for fibrinogen result before transfusion.

2. Treatment of bleeding in patients with von Willebrand disease or Hemophilia A **only**:
   - when factor concentrates are unavailable (remote geographic region); and
   - DDAVP is unavailable or ineffective

Risk of Event	Event
1 in 20	Febrile non-hemolytic transfusion reaction per pool of platelets
1 in 100	Minor allergic reactions (urticaria)
1 in 300	Febrile non-hemolytic transfusion reaction per unit of RBC (1 'donor exposure')
1 in 700	Transfusion-associated circulatory overload per transfusion episode
1 in 7,000	Delayed hemolytic transfusion reaction
1 in 10,000	Transfusion-related acute lung injury (TRALI)
1 in 10,000	Symptomatic bacterial sepsis per pool of platelets
1 in 40,000	ABO-incompatible transfusion per RBC transfusion episode
1 in 40,000	Serious allergic reaction per unit of component
1 in 60,000	Death from bacterial sepsis per pool of platelets
1 in 153,000**	Transmission of hepatitis B virus per unit of component
1 in 250,000	Symptomatic bacterial sepsis per unit of RBC
1 in 500,000	Death from bacterial sepsis per unit of RBC
< 1 in 1,000,000	Transmission of West Nile Virus
1 in 2,300,000	Transmission of hepatitis C virus per unit of component
1 in 4,000,000	Transmission of Chagas disease per unit of component
1 in 4,300,000	Transmission of HTLV per unit of component
1 in 7,800,000	Transmission of human immunodeficiency virus (HIV) per unit of component

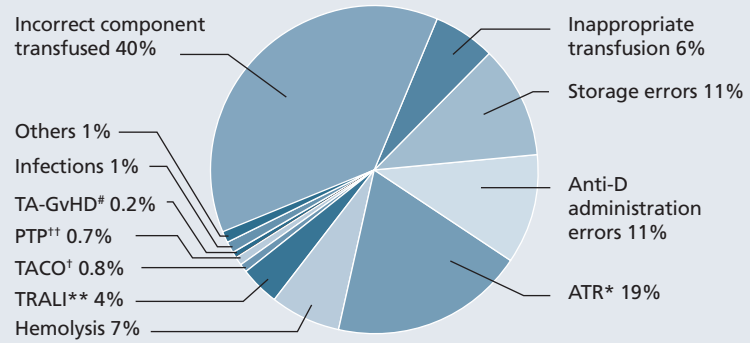
* All of these risk frequencies are likely to have quite wide confidence intervals.

** Where time permits, consider hepatitis B vaccination in prospective transfusion recipients, especially for those requiring repeated infusions of blood or blood products (www.phac-aspc.gc.ca: Immunization Guide, part 4, pg. 194).

Risk of death per 1 unit component
(likely an under-estimate)

- Note: patient risk should be determined as a multiplication of the risk by the number of units transfused (or 'donor exposures').
- Serious Hazards of Transfusion Program (United Kingdom) 1996-2004.
  - 1 in 270,000 components issued possibly, probably or definitely related to patient death[44,45]
- United States (Food and Drug Administration) 2007.
  - 1 in 428,846 components transfused resulted in a death from transfusion[46]
- The Hemovigilance Network in France 1994-98.
  - 1 in 192,231 components transfused resulted in a death from transfusion[47]

Serious Hazards of Transfusion (SHOT), United Kingdom
Major Adverse Events Reported 1996-2009 (6653 Reports)[44]



* Acute transfusion reactions (ATR) include fever, allergic, anaphylactic, hypotensive reactions

** Transfusion-related acute lung injury (TRALI)

† Transfusion-associated circulatory overload (TACO)

†† Post-transfusion purpura (PTP)

Transfusion-associated graft vs host disease (TA-GvHD)

Risk of Event	Event
1 in 100	**Hives** (itchy skin rash)
1 in 300	**Fever**
1 in 700	**Heart failure**
1 in 7,000	Delayed **hemolysis**. Hemolysis is when your red blood cells are destroyed
1 in 10,000	**Lung injury**
1 in 10,000	Symptomatic **bacterial sepsis**, per pool of platelets. **Sepsis** is when you get an infection in your bloodstream or tissue
1 in 40,000	Wrong ABO (blood) group, per unit of red blood cells
1 in 40,000	**Anaphylaxis**, which is an extreme sensitivity to a drug or substance that can result in death
1 in 60,000	Death from **bacterial sepsis**, per pool of platelets
1 in 153,000	**Hepatitis B Virus (HBV)** transmission per unit of component. Hepatitis is an inflammation of the liver. **HBV** is a virus that is spread through contact with infected blood, blood products and body fluids
1 in 250,000	Symptomatic **bacterial sepsis**, per unit of red blood cells
1 in 500,000	Death from **bacterial sepsis**, per unit of red blood cells
< 1 in 1,000,000	Transmission of **West Nile Virus**
1 in 2,300,000	**Hepatitis C Virus (HCV)** transmission, per unit of component. Hepatitis is an inflammation of the liver. **HCV** is a virus that is spread through injection drug use, tattooing, and body piercing
1 in 4,000,000	Transmission of **Chagas Disease**. **Chagas Disease** is a parasite that can be transmitted through transfusion
1 in 4,300,000	**Human T-cell lymphotropic virus (HTLV)** transmission, per unit of component. **HTLV** is a virus that can be transmitted by exposure to blood or sexual contact, and can cause a form of cancer of the blood
1 in 7,800,000	**Human Immunodeficiency Virus (HIV)** transmission, per unit of component. **HIV** is the virus that causes AIDS. HIV attacks the immune system

Frequency of Non-Transfusion Associated Risks for Comparison with Risks of complications of Blood Transfusion

Hazard	Probability
1 in 10 [48]	Dying from lung cancer after smoking 1 pack a day for 30 years
1 in 60 [49]	Stroke within 30 days of cardiac surgery
1 in 100 [50]	Death associated with hip replacement surgery
1 in 10,000 [51]	Annual risk of death in a motor vehicle crash
1 in 60,000 [51]	Annual risk of being murdered in Canada
1 in 200,000 [52]	Death from anesthesia in fit patients
1 in 300,000 [53]	Death from oral contraceptives age < 20 years
1 in 1,000,000 [51]	Annual risk of death from accidental electrocution in Canada
1 in 5,000,000 [51]	Annual risk of death from being struck by lightening in Canada

Ⓐ Reporting

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

ATTENTION

Report all transfusion reactions to your hospital's transfusion service.

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*. In Québec, the hospital's transfusion service reports all transfusion reactions to Québec Hemovigilance System which then reports to TTISS.
- Reactions relating to the quality of the product must be reported directly to CBS/HQ.

How

- CBS/HQ 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/HQ and Public Health Agency of Canada
  - In Québec, the transfusion service reports all transfusion reactions to the Québec Hemovigilance System which then reports to TTISS (Transfusion Transmitted Injuries Surveillance System)

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

Ⓑ Reaction by Symptom

Fever

MANAGEMENT ALGORITHM

Fever (and/or Chills/Rigors)

> 1°C increase in temperature
AND temperature > 38°C during or up to 4 hours post infusion

↓

Immediate Management:

1. Stop transfusion & maintain IV access
2. Take patient's vital signs
3. Re-check identification of patient & blood product
4. Physician assessment required
5. Notify hospital transfusion service (blood bank), even if transfusion restarted or completed

↓

Clerical error or serious symptoms?

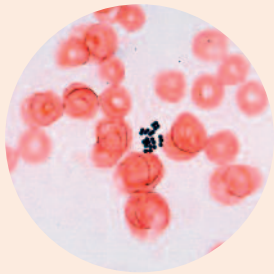
Temperature ≥ 39°C, hypotension/shock, tachycardia, rigors/chills, anxiety, dyspnea, back/chest pain, hemoglobinuria/oliguria, bleeding from IV sites, nausea/vomiting

No	Yes
↓	↓
Administer acetaminophen 325 mg	**DO NOT RESTART TRANSFUSION**
↓	↓
Continue transfusion **cautiously** under observation; likely a febrile non-hemolytic transfusion reaction	**SUSPECT** **1. Hemolytic transfusion reaction;** **OR** **2. Bacterial contamination** • Collect blood bank samples to re-check ABO-group • Clamp tubing, send unit to hospital blood bank along with attached IV solutions for bacterial cultures and gram stain • Send first post-transfusion urine sample • Send blood cultures on patient taken from a different IV site
↓	
Stop the transfusion if patient develops any of the above symptoms	

BACTERIAL SEPSIS OR CONTAMINATION

ETIOLOGY [54]

- 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 of the product
- Organisms
  - Serious morbidity and mortality occur most frequently with gram-negative bacteria,[55] but are also reported with gram-positive skin bacteria
  - A number of bacteria have been implicated, including:[54,56]



Direct Smear Atlas: A CD-ROM of Gram-Stained Preparations of Clinical Specimens. Lippincott Williams & Wilkins.

Gram-negative	Gram-positive
• Escherichia coli • Serratia marcescens • Klebsiella pneumonia • Pseudomonas species • Yersinia enterocolitica	• Staphylococcus aureus • Staphylococcus epidermidis • Bacillus cereus

INCIDENCE [47,54,55,57,58,59]

	Bacterial Contamination	Symptomatic Septic Reactions	Fatal Bacterial Sepsis
Buffy coat platelet pool	1 in 1,000	1 in 10,000	1 in 60,000
1 unit of RBC	1 in 50,000	1 in 250,000	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 20-24°C for preservation of function
- These figures were established prior to measures for bacterial detection and may now be over-estimates

CLINICAL PRESENTATION

- Clinical features of transfusion-associated sepsis may include: [58,60]
  - 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 [59,60]

- If transfusion-transmitted bacterial infection is suspected:
  - **Stop the transfusion!**
  - **Notify the hospital transfusion service (blood bank)**
    - 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 (clamped) for culture and gram stain to the hospital transfusion service**
  - **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

ATTENTION

Stop transfusion immediately if bacterial infection is suspected.

ATTENTION

Arrange for Gram stain on unit(s) suspected of being contaminated.

ATTENTION

Start antibiotic therapy immediately, do not wait for results of blood cultures.

PREVENTION

- The skin is disinfected at the donation site to reduce bacterial contamination by skin flora.
- 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).
- Apheresis and buffy coat platelets are cultured by CBS/HQ prior to issue to hospitals.
- RBCs are stored at 1-6°C in a monitored blood bank refrigerator.

ATTENTION

Keep RBCs in fridge or cooler until immediately prior to transfusion!

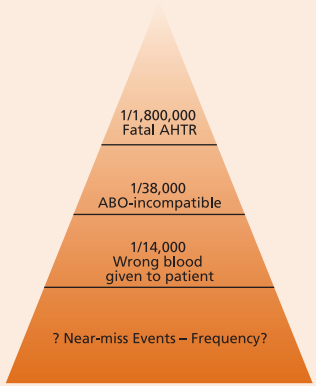
ACUTE HEMOLYTIC TRANSFUSION REACTION

ETIOLOGY

- Acute hemolytic transfusion reactions may be associated with:
  - ABO-incompatibility
  - Other blood group incompatibilities
    - There are 29 blood group systems (in addition to ABO) that may cause incompatibility
  - Rare cases when group O platelets with high titers of anti-A and/or anti-B are transfused to a non-group O recipient[61]
- **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[62]
  - 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 due to limitations of the laboratory assay
    - Uncrossmatched blood transfused to a patient who is alloimmunized

INCIDENCE

- 1 in 38,000 red cell transfusions are ABO-incompatible due to transfusing the wrong blood to a patient.[62]
- Less than 10% of ABO-incompatible transfusions result in a fatal outcome.[62]
- Over 50% of patients have no morbidity from an ABO-incompatible transfusion.



- Risk of death correlates with the amount of incompatible blood transfused.[63]

CLINICAL PRESENTATION[64]

- Most common clinical presentation is:
  - **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 a clerical error. Check identity of patient vs. patient identity on blood product label.
- Notify hospital transfusion service (blood bank).
- Send samples to hospital transfusion service to re-check ABO-group.
- Return residual of blood product(s) and tubing (clamped) to the hospital transfusion service.
- Send first post-transfusion urine sample.
- Provide supportive care.
  - Maintain good urine output
  - Manage DIC and hemorrhage as clinically indicated

ATTENTION

Stop transfusion immediately if acute hemolytic reaction suspected.

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 is incorrect (armband errors do occur)

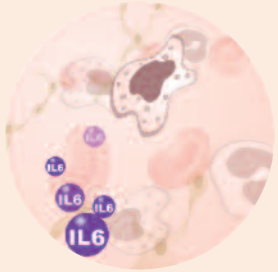
ATTENTION

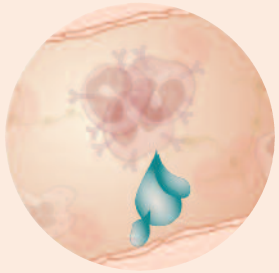
Check the blood product label with the patient's arm band identification, NOT with a hospital card or chart.

FEBRILE NON-HEMOLYTIC TRANSFUSION REACTION (FNHTR)

ETIOLOGY

- Attributable to:[65]
  - 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 [66]

	Incidence
RBC	1 in 300
Platelet pool	1 in 20

CLINICAL PRESENTATION

- Fever usually occurs during or up to 4 hours post transfusion.
  - May be associated with chills, rigors, nausea, vomiting and hypotension
- Fever is not always present (i.e., chills, nausea, etc., alone).

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 definitively been shown to be effective in preventing FNHTR.[67,68]
- In patients with significant and recurrent FNHTR, the following measures have been used but efficacy is unproven:
  - Acetaminophen, corticosteroids, fresh components, plasma-depleted components, washed red blood cells (washing platelets results in 50% loss of platelets)
- 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. Physician assessment required
5. Notify hospital transfusion service (blood bank)
6. Return clamped blood unit with tubing attached

↓

Consider:

- **TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**
- **TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)**
- **ANAPHYLAXIS**
- If TRALI is suspected, notify hospital transfusion service (blood bank) so that special donor and recipient testing can be performed
- Order STAT chest X-ray
- Oxygen, diuresis, and supportive care as required

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)[69,70]

DEFINITION OF ACUTE LUNG INJURY (ALI)

- Acute onset.
- Hypoxemia:
  - PaO_2 / FiO_2 < 300 mmHg; OR
  - Oxygen saturation is < 90% on room air; OR
  - Other clinical evidence
- Bilateral lung infiltrates on the chest radiograph.
- No evidence of circulatory overload.

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 (see orange box to the right)

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 (see orange box to the right)

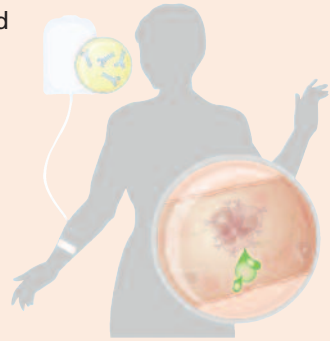
RISK FACTORS FOR ACUTE LUNG INJURY

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

ETIOLOGY

- Presently not fully defined. Two postulated mechanisms have been implicated:[70,71]
  1. Antibody-mediated: 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 80% of cases).[72,73]
     - Antibodies are most common in multiparous female donors as a consequence of prior pregnancies
  2. Neutrophil priming hypothesis: Biologic response modifiers such as biologically active lipids in the transfused component may induce TRALI in a susceptible patient.[74]



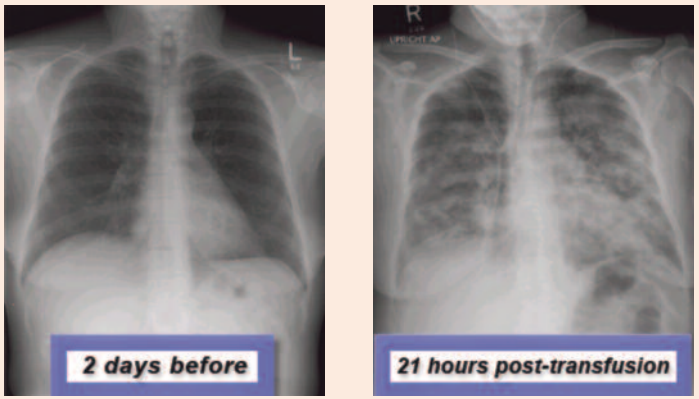
INCIDENCE

- 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.[72,75] (Both studies were performed before TRALI reduction measures.)
- The incidence of TRALI may be decreasing with implementation of TRALI reduction measures with SHOT reporting 50% reduction in cases (see Prevention).[44]
- 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.[72]
- 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.[72]
  - TRALI is currently thought to be the most common cause of transfusion-associated fatalities[44,56]
- Milder forms of TRALI are thought to exist and may present as transient hypoxia.[76]
- Acute transient leukopenia may be observed after a TRALI reaction.[77]

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.[78]
- 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 CBS).

PREVENTION

- Adherence to evidence-based transfusion guidelines.
- Component strategies to reduce TRALI include:
  - Plasma for transfusion predominantly from male donors
  - Buffy coat platelet pools suspended in male plasma
  - Plateletpheresis collected from male donors or never pregnant females
- Deferral of donors confirmed to be implicated in an episode of TRALI, and with either antibodies or implicated in multiple episodes.

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO) [79]

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).[80]
- Patients over 60 years of age, infants, and patients with severe euvolemic anemia (hemoglobin < 50 g/L) are particularly susceptible.

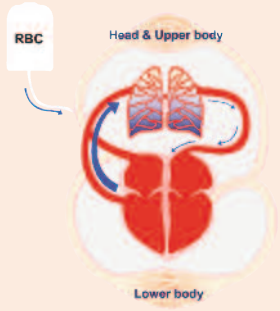
CLINICAL PRESENTATION

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

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.

Transfusion-associated circulatory overload (TACO)



ATTENTION

Interrupt transfusion.

Administer oxygen and diuretics if required.

Consider restarting transfusion at reduced rate.

PREVENTION

- Pre-transfusion assessment is important to identify patients at risk and management should be adjusted accordingly.
- Preventative measures include:
  - Avoid transfusing more than one unit at a time
  - 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

ATTENTION

In patients at risk, avoid transfusing more than one unit at a time.

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. Physician assessment required
5. Notify hospital transfusion service (blood bank) 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 body

No	Yes
↓	↓
Consistent with minor allergic reaction	**DO NOT RESTART TRANSFUSION** • Notify the patient's physician **STAT** • Notify the hospital transfusion service (blood bank) immediately
↓	↓
Give diphenhydramine 25-50 mg IV/po	**SUSPECT ANAPHYLACTIC REACTION OR SEVERE ALLERGIC REACTION**
↓	
Continue transfusion cautiously	
↓	
Stop transfusion if patient develops any of the above symptoms	

ANAPHYLAXIS

ETIOLOGY[81]

- 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, α-1-antitrypsin, transferrin, C3, C4, etc.)
  - Transfusing an allergen to a sensitized patient (e.g., penicillin, ASA, etc. consumed by donor)
  - Passive transfer of IgE (to drugs, food)
- 1 in 500 blood donors are IgA deficient (IgA < 0.05 mg/dL), and 1 in 1,500 blood donors have anti-IgA, but most are NOT at risk of an anaphylactic transfusion reaction (reasons are not clear at this time).[82]
- Haptoglobin deficiency is not uncommon in Asian patients (1 in 1,000) and has been associated with anaphylactic reactions.[83]

INCIDENCE

- Transfusion-associated anaphylactic shock is rare.[84]
- Anaphylaxis accounts for approximately 3% of transfusion associated fatalities.[56]

CLINICAL PRESENTATION [81]

- 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 impending doom), hypotension, gastrointestinal symptoms (nausea, vomiting), rarely death.
- Potentially life-threatening.

TREATMENT

- **Stop the transfusion! Do not restart.**
- If severe urticarial reaction involving > 2/3 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.

ATTENTION

Stop the transfusion if patient has anaphylactic reaction. Do not restart.

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:
  - IgA-deficient blood products from IgA deficient donors, available from CBS/HQ
  - Washed RBCs (2L normal saline in 6 wash cycles) or platelets [81,85]

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.[86]

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 of the body surface area; and,
  2. There are no associated symptoms suggesting a severe allergic reaction.

ATTENTION

Interrupt transfusion.
Give diphenhydramine.
Restart transfusion slowly.

PREVENTION

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

Hypotension[87]

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
4. Physician assessment required

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
6. Anaphylaxis

No
unrelated to transfusion

Possibly resume transfusion after reassessing

Yes

Do not restart transfusion. Refer to appropriate sections.

** Definition refers to adult patients only*

BRADYKININ MEDIATED HYPOTENSION

ETIOLOGY

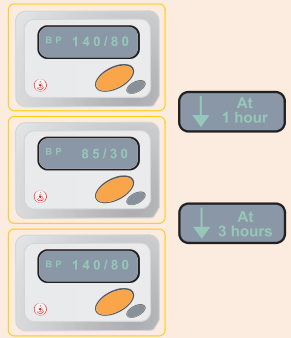
- Bradykinin is believed to play a major role in generating hypotension.
- Angiotensin-converting enzyme is the main enzyme responsible for degradation of bradykinin.
  - Some individuals have a genetic polymorphism resulting in a decrease in bradykinin degradation

INCIDENCE

- Unknown.

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.
- 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 re-start.
- Provide supportive care, including intravenous fluids.
- Consider acute hemolytic transfusion reaction, sepsis, TRALI and allergic reactions in the differential diagnosis.

ATTENTION

Monitor patient for first 15 minutes and vital signs at 15 minutes.

Stop transfusion if hypotension develops.

PREVENTION

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

Hemolysis after Transfusion

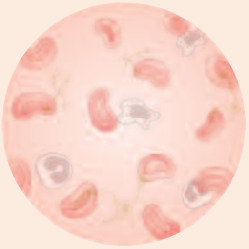
HEMOLYSIS NOT RELATED TO RBC ALLOANTIBODIES

- Hemolysis may also occur in the following settings and should be considered in the differential diagnosis of hemolysis after transfusion:
  - Use of hypotonic IV solutions with RBC transfusions
  - Medical device-related (e.g., cell saver or blood warmer malfunction)
  - Overheating of RBCs due to improper storage (e.g., RBCs 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
  - Non-transfusion-related causes
- Most are benign, but life-threatening hemolysis with severe anemia and renal failure may occur.

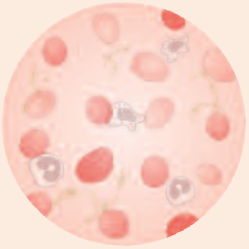
DELAYED HEMOLYTIC TRANSFUSION REACTIONS

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.[88]
- 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.[88]

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).[89]

COMPLICATIONS

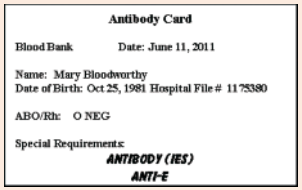
- Most are benign, but life-threatening hemolysis with severe anemia and renal failure may occur.

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.
- Notify patient and provide an antibody card for the patient to carry in their wallet.



Antibody Card

Blood Bank Date: June 11, 2011

Name: Mary Bloodworthy
Date of Birth: Oct 25, 1981 Hospital File # 1175380

ABO/Rh: O NEG

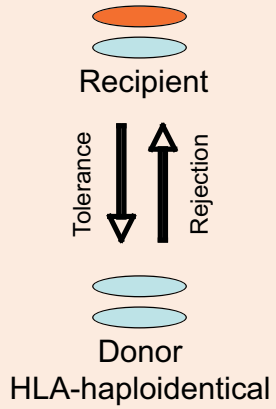
Special Requirements:
ANTIBODY (IES)
ANTI-E

Cytopenias after Transfusion

TRANSFUSION-ASSOCIATED GRAFT VS HOST DISEASE (TA-GvHD)[90,91]

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).[92]
  - 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 non-matching HLA determinants on the recipient's cells



INCIDENCE

- Unknown; there were 13 cases reported in the UK SHOT program from 1996 to 2001 with no further reports up to 2009.[44]

CLINICAL PRESENTATION

- Fever, rash, liver dysfunction, and diarrhea commencing 1-2 weeks post-transfusion followed by pancytopenia later.
- Overwhelming infections are the most common cause of death.
- Mortality is > 90%.
- Diagnosis can be made by biopsy of skin, liver, or bone marrow.
- Confirmation requires documentation of the presence of donor lymphocytes (e.g., HLA typing, short tandem repeat analysis).

TREATMENT

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

PREVENTION

- For patients at risk (see below), it is critical to irradiate cellular blood components (RBC and platelets).

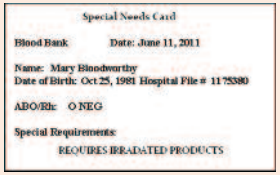
PATIENTS REQUIRING IRRADIATED BLOOD[93]

- Patients with congenital immunodeficiency states
- Intrauterine transfusions
- Neonatal exchange transfusions
- Patients with lymphoproliferative diseases
- Patients undergoing bone marrow or stem cell transplants
- Recipients of directed transfusions from family members
- Recipients of HLA-matched platelets
- Patients treated with purine analogs (e.g., fludarabine), purine antagonists (e.g., bendamustine), alemtuzumab and anti-thymocyte globulin

ATTENTION

Immunocompromised patients must receive irradiated blood.

- Notify patient in need of irradiated blood and provide a card for the patient to carry in their wallet.


Special Needs Card

Blood Bank Date: June 11, 2011

Name: Mary Bloodworthy
Date of Birth: Oct 25, 1981 Hospital File # 1175380

ABO/Rh: O NEG

Special Requirements:
REQUIRES IRRADIATED PRODUCTS

POST-TRANSFUSION PURPURA (PTP)[94]

ETIOLOGY

- Transfusion of platelet antigen-positive RBCs, plasma, or platelets to a patient who lacks 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; more than 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 a previous pregnancy.
- Occurs post-transfusion at a mean 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/HQ).
- 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).

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

ATTENTION

Patients affected by PTP, are at risk of NAIT.

TRANSFUSION-RELATED ALLOIMMUNE THROMBOCYTOPENIA

- Uncommon cause of thrombocytopenia.
- Due to platelet specific donor alloantibodies to patient platelet antigens.[95]

TRANSFUSION-RELATED ALLOIMMUNE NEUTROPENIA[96]

- Rare cause of neutropenia.

Virus, Parasite and Prion Infections

(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.
- Current 'window period' estimates are:[97]
  - 10 days for HIV
  - 8 days for HCV
  - 38 days for HBV
- **Figures in chart below are risk per donor exposure: (i.e. 1 unit of RBC)**

HIV Virus

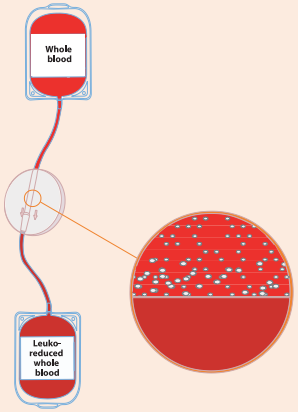
HIV	1 in 7.8 million[97]
Hepatitis C virus (HCV)	1 in 2.3 million[97]
Hepatitis B virus (HBV)	1 in 153,000[97]
Human T-cell lymphotropic virus	1 in 4.3 million[97]
West Nile Virus (WNV)	< 1 in 1 million[98]

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

Virus	Outcome
HIV	Chronic infection with progressive loss of CD4+ lymphocytes leading to opportunistic infections, immune system dysfunction, and direct viral effects on multiple organ systems.[99]
HCV	80% of recipients develop chronic HCV. 30% develop severe progressive hepatitis with long-term consequences of cirrhosis and risk of hepatocellular carcinoma.[100]
HBV	The vast majority of cases resolve by developing immunity. In less than 5% of cases, chronic infection occurs with the likelihood of chronic liver disease. Rarely, HBV presents as acute fulminant hepatitis.[100]
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.[99]

Cytomegalovirus (CMV):[101,102,103]

- 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/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.[104]
- The incremental benefit of providing CMV-seronegative components, in addition to leukoreduction, in the prevention of CMV transmission is unknown.

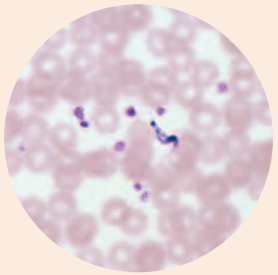


West Nile Virus (WNV)

- No reported cases of transfusion transmitted WNV in Canada since nucleic acid testing of donations began in 2003.[105]
- Since 2003 in the USA, there have been 9 confirmed cases of transfusion-transmitted WNV.[106,107]
- Facts about transfusion-transmitted WNV:
  - 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, post-partum and post-operative patients have been affected

PARASITES

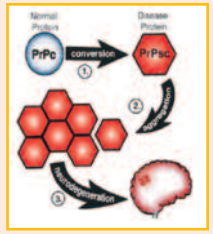
Chagas Disease



- Chagas Disease is caused by the protozoan Trypanosoma cruzi found predominantly in Central and South America.
- Acute infection is often unrecognized but if untreated, can lead to chronic infection including cardiac involvement in 30%.
- The protozoan is transmitted through contact with feces of an infected triatomine bug but can also be transmitted from mother to child or through transfusion or transplantation.
- There have been 7 reported cases of transfusion transmitted Chagas in US and Canada, mostly with platelet products.[108]
- Since May 2010, at risk donors in Canada are tested for Chagas disease.
- The current risk of transfusion-transmission is estimated to be 1 in 4 million, based on U.S. data.[109]

PRIONS

Variant Creutzfeldt-Jakob Disease (vCJD)



Public Health Agency of Canada

- 4 suspected cases of transfusion-associated transmission have been reported in the U.K.[110]
- 1 suspected case of transmission from U.K.-derived Factor VIII concentrate.[111]
- At present, high risk blood donors (resident in the UK or France for more than 3 months, or Saudi Arabia for more than 6 months between 1980-1996, or in Europe for more than 5 years since 1980) are deferred in Canada.

OTHER TRANSFUSION-TRANSMISSIBLE AGENTS [107,108,112]

- Other rare infectious agents confirmed to be transmitted by blood components that may cause symptomatic infection include:
  - **Viral** – Parvovirus B19, Hepatitis A, Dengue, Chikungunya, Tick-borne encephalitis, Colorado Tick Fever, Human Herpes Virus 8, SEN virus and Simian foamy virus
  - **Protozoal** – Malaria, Babesiosis, Leishmaniasis, Toxoplasmosis
  - **Helminthic** – Filariasis
  - **Spirochetal** – *Treponema pallidum* (Syphilis)
  - **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 virus, Simian foamy virus and XMRV.

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.[113]

Complications[114]

- 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.[115]
- Number of RBCs transfused does not accurately predict the need for platelet and FP transfusion; frequent laboratory measurements are required to guide transfusion decisions.
- Although formula replacement of blood components is not recommended, it may be required when coagulation tests are not rapidly available.[116]

ATTENTION

Use laboratory monitoring where possible to guide the use of blood components.

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):[117]
  - < 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.[117]
- Consequences of hypothermia:
  - Platelet dysfunction
  - Decreased coagulation factor activity
  - Reduced clearance of citrate
  - Decreased cardiac output
  - Hypotension
  - Arrhythmias (especially if cold blood is transfused rapidly through a central line)

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 and 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

4. Metabolic acidosis

- Rare; from acid pH of blood products.
- Usually, metabolic alkalosis occurs due to bicarbonate production from citrate metabolism.
- May be an indicator of lactic acidosis in patients with tissue hypoperfusion.

5. Hyperkalemia[118]

- Release of potassium from stored RBCs increases with storage time and after irradiation.
- Potassium concentration in a SAGM-RBC unit is approximated by the number of days of storage (110 mL of supernatant/unit).
  - For example, a 42 day old RBC has a potassium concentration of approximately 45 mmol/L[119]
- Order bloodwork q1h (e.g., CBC, INR, PTT, fibrinogen, calcium, arterial blood gas, potassium).

Note: For discussion of the changes in electrolytes and acid-base balance with massive transfusion, see Wilson et al.[120]

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 > 50 x 10^9/L (with head injury > 100 x 10^9/L)
    - INR < 1.5
    - Fibrinogen > 1.0 g/L
- **Watch for hypocalcemia, acidosis and hyperkalemia.**
- **Use SQ40 SE Pall® filter** with blood tubing to minimize the number of times the blood tubing has to be changed.
  - Change SQ40 SE filter q10 RBC units or if blocked (and change blood tubing within the number of hours specified by hospital policy)
  - Change blood tubing q2-4 RBC units if SQ40 SE not used

Blood Conservation in the Perioperative Setting

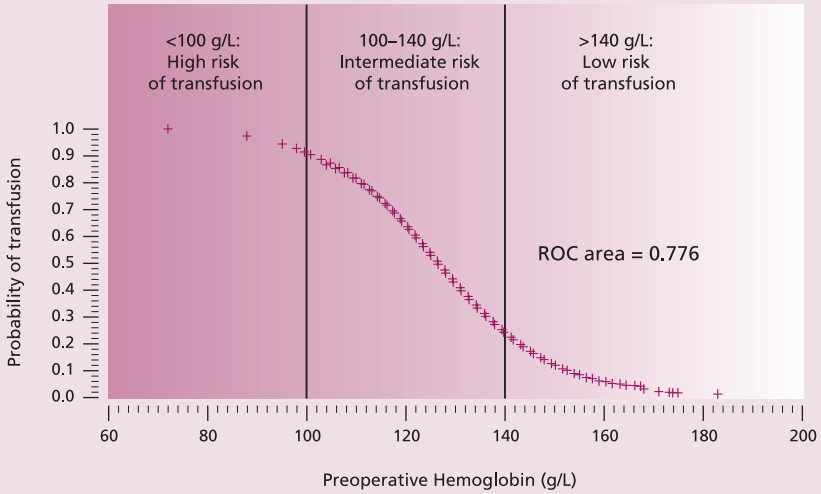
- There are currently several perioperative blood conservation strategies available to patients.
- Patients that are at high risk of perioperative transfusions (> 10% chance of allogeneic RBC transfusion) should be identified as early as possible, preferably at least 28 days before surgery, to allow institution of appropriate blood conservation modalities.
  - As transfusion risk varies from institution to institution and surgeon to surgeon for the same procedure, each institution must determine its own requirements for transfusion

ATTENTION

Offer patients blood conservation strategies if they have a > 10% chance of blood exposure.

Likelihood of Transfusion

- The likelihood of transfusion is proportional to the preoperative hemoglobin level of the patient.
  - Shown here is the probability of transfusion for patients undergoing cardiac surgery[121]



Blood Conservation Strategies

The following blood conservation strategies are available, listed according to when they should be implemented perioperatively:

Time until Surgery	Blood Conservation Strategies Available	Page
> 35 days	Investigate and treat anemia	–
	Delay surgery until anemia corrected	–
	Iron	78
14-35 days	Delay surgery until anemia corrected	–
	Autologous blood donation	80
	Erythropoietin weekly dosing regimen	86
	Iron	78
10-13 days	Delay surgery until anemia corrected	–
	Erythropoietin daily dosing regimen	86
	Iron	78
< 10 days before surgery	Delay surgery until anemia corrected	–
Intraoperative	Attention to surgical hemostasis	76
	Antifibrinolytics and DDAVP	88, 90
	Intraoperative cell salvage	84
	Regional anesthesia	90
	Topical hemostatic agents (e.g., fibrin sealants)	90
	Other measures, mainly investigational	91
	Adherence to strict transfusion guidelines	20

1. GOOD SURGICAL TECHNIQUE

- Using good surgical technique(s) is critically important in reducing a patient's exposure to allogeneic blood.

Recommended surgical practices

- The following **good surgical practices** are highly recommended:
  - Assess and treat nutritional status preoperatively
  - Careful ligation of blood vessels
  - Avoid tissue trauma
  - Optimal use of electrocautery
  - Meticulous attention to surgical hemostasis
  - Utilize avascular tissue planes
  - Appropriate use of topical hemostatic agents
  - Prevent and treat coagulopathy associated with massive transfusion

Consider stopping anti-platelet and anticoagulants before major surgery

- **Acetylsalicylic Acid (Aspirin®) and Clopidogrel (Plavix™)**[122]
  - Primary prevention: 48 hours minimum, 7-10 days preferable
  - Secondary prevention (after remote MI, stroke, peripheral artery disease)
    - low risk of bleeding procedure (e.g., cataract surgery, plastic surgery): no need to stop ASA or clopidogrel
    - high risk of bleeding procedure (e.g., neurosurgical procedure): 48 hours minimum, 7-10 days preferable
  - Secondary prevention (high risk for arterial thrombosis – recent percutaneous coronary intervention, MI, stroke OR coronary stent < 12 months)
    - consult patient's cardiologist or neurologist for expert advice
    - only stop ASA and clopidogrel if risk of bleeding exceeds risk of cardiovascular complications

ATTENTION

Do not stop ASA or clopidogrel without consultation of patient's cardiologist or neurologist, if:

- recent thrombosis (MI, stroke)
- recent percutaneous coronary intervention (PCI)
- coronary stent in last 12 months

- **Dabigatran (Pradax™)**
  - Consider stopping therapy 2-4 days before major surgery in patients with normal renal function
  - In patients with renal dysfunction (creatinine clearance < 50 mL/min) consider stopping 4-5 days before major surgery
- **Rivaroxaban (Xarelto®)**
  - Consider stopping therapy 2-3 days before major surgery in patients with normal renal function
  - In patients with renal dysfunction (creatinine clearance < 50 mL/min) consider stopping 3-4 days before major surgery
- **NSAIDs**
  - Consider stopping therapy 4-7 days before major surgery
  - Celecoxib does not inhibit platelet aggregation at usual doses

Minimize blood sampling and loss[123]

- Restrict diagnostic phlebotomy.
- Use small volume tubes and testing methods.
- Conduct bedside microanalysis.
- Remove arterial and venous catheters when no longer necessary.

Preoperative patients on Warfarin:[124]

- If low risk of thromboembolic events (e.g., primary prophylaxis of atrial fibrillation):
  - Stop warfarin 4-5 days preoperatively; repeat INR 1 day preoperatively
  - If INR > 1.5 then give 2 mg oral vitamin K
  - Then repeat INR preoperatively
- If high risk of thromboembolic events (e.g., recent deep vein thrombosis):
  - Consider switch to unfractionated or low molecular weight heparin 4 days preoperatively; consult with hematology on timing and preferred regimen
- For urgent (< 6 hours) reversal of Vitamin K antagonist effect prior to surgery (see pages 120-121).[125]
  - Prothrombin Complex Concentrates
  - Vitamin K I.V.

2. IRON

- Very little data are available in the literature on the efficacy of iron in perioperative patients.
- There are several randomized trials of iron therapy administered perioperatively, finding that:
  - **Preoperative iron** may be helpful **for patients with low preoperative hemoglobin levels,** but not confirmed beneficial in all studies[126,127,128,129]
  - **Randomized trials failed to confirm a benefit of post-operative iron therapy in patients that were not anemic preoperatively**[130,131,132,133,134,135]

ATTENTION

Routine post-operative iron therapy in preoperatively non-anemic patients is NOT useful.

Dosage

- 150-200 mg of elemental iron/day for:
  - patients with pre-operative iron deficiency
  - Iron should be administered on an empty stomach for maximal absorption
- Vitamin C (ascorbic acid) as an adjunct to increase iron absorption is **not recommended** if the elemental iron dosage is > 60 mg.[136]

ATTENTION

Ensure anemic patient is prescribed 150-200 mg of elemental iron (e.g., ferrous fumarate 300 mg po b.i.d. OR ferrous sulfate 300 mg po t.i.d.).

Commonly Used Iron Replacement Therapies	Dose mg	Elemental mg
Ferrous gluconate	300	35
Ferrous sulfate	300	60
Ferrous fumarate (Palafer®)	300	100
Polysaccharide-iron complex (Triferex®)	150	150
Proferrin	398	11

Common Adverse Events*

- **GI upset** (diarrhea, nausea, constipation).
- **Dark stools.**

* See product monograph for details

INTRAVENOUS IRON

- There is currently insufficient evidence to support the routine use of intravenous iron in **elective surgery patients** or in conjunction with autologous blood donation.[137]
- Patients with **iron deficiency anemia** (whose surgery should not be delayed to allow for oral iron therapy to correct the anemia) may be treated with **intravenous iron,** in addition to oral iron.[138]

  Dosage
  - Check your hospital's formulary to determine the recommended type of parenteral iron (iron dextran or iron sucrose)
  - Review the risks identified in the product monograph and inform your patient about the risks
  - **Give only sufficient iron to correct the anemia (e.g., 1000 mg of elemental iron)**
  - Do not attempt to give a full replacement dose as the patient can replete their iron stores with oral iron in the post-operative period
  - If considering iron therapy, it is important to measure patients iron status to ensure iron therapy will not lead to iron overload

PREOPERATIVE AUTOLOGOUS BLOOD DONATION (PAD)

General Principles

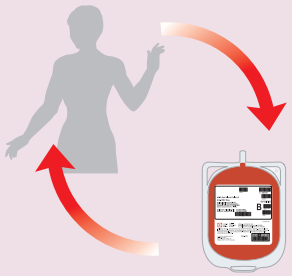
- Avoid automatically referring all patients who are having major surgery – it is over-simplistic and should be discouraged.[139]
- Autologous blood donation reduces but does not eliminate the need for allogeneic blood.[140]
  - 9% of autologous donors undergoing elective surgery receive allogeneic blood in addition to autologous blood[141]
  - Autologous blood donation reduces the chance of allogeneic transfusion (odds ratio 0.17, 95% CI 0.08-0.32), but increases the likelihood of all transfusions (autologous plus allogeneic; odds ratio 3.03, 95% CI 1.70-5.39) in randomized studies[142]
- Each institution should have a policy, based on its current blood exposure rates, to guide the use of PAD.

ODDS RATIO

The odds ratio is a way of comparing whether the probability of a certain event is the same for two groups. An odds ratio of 1 implies that the event is equally likely in the two groups. An odds ratio of less than one implies that the event (e.g., allogeneic transfusion) is less likely; conversely, an odds ratio greater than 1 implies that the event (e.g., any transfusion) is more likely.

Cost-effectiveness of Autologous Blood Donation

- Studies suggest poor cost-effectiveness[143,144] mainly because:
  - The risks of viral transmission by allogeneic blood are very low
  - The cost of autologous blood collection is higher than that for allogeneic transfusion
  - The wastage rate of autologous blood is high (30-50% of units are discarded)



Which Patients Are Eligible?

- **Patients with at least a 10% chance of blood exposure during elective surgery should be considered.** At some hospitals this may include:[145]
  - cardiac surgery[146,147]
  - major vascular surgery
  - revision hip replacement
  - major spine surgery
  - radical prostatectomy
  - hepatic resection

ATTENTION

The **same criteria** should be used for **transfusing allogeneic blood** and **autologous blood.**

Risks and Benefits of Autologous Transfusion at the Time of Collection and Transfusion

It is unclear at the present time if autologous blood transfusion is safer than allogeneic transfusion.

- **Autologous blood should only be collected from patients with a greater than 10% chance of allogeneic blood exposure**

BENEFITS[148]

1. Possibly reduces post-operative infections.
2. Reduces demand on allogeneic blood supplies.
3. Reduces transfusion-transmitted infections.
4. Avoids red cell alloimmunization.
5. Prevents some adverse transfusion reactions (febrile reactions, transfusion-related acute lung injury, allergic reactions, and delayed hemolytic transfusion reactions).

RISKS AT DONATION

1. Severe reaction at time of donation, requiring hospitalization, (loss of consciousness and cardiac ischemia) is estimated at 1 in 16,783 donations (12-fold higher risk than for volunteer donors).[149]
2. Iatrogenic anemia – average 10 g/L hemoglobin drop per unit donated.[148]
3. Unit lost, damaged, or prematurely discarded.
4. Surgery cancelled, resulting in outdated autologous unit.

RISKS AT TRANSFUSION[148]

1. Bacterial contamination.
2. ABO-incompatible transfusion (wrong blood given to the patient)
3. Transfusion-associated circulatory overload.
4. Transfusion of allogeneic blood when autologous available.

Technical Aspects

AVAILABILITY

- Autologous blood donation is available through CBS/HQ, and some hospitals.
  - Request for autologous collection form available from CBS or HQ

TIMING

- For optimal benefit, all units should be collected between **21 and 34 days prior to surgery** to allow for regenerative erythropoiesis.[150]

ATTENTION

Do not collect blood in the 2 weeks prior to surgery.

DAYS UNTIL SURGERY WHEN 1ST UNIT COLLECTED

Units of RBC regenerated after 2 units collected

STORAGE

- Current Canadian standards allow that autologous red blood cells can be **stored for 42 days as RBC (see page 10).**
  - Usually 1-3 units are collected depending on the anticipated need for transfusion
  - 250 mL frozen plasma available from CBS autologous donation (on physician's order)

ORAL IRON

- **Oral iron is recommended only for patients with reduced iron stores.**
  - In the absence of reduced iron stores neither intravenous nor oral iron enhance the success of autologous blood collection[151]

COMMON EXCLUSION CRITERIA FOR PAD

1. Recent myocardial infarction or unstable coronary syndrome (last 6 months)
2. Stenotic valvular heart disease
3. Anemia (hemoglobin level requirement is set by the blood centre or hospital policy; generally 120 g/L)
4. Bacterial infection

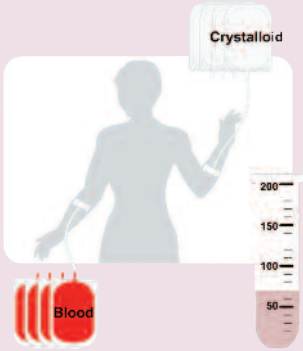
ACUTE NORMOVOLEMIC HEMODILUTION (ANH)[152]

Principles

- Very little data on the efficacy and safety of ANH and its widespread use at this time cannot be recommended.[140,153]
- Whole blood is withdrawn when anesthesia is initiated and is replaced with crystalloid/colloid to maintain normovolemia.
- The blood is stored at room temperature (RT) in the operating room (on a continuous rocker; stored at RT for 8 hours) and re-transfused after bleeding ceases or if the patient has an unacceptably low hemoglobin level.

Indication

- It is uncertain which patient populations would best benefit from the use of ANH.
  - ANH may be useful in patients with excellent physical health (ASA I) undergoing major surgery with predicted large intraoperative blood loss
  - ANH may be an acceptable alternative for some Jehovah's Witnesses



Efficacy and Safety of ANH

- **The medical literature is controversial on the efficacy and safety of ANH.**

EFFICACY

- A meta-analysis of 42 trials including a total of 2,233 patients found that acute normovolemic hemodilution (ANH):[153]
  - did not affect the likelihood of receiving allogeneic transfusion
  - produced a small reduction in perioperative blood loss and volume of allogeneic blood transfused
- Theoretically, ANH is only of value if at least 4 units of whole blood are removed by a trained physician and total blood loss expected is > 3 L, given that the patient has:
  - a high starting hemoglobin (> 130 g/L)
  - no renal insufficiency
  - no history of cardiovascular disease
    Note: Risk of transfusion-associated circulatory overload at time of re-infusion.
  - no history of cerebrovascular disease

SAFETY

- The safety of the procedure is not proven[153]

Recommendation

- **ANH should NOT be encouraged outside of a clinical trial setting.**

INTRAOPERATIVE CELL SALVAGE[154]

Principles

- A patient's own blood shed at the time of an operation is collected in such a way that it can be re-infused into the patient (auto-transfusion).
- Up to 80% of red cells can be recovered.[155]

Indication

- Meta-analysis of 75 studies:[156]
  - Cell salvage in orthopedic surgery (all types of salvage devices, washed and unwashed)
    - Relative risk of transfusion 0.46 (95% CI 0.37-0.57)
  - Cell salvage in cardiac surgery (unwashed only)
    - Relative risk of transfusion 0.77 (95% CI 0.69-0.86)
  - No increase in adverse events in the treatment group
  - Consider in the setting of: trauma, hepatic resection, major orthopedic and spine surgery, or ruptured aneurysm with appropriate quality assurance
  - Meta-analysis of 31 randomized controlled trials, including 2282 patients, in the setting of cardiac surgery found that cell salvage decreased the risk of allogeneic blood exposure (OR 0.63, 95% CI 0.43-0.94, P=0.02)[157]
  - May be an acceptable alternative for some Jehovah's Witnesses (see Appendix B, pg. 137)

Complications

- Complications include:
  - **Air embolism – ensure air is removed prior to re-infusion**
  - Thrombocytopenia and dilutional coagulopathy
  - Bacterial contamination (rare)
  - Tumour dissemination in cancer surgery
  - Hemoglobinemia – ensure correct wash fluids are used and a formal maintenance program is performed on equipment

ATTENTION

Air embolism is a risk of intraoperative cell salvage.

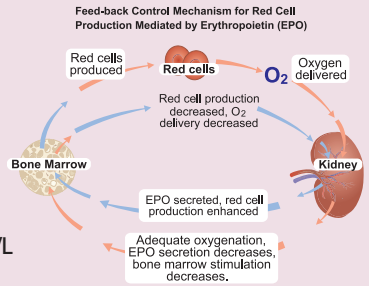
Contraindications

- Malignant cells in operative field.
- Bacterially-contaminated operative fluid, ascitic fluid, or amniotic fluid in operative field.
- Use of hypotonic solutions in the operative field.
- Use of topical thrombogenic agents in the operative field.

ERYTHROPOIETIN IN ELECTIVE SURGERY

Principles

- Erythropoietin stimulates erythropoesis and is produced in response to hypoxia by the renal cortex. Regulation is by classical negative feedback inhibition.
- Erythropoietin is administered prior to elective surgery to increase hemoglobin and thereby reduce the rate of allogeneic transfusion.[158]
  - Expected rise in hemoglobin is 10-20 g/L
- Erythropoietin can be administered to enhance the collection of autologous blood (PAD).[159,160]
  - Combined use only recommended for patients with very high likelihood of allogeneic blood exposure and high expected blood loss (e.g., major spine surgery)



Eligibility

- Patients with a **hemoglobin < 130 g/L** and a probability of requiring a blood transfusion of 10% or greater.[158,161,162]

Dosage

- Preferred dose: 600 U/kg sc qwk for up to 4 doses commencing 28 days before surgery.[163,164,165]
  - **e.g., 30,000 or 40,000 U sc qwk x 4 weeks, start 28 days pre-op**
- Alternative dose: 300 U/kg sc qd x 15 days commencing 10 days preoperative.[166]
  - **e.g., 20,000 U sc qd x 15 days, start day 10 pre-op**
- Supplemental iron advised.[160,167]

Contraindications (in elective surgery patients)

- Uncontrolled hypertension.
- Hypersensitivity to mammalian-derived cell products, albumin, or other components of the product.
- Contraindicated in patients scheduled for elective surgery not undergoing PAD with severe coronary, peripheral artery, carotid, or cerebrovascular disease, including recent MI or stroke.

For more details, refer to product monograph.

Adverse Effects

- Safety of short-term use before surgery has not been thoroughly studied.
  - A recent study found an increased risk of thrombosis in patients undergoing elective spine surgery.[168]

For more details, refer to product monograph.

ANTIFIBRINOLYTICS

General Principles[169,170]

- Antifibrinolytics are administered to prevent/treat increased fibrinolysis during surgery, particularly cardiac surgery.
- There are two types of antifibrinolytics:
  1. Aprotinin – a proteinase inhibitor derived from bovine lung that inhibits plasmin
     - Currently under a marketing suspension due to safety concerns that are being reviewed by Health Canada
  2. Tranexamic acid and aminocaproic acid – inhibitors of plasminogen

Indications

1. Antifibrinolytics in Cardiac Surgery

- Prophylactic administration is preferred rather than at time of marked hemorrhage.
- Tranexamic acid is less potent but has a better safety profile than aprotinin.[169,170]
- Neither drug has shown to reduce adverse event rates outside of bleeding and transfusions.
- As in other drugs, use only when potential benefits outweigh risks.

Dosage in Cardiac Surgery

Tranexamic acid	20-100 mg/kg ± 2-4 mg/kg/hr for duration of surgery[171]

2. Antifibrinolytics in Non-cardiac Surgery[170]

- Used in orthopedic surgery, trauma, and hepatic surgery.
- Preliminary evidence suggests that antifibrinolytics reduce allogeneic blood exposure, but safety has not been fully assessed.
  - The most recent meta-analysis included 252 RCTs that recruited over 25,000 participants
  - In the **tranexamic acid trials**, there was a significant reduction in allogeneic transfusion (RR 0.61, 95% CI 0.53-0.70)
- The CRASH-2 study, which included over 20,000 patients (most from developing countries), provides strong evidence of benefit for low dose tranexamic acid in patients with traumatic hemorrhage (dose used: 1 g loading over 10 minutes, then infusion of 1 g over 8 hours).[172]

Adverse Effects

- Aprotinin: **hypersensitivity reactions.**
  - Reactions vary from skin flushing to severe circulatory depression; higher risk on second exposure[173]
  - May increase possibility of renal dysfunction in cardiac patients with, or at risk for, renal disease
  - May increase mortality[169]
- Tranexamic acid: GI upset, seizures.
  - Data from meta-analyses do not suggest an increased risk of thrombosis[170]

Contraindications[174]

- Tranexamic acid – patients at elevated risk of thrombosis, pregnancy, hematuria; dose adjustment required in renal failure.

Refer to product monograph for more details.

ATTENTION

Use antifibrinolytics with caution in patients with urinary tract bleeding! (Clot may cause ureteric obstruction).

DDAVP

- There is no convincing evidence that DDAVP minimizes perioperative allogeneic RBC transfusion in patients who do not have congenital bleeding disorders and its routine use is not recommended.[175,176,177]
- There is preliminary evidence that its use may be beneficial in some patients with acquired bleeding disorders as diagnosed by new point-of-care platelet function devices.[177]

ATTENTION

DDAVP is not indicated as a routine practice in the prevention or treatment of bleeding after cardiac surgery.

REGIONAL ANESTHESIA

- One systematic review of literature found that the use of **neuroaxial blockage with epidural or spinal anesthesia** reduced the risk of:[178]
  - transfusion
    - risk of transfusion was reduced by 50%
  - venous thromboembolism
  - pneumonia and respiratory depression

TOPICAL AGENTS[179]

- Fibrin sealants
  - Mixture of fibrinogen, thrombin, calcium chloride and anti-fibrinolytic agent (e.g., Tisseel)[180]
  - Meta-analysis of 18 trials indicates effectiveness in reducing peri-operative allogeneic blood transfusion (RR 0.63 95% CI 0.45-0.88)[181]
- Topical thrombin
  - Bovine thrombin products may induce immune response
  - Recombinant human thrombin available (e.g., Recothrom®)[182]
  - No data on effectiveness in reducing peri-operative allogeneic blood transfusion.

OTHER BLOOD CONSERVATION STRATEGIES UNDER CLINICAL INVESTIGATION

The following blood conservation strategies are under investigation.

- **There are insufficient data to support the routine use of these interventions at the current time**:
  - Blood substitutes (hemoglobin-based oxygen carriers, human and bovine)

    Note: At the present time there are no blood substitutes licensed for clinical use in Canada.
  - Recombinant factor VIIa
    - The effectiveness of rVIIa as a general hemostatic drug, either prophylaxically or therapeutically, remains unclear[183]
  - Hypervolemic hemodilution
  - Controlled hypotension

General Principles[184,185]

- Erythropoietin (EPO) is synthesized by DNA technology:
  - Some formulations are stabilized with human albumin
  - Formulations without human albumin are preferred for Jehovah's Witness patients
- Requires readily available iron for full efficacy.
- Takes time to increase hemoglobin (weeks).
- Erythropoietin response to anemia may be blunted in the presence of malignancy, chemotherapy, HIV infection, and chronic inflammatory diseases.

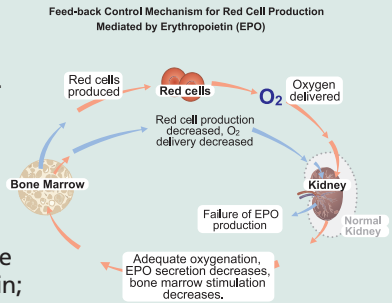
Contraindications[186,187]

- Uncontrolled hypertension.
- Hypersensitivity to mammalian-derived cell products, albumin, or other components of the product.
- Who for any reason cannot receive adequate antithrombotic treatment.
- Patients scheduled for elective surgery not undergoing PAD, with severe coronary, peripheral artery, carotid, or cerebrovascular disease, including recent MI or stroke.

Refer to product monograph for more details.

Indications

- Chronic renal failure.
- Anemia associated with malignancy.
- HIV infection.



CHRONIC RENAL FAILURE (CRF)[188,189]

Rationale

- Patients with end-stage renal disease are unable to produce erythropoietin; it is administered as a replacement therapy.

Eligibility

- Patients with clinically and biochemically established CRF with a hemoglobin < 90-110 g/L should be considered.[190,191]
- Usually erythropoietin is considered when the creatinine clearance is < 30 mL/min/1.73 m^2.
- Other causes of anemia must be excluded or successfully treated:
  - Initial laboratory work up should include a CBC, reticulocyte count, serum ferritin, and transferrin saturation

Target therapeutic outcome

- To maintain the hemoglobin in the range of 100 to120 g/L.[187,192,193]

Iron[194]

- Assess iron status every 3 months.
- Sufficient iron should be administered to maintain the serum ferritin > 100 ug/L (not on hemodialysis) or > 200 ug/L (on hemodialysis) AND iron saturation > 20%.
- Intravenous iron is frequently utilized for patients who fail oral iron.
- Intravenous or oral iron is acceptable for CRF patients not on hemodialysis.
- Patients should be monitored to prevent iron overload.
- Stop iron if ferritin > 500 ug/L.

Refer to intravenous iron product monographs for more details.

Dosage

- Starting dose: Epoetin alfa[187] (Eprex®) 300 u/kg subcutaneously (sc) per week or darbepoietin[194] (Aranesp™) 0.45 ug/kg sc per week.
- Maintenance dose: adjust dose to maintain a hemoglobin level of 100 to 120 g/L.
  - Adjust dose per product monograph to avoid major fluctuations in hemoglobin level
- Where inadequate responses occur, re-examine for other causes of anemia.

ANEMIA ASSOCIATED WITH MALIGNANCY

Eligibility[195,196]

- **Patients with chemotherapy-induced anemia; AND**
- **Hemoglobin < 100 g/L and/or requiring red cell transfusions**
  - Other contributing causes of anemia must be excluded or successfully treated
  - Carefully weigh the risks of thrombo-embolism in patients prescribed erythropoietin
    - The relative risk of thromboembolic complications is increased (RR 1.67, 95% CI 1.35-2.06)[197]
  - Erythropoietin should not be used in treatment of anemia associated with malignancy in patients not receiving chemotherapy
    - A meta-analysis of 53 studies including 13,933 patients suggested erythropoietin therapy increases the risk of death compared to placebo (Hazards Ratio 1.17, 95% CI 1.06-1.30)[198]
    - Red blood cell transfusion should be considered the preferred strategy in patients undergoing potentially curative treatment

Target outcome

- To maintain the lowest hemoglobin level sufficient to avoid RBC transfusions.
- Erythropoietin increases the hemoglobin level and decreases the likelihood of transfusion (RR 0.58-0.67).[195]

Dosage

- Iron status should be assessed and iron deficiency treated.
- Concurrent iron therapy recommended unless there are concerns of iron overload.
- Start erythropoietin with a dose of either:
  - Eprex 150 U/kg sc 3 times/week or 40,000 U sc weekly; or Darbepoetin 2.25 ug/kg sc weekly or 500 ug every 3 weeks sc
- Adjust dose per product monograph to avoid major fluctuations in hemoglobin level.

HIV INFECTION

Eligibility

- Highly active antiretroviral therapy (HAART) decreases the incidence of anemia.[199]
- Erythropoietin was originally indicated for patients with anemia taking zidovudine.
- Similar responses to erythropoietin are obtained in zidovudine- and non-zidovudine-treated patients.[200,201,202,203]
- Erythropoietin significantly decreases the percentage of patients requiring transfusion and reduces the number of units required for patients continuing to require transfusion.
- Erythropoietin is unlikely to produce a response in patients with serum erythropoietin > 500 u/L.[204,205]
- Other contributing causes of anemia must be excluded or successfully treated.[206]

Target therapeutic outcome

- To maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.

Therapeutic regimen

- Iron supplementation should be used with caution, as it may be associated with accelerated progression of disease.[205]
- Start erythropoietin with a dose of:
  - **Eprex 100 U/kg sc 3 times/week;** dose adjust as per package insert

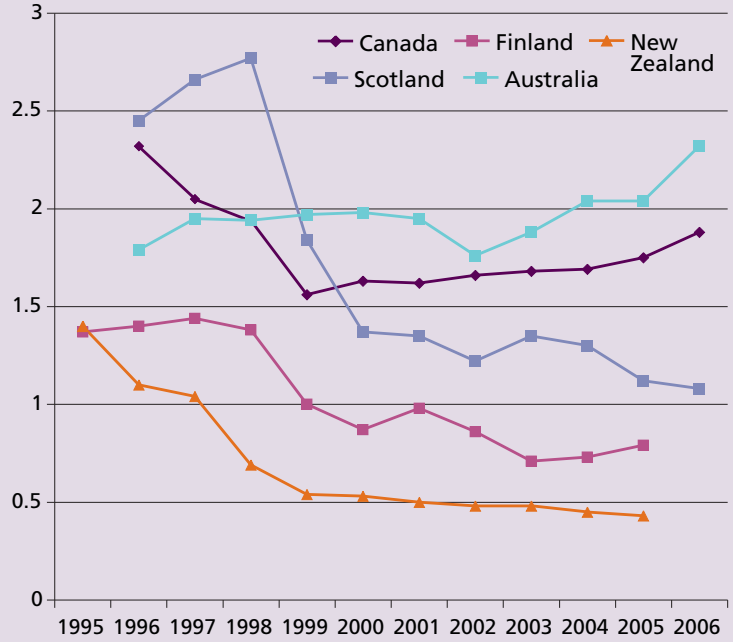
Ⓐ Basics

- Albumin is a plasma protein synthesized by the liver and catabolized by the endothelium (daily turnover 9-12 g; average total body albumin of a 70 kg patient is 280 g; ~60% interstitial).[207]
- Manufactured by cold ethanol fractionation from a pool of approximately 10,000 blood donors.
- Viral inactivation steps include cold ethanol fractionation, and heat inactivation.
- In 2009-2010, 6.3 million grams of albumin were used in Canada, at a cost of about $18.4 million dollars.

ATTENTION

Albumin is a blood product. Consent required.

Albumin Use kg per 10,000 Persons[208]



Ⓑ Administration & Infusion Practices

Dosage

- **Caution: Administering 25% albumin in error, instead of 5%, could result in severe circulatory overload.**
- For dosage, see specific indications listed below.
- Intravascular volume response:

500 mL 5% albumin	100 mL 25% albumin*
↓	↓
= 25 grams of albumin	= 25 grams of albumin
↓	↓
500 mL increase in intravascular volume	450 mL increase in intravascular volume (350 mL from interstitial pool)

*25% albumin usually restricted to use in patients with liver failure

ATTENTION

Administering 25% albumin instead of 5% in error could result in circulatory overload!

Administration[209,210]

- No crossmatch is required.
- Use regular IV tubing.
- Fluid compatibility: all IV solutions.
- Record lot number and volume of albumin administered in patient chart.

Adverse reactions / Risks

- Anaphylaxis – rare.
- Circulatory overload.
- Hypotension – rare case reports of transient hypotension in patients on angiotensin-converting enzyme inhibitors.[211]
- There are no reports of HIV, HCV, or other viruses transmitted through albumin.

Indications

ALBUMIN MAY BENEFIT THE FOLLOWING GROUPS OF PATIENTS:

1. Paracentesis

(According to American Association of the Study of Liver Disease Practice Guidelines[212])

- Routine post-paracentesis albumin infusion is expensive and has not been shown to decrease morbidity and mortality.
  - **Paracentesis < 5 L** – unnecessary
  - **Paracentesis > 5 L** – albumin can be considered for patients with refractory cirrhotic ascites with peripheral edema on maximal diuretic therapy

Volume of ascites	# vials of 100 mL 25% albumin*
< 5 L	0
5-8 L	2
8-12 L	3
12-15 L	4-5

* 8 grams albumin per L of fluid removed for paracentesis > 5 L. [213]

- One randomized study (n=60) suggests that **starch** (20 mL/kg; e.g., 1000-1500 mL pentastarch) **may be an effective alternative to albumin.**[214]
- There is preliminary evidence that midodrine[215] and terlipressin[216] may be alternative therapies to intravenous albumin in this setting.
- **Malignant ascites** – there is no evidence to support the use of albumin in patients with malignant ascites post-paracentesis.[217]

ATTENTION

There is no evidence to support the use of albumin in patients with malignant ascites post-paracentesis.

2. Spontaneous bacterial peritonitis

- One RCT (n=126) found that patients resuscitated with antibiotics alone compared to antibiotics plus albumin had a higher mortality (OR 4.5, 95% CI 1.0 to 20.9).[218]
  - This study has been criticized for lack of a formalized resuscitation protocol in the control arm

DOSAGE

- 25% albumin – 1.5 g per kg within 6 hours of diagnosis and 1.0 g per kg on day 3.
  - For example: For a 70 kg patient = 4 x 100 mL of 25% albumin on day 1 and then 3 x 100 mL of 25% albumin on day 3

3. Hepatorenal syndrome

- Preliminary data suggests that albumin **in conjunction with** terlipressin[219,220,221] or midodrine/octreotide[222] may be effective in salvaging some patients with type 1 hepatorenal syndrome who are candidates for liver transplantation.
  - This therapy has not been shown to change mortality rates in hepato-renal syndrome
  - Albumin alone, without terlipressin or other agent is ineffective

DOSAGE

- 100-200 mL of 25% albumin daily with above agents, up to a maximum of 14 days.[220,221,222]

ATTENTION

Use of Intravenous albumin alone is ineffective for hepatorenal syndrome.

4. Plasma exchange

- Currently, the majority of patients undergoing therapeutic plasma exchange are replaced with albumin ± crystalloid or starch, with the exception of patients with thrombotic thrombocytopenic purpura (TTP) who are replaced with cryosupernatant or frozen plasma.

THE CURRENT MEDICAL LITERATURE CAN NOT CONFIRM ANY BENEFIT OF INTRAVENOUS ALBUMIN IN THE FOLLOWING SUBGROUPS OF PATIENTS: [223]

1. Resuscitation

- Current evidence: **albumin is not superior to crystalloid for resuscitation in intensive care.**
- A large randomized controlled trial[224] showed:
  - No overall advantage of albumin over crystalloid for resuscitation in intensive care
  - A *non-significant* trend to increased relative risk of death with albumin compared with crystalloid in trauma (OR 1.36, 95% CI 0.99-1.86)
  - A significantly increased risk of death in trauma patients with brain injury receiving albumin compared with crystalloid (OR 1.62, 95% CI 1.12-2.34)
  - A *non-significant* trend to improved survival with albumin compared to crystalloid in severe sepsis (OR 0.87, 95% CI 0.74-1.02)

*** ODDS RATIO**

The odds ratio is a way of comparing whether the probability of a certain event is the same for two groups.

An odds ratio of 1 implies that the event is equally likely in both groups.

An odds ratio greater than 1 implies that the event (e.g., death) is more likely in the first group (here the albumin group).

2. Hypoalbuminemia

- Current evidence: **albumin is NOT superior to crystalloid for treatment of hypoalbuminemia.**
- One meta-analysis showed a significant increase in mortality and another showed a non-significant increase in mortality compared to crystalloid:

	Odds Ratio (OR)*	OR Range	% increase in mortality
Cochrane Injuries Group [223]	1.69	1.07-2.67	69% (7 to 167%)
Wilkes et al [225]	1.59	0.91-2.78	59% (-9 to 178%)

3. Severe burns

- 4 small randomized controlled trials with important methodological limitations in patients with thermal injuries failed to show that 5% albumin was superior to crystalloids.[223,226]
- There is currently a wide variation in fluid resuscitation practice in burn patients.[227]
- Current expert opinion recommends resuscitation with lactated Ringer's solution according to the Parkland formula, with addition of colloids if the fluid volume exceeds 4 mL/kg/%burn (known as 'fluid creep') and urine output is less than 0.5 mL/kg/hour, with hemostatic instability after the first 8-24 hours.[228,229]
- Intravenous albumin should only be commenced after transfer to a specialized burn centre.

PARKLAND FORMULA

Parkland formula = 4 mL/kg/%burn over the first 24 hours, with half of the total fluid given in the first 8 hours to target urine output to 0.5-1.0 mL/kg/hr.

ATTENTION

Intravenous albumin should only be commenced after transfer to a specialized burn centre.

4. Hypotension during dialysis

- There are currently no data to support the use of albumin in the treatment of hypotension during dialysis.
  - Small comparison trials of normal saline, albumin (20%), and starch did not suggest a superiority of albumin over the other agents[230]
  - A small RCT concluded that 5% albumin was no more effective than normal saline for the treatment of hypotension during dialysis[231]

5. Cardiac surgery[232]

- There is no evidence to support the use of albumin, as compared to starch or crystalloid, for either:
  - i. Priming fluid for cardiopulmonary bypass
  - ii. Post-cardiopulmonary bypass
- There is no evidence from randomized clinical trials in cardiac surgery patients that fluid replacement with albumin is associated with a better pulmonary, cardiac, or renal outcome.

6. Acute Lung Injury

- Two small, industry funded randomized control trials (n=40[233], n=37[234]) in hemodynamically stable patients found the combination of furosemide and intravenous albumin to result in weight loss of 10 kg over 5 days, without improvement in the rate of extubation success or mortality.

A Basics

IVIG is the fraction extracted from donated plasma that contains the immunoglobulins, with > 90% as IgG.

Products Available [235,236]

- Products are supplied by CBS or HQ.
- Informed consent is required as for any blood component or product.

Refer to product's package insert for further details.

ATTENTION

IVIG is a blood product. Consent required.

IVIG PRODUCTS LICENSED IN CANADA*

Product	IGIVnex	Gamunex	Privigen	Gammagard Liquid	Gammagard S/D	Vivaglobulin
Manufacturer	Talecris	Talecris	CSL Behring	Baxter Corporation	Baxter Corporation	CSL Behring
Plasma Source	Canada	United States	United States	United States	United States	United States
IgG (g/L)	98 ± 20	100 ± 10			> 90	160
IgA (mg/L)	46 mcg/mL (average)	46 mcg/mL (average)	2.5-12 mcg/mL (5.6 mcg/mL average)[237]	≤ 140 mcg/mL	≤ 2.2 mcg/mL (in 5% solution)	Not indicated in product monograph
Sugar content	Not specified	Not specified	Contains no carbo-hydrate stabilizers	Not specified	20 mg/mL (2%) glucose (in 5% solution) no sucrose	Not specified
Osmolality (mOsmol/kg)	258	258	320	240-300	Not indicated in product monograph	Not indicated in product monograph
Form	Liquid	Liquid	Liquid	Liquid	Lyophilized	Liquid
Route of admin-istration	IV	IV/SC	IV	IV	IV	SC

* Consult appropriate package insert for more details, or for information on other products that may be supplied if licensed products are not available.

Cost

- IVIG costs $60 to $75 per gram depending on US$ exchange rate.
  - A single course of treatment for a 70 kg patient with the commonly prescribed dose of 1 g/kg each day for 2 days, costs $8,000-$10,000

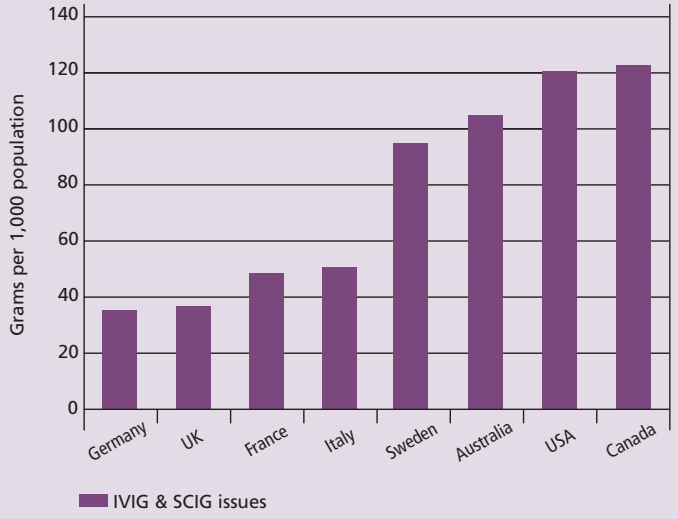
In 2009-2010

Canada spent approximately $300 million on IVIG.[238]

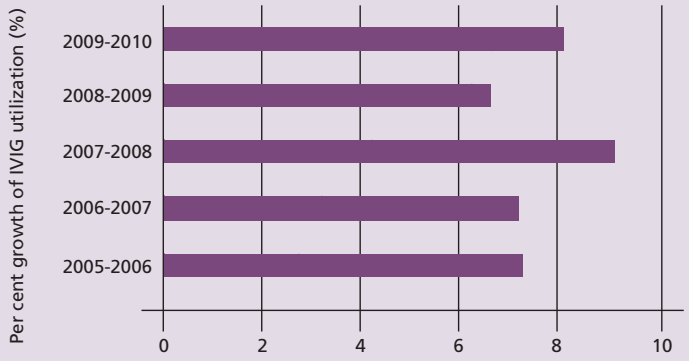
Availability & Consumption

- Approximately 30% of the IVIG used in Canada is derived from Canadian plasma,[236,238] which is processed separately from other source plasma.
- The rest is derived from paid U.S. donors.
- Canada has the highest *per capita* consumptions of IVIG in the world.[236]

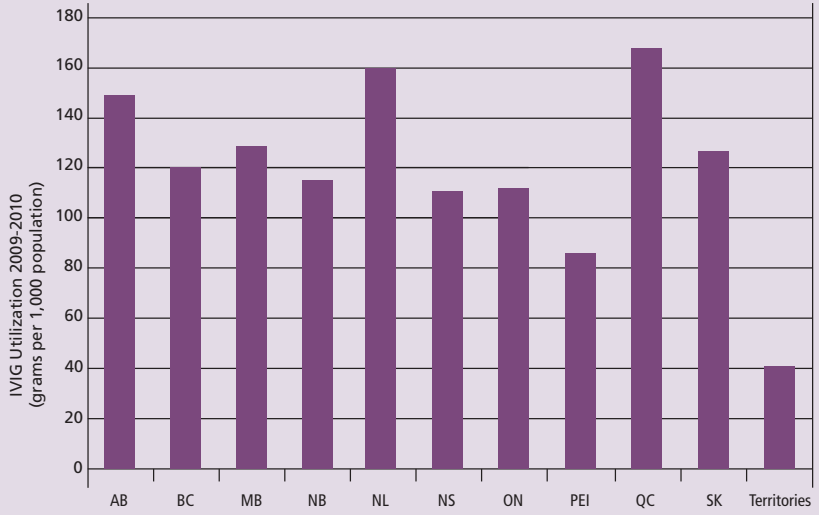
Comparison of Immune Globulin (IVIG and SCIG) Issues in Selected Countries [238,239]



Growth of Canadian IVIG Utilization (%)



IVIG Utilization in Canada by Province/Territory (per 1,000 population), 2009-2010



Manufacturing

- IVIG is manufactured from pooled plasma obtained from several thousand donors per pool.
- The constituent plasma units are tested for human immunodeficiency virus (1 and 2), hepatitis B, hepatitis C, human T-cell lymphotropic virus (I and II), and parvovirus B19.
- The process includes rigorous viral inactivation steps, e.g., caprylate, low pH, chromatography, solvent detergent treatment.
- There is no evidence of transmission of prion disease (e.g., variant CJD) through IVIG.
- Steps in manufacturing are believed to reduce the risk of transmission of prion disease.[240]

B Administration & Infusion Recommendations

Administration

- Administer as 5 or 10% solution, usually dispensed by the hospital blood bank or pharmacy.
- Safe for use in pregnancy.

  Refer to package insert for further details.

Dose Calculator

http://www.transfusionontario.org/dose/

IVIG INFUSION RATES*

Product	Initial Rate	Maximum Rate	Comment
IGIVnex	0.6-1.2 mL/kg/hour (0.01-0.02 mL/kg/min) for 30 minutes	Increase gradually to a maximum rate of 3.6 mL/kg/hour if initial dose is tolerated	Time to infuse 70 g is approximately 3 hours
GAMUNEX™	0.6-1.2 mL/kg/hour (0.01-0.02 mL/kg/min) for 30 minutes	Increase gradually to a maximum rate of 8.4 mL/kg/hour if initial dose is tolerated	Time to infuse 70 g is approximately 1 3/4 hours
GAMMAGARD® SD™	A 5% solution should be used for initial infusion at 0.5 mL/kg/hour. If well tolerated, use 10% solution subsequently at the same rate. Use filter supplied with product	Increase gradually to a maximum rate of 4 mL/kg/hour if initial dose is tolerated	Use of antecubital vein is recommended, especially for 10% solution
GAMMAGARD® Liquid	0.5 mL/kg/hour (0.01 mL/Kg/min) for 30 minutes	Increase gradually to a maximum rate of 5.0 mL/kg/hour if initial dose is tolerated	
Privigen	0.3 mL/kg/hour (0.005 mL/kg/min)	Increase gradually to maximum rate of 2.4-4.8 mL/kg/hour (0.04-0.08 mL/kg/min or 4-8 mg/kg/min)	Product monograph recommends slower rate to be used for patients with ITP

* Refer to package insert for further information.

Note: IVEEGAM™ is rarely used. For IVEEGAM and unlicensed products, refer to the package insert.

Adverse reactions

- In the event of an adverse reaction, stop the transfusion and assess the patient; if the adverse reaction is minor, the transfusion may be continued at a reduced infusion rate.
- Report all adverse reactions to your hospital transfusion service.

ADVERSE REACTIONS TO IVIG [235,241,242,243]

Reaction	Severity	Frequency**	Comment/Treatment
Anxiety, chills/fever, rash, flushing, headache, chest, back or abdominal pain, nausea/vomiting, tachycardia, hypo- or hypertension	Mild-moderate	Common	Slow or pause IVIG treatment. Symptomatic treatment. Recurrent reactions – pre-medicate and/or change to another manufacturer's IVIG product
Aseptic Meningitis	Moderate	Rare	Stop infusion. Administer analgesics. Usually resolves spontaneously in 24-48 hours
Anaphylaxis	Severe	Rare	Stop infusion. **May require epinephrine promptly.** Often reaction to IgA in an IgA-deficient patient
Acute renal failure	Severe	Rare (120 cases reported to FDA in 13 years)	Usually with sucrose-containing product (none currently licensed in Canada). Predisposing factors: age > 65, diabetes mellitus, pre-existing renal insufficiency
Hemolysis[244]	Mild-Severe	Uncommon	More common in non-blood group O patients
Thrombo-embolic events[245]	Severe	Rare (anecdotal reports)	Causative relationship not clearly established. Possibly related to increases in viscosity
Infectious disease transmission	Severe	No reported case since HCV in 1995.[246] No known case of transmission of HIV or HBV	Modern viral reduction measures are robust. Prion (vCJD) transmission remains an entirely theoretical risk

** Reactions are more likely with faster rates of infusion.

Indications

Immunology

- There is good evidence to support the use of IVIG in congenital and acquired immunoglobulin deficiency, with the following conditions:
  - Significant quantitative or functional antibody deficiency that has been established
  - Clinical evidence consistent with defective humoral immunity (e.g., recurrent infection)
  - Treatable conditions to which antibody deficiency may be secondary must be excluded
  - Clinical condition severe enough to interfere with the activities of daily living
- Subcutaneous immunoglobulin also available for home-based immunoglobulin replacement therapy. Consult a transfusion medicine specialist or immunologist for additional information.

IVIG IN IMMUNOGLOBULIN DEFICIENCY[247,248,249,250]

Diagnosis	Efficacy	Dose
Primary immune deficiencies, combined immunodeficiency syndromes, IgG subclass deficiencies, hyper-IgM syndrome	Benefit established	Starting dose of 0.4-0.6 g/kg IV monthly for three months, depending on the severity of deficiency. Dose should then be tailored to maintain nadir of the IgG level above 7 g/L in most patients. SCIG dosing: 100-150 mg/kg per week.
Acquired hypogammaglobulinemia, e.g., in chronic lymphocytic leukemia,[251] multiple myeloma[252]	Benefit established in adult population. Not recommended for routine use in pediatric population.	0.4 g/kg every three weeks for 4-6 months. Dose should then be tailored.
Patients with advanced HIV and recurrent serious infections unresponsive to antiviral therapy[253]	Benefit established	As above

IVIG IN SOLID ORGAN TRANSPLANTATION[254]

Diagnosis	Efficacy/Comment	Dose
Acute antibody mediated rejection in patients who have received living donor/deceased kidney donor transplant	Benefit established	0.1 g/kg/treatment day or as a set dose of 2 g/kg total
Steroid-resistant rejection in patients who have received a living/deceased donor kidney transplant	Benefit established. Consider IVIG to improve graft survival when other therapies are unacceptable or ineffective.	Total dose of 2-3.5 g/kg administered over a period of up to 10 consecutive days
Kidney transplant from living donor to whom the patient is sensitized (HLA or ABO)	Possibly effective. There is uncertainty about the best strategy for these patients.	2 g/kg/month (maximum dose 180 g) for 4 months or 0.1 g/kg in association with plasmapheresis in the perioperative period

Hematology

IVIG IN HEMATOLOGICAL DISORDERS AND BONE MARROW/STEM CELL TRANSPLANTATION[250,255,256,257,258]

Diagnosis	Efficacy/Comment	Dose
Idiopathic Thrombocytopenic Purpura (ITP) refractory to standard treatment, platelet count < 20 x 10^9/L	Benefit established	1 g/kg for 1-2 days
ITP with persistent or life-threatening bleeding and platelet count < 50 x 10^9/L	Benefit established	1 g/kg for 1-2 days
Thrombocytopenia associated with HIV unresponsive to antiviral therapy, platelet count < 20 x 10^9/L or < 50 x 10^9/L with bleeding	Benefit established	1 g/kg for 2 days
ITP in pregnancy ◆ platelet count < 10 x 10^9/L ◆ platelet count 10-30 x 10^9/L in 2nd or 3rd trimester ◆ platelet count < 30 x 10^9/L and bleeding at any stage in pregnancy	Appropriate initial treatment	1 g/kg; longest inter-treatment interval consistent with maintaining adequate platelet count
Post-transfusion purpura	Anecdotal evidence suggests IVIG is the preferred treatment	1 g/kg for 2 days
Fetal/neonatal allo-immune thrombocytopenia (F/NAIT) (treatment of mother or fetus)[256,259]  **Pediatrics** For infants, review of literature suggests IVIG if platelets are below 50 x 10^9/L and platelet transfusion if platelets are below 30 x 10^9/L (even without bleeding).	Considered standard first-line antenatal treatment. Considered adjunctive therapy for newborn with F/NAIT. Appropriate consultation advisable with high-risk pregnancy and neonatal unit.	Maternal dose: 1 g/kg weekly. Infant: an initial dose of 1 g/kg might provide benefit when platelets are not available
Pure red cell aplasia (PRCA) (viral or immunologic)	Considered first line therapy for PRCA associated with parvovirus B19 occurring in an immunocompromised patient. Reasonable option for immunologic PRCA in patients who have failed other therapies.	0.5 g/kg weekly for 4 weeks
Hemolytic transfusion reaction (HTR)	Not recommended for prophylaxis or routine treatment of HTRs. May be of possible benefit in patients with sickle cell disease with serious, life-threatening delayed HTR.	Not indicated. Determine in consultation.
Hemolytic disease of the newborn (HDN)	Not recommended for use in management of HDN without established hyperbilirubinemia. Recommended if total serum bilirubin is rising despite intensive phototherapy or if level is within 34-51 umol/L of the exchange level.[260]	0.5 g/kg. Dose may be repeated in 12 hours.
Rare cases of auto-immune hemolytic anemia or neutropenia, auto-antibodies to factor VIII or von Willebrand factor, acquired red cell aplasia due to parvovirus B19	Anecdotal evidence only; consider use only after failure of other treatments or in urgent situations	1 g/kg for 2 days
Allogeneic bone marrow/ stem cell transplant[261]	No advantage over placebo in HLA-identical sibling donors. Not recommended for routine prophylaxis. May be used for CMV-induced pneumonitis following transplantation in combination with ganciclovir.	Not indicated. Determine in consultation.
Autologous bone marrow/ stem cell transplant[262]	No benefit	Not indicated

Neurology

IVIG IN NEUROLOGICAL DISORDERS* [258,263,264]

Diagnosis	Efficacy/Comment	Dose
Guillain-Barre Syndrome (including Miller-Fisher syndrome and other variants)	Benefit established. Recommended as treatment option within 2 weeks of symptom onset for patients with severe and/or progressing symptoms. May be considered as a treatment option for relapsed patients who initially responded to IVIG.	Total dose of 2 g/kg divided over 2-5 days (adults) or 2 days (children). Evaluate response at 4 weeks.
Chronic inflammatory demyelinating polyradiculopathy	Benefit established; option for short-term management of new-onset CIDP or relapse. Option for long-term therapy in combination with other immunosuppressive therapy.	Total dose of 2 g/kg divided over 2-5 days: maintenance therapy should be individualized
Multifocal motor neuropathy	Benefit established. Recommended as first-line therapy. Diagnosis should be made by neuromuscular specialist.	Total dose of 2 g/kg divided over 2-5 days; maintenance therapy should be individualized and tailored to the lowest dose that maintains clinical efficacy (usually 1 g/kg or less).
Myasthenia gravis	May be effective in selected circumstances. Use should be reserved for severe exacerbations or crises. Should not be used as maintenance therapy. Appropriate consultation advisable.	2 g/kg over 2-5 days: maintenance therapy should be individualized
Lambert-Eaton Syndrome	Option for treatment. Appropriate consultation advisable.	Total dose of 2 g/kg divided over 2-5 days: maintenance therapy should be individualized
Stiff person syndrome	Effective in the short-term; long-term outcomes unknown	Total dose of 2 g/kg divided over 2 days
Multiple sclerosis (relapsing-remitting)	Possible benefit on relapse rate but efficacy compared to other agents not known. Option for treatment of patients who fail, decline or are not able to take standard immunomodulatory drug therapies.	1 g/kg monthly with or without induction of 2 g/kg divided over 2-5 days (adults) or 2 days (children); maintenance therapy should be individualized
Epilepsy	Ineffective	Not indicated
Amyotrophic lateral sclerosis (ALS)	Ineffective	Not indicated
Acute disseminated encephalomyelitis (ADEM)	Possible benefit. Consider when first-line therapy with high-dose corticosteroids fails or when there are contraindications to steroid use.	Total dose of 2 g/kg given over 2-5 days (adults) or 2 days (children)
Alzheimer's disease	Possible benefit. Clinical trials are ongoing.[265]	Not currently indicated outside the setting of a clinical trial
Opsoclonus-myoclonus syndrome	Possible treatment option. Objective evidence of clinical improvement required for sustained use.	Total dose of 2 g/kg given over 2-5 days (adults) or 2 days (children)

* Other conditions where IVIG is not of proven value include paraprotein polyneuropathy, neurological vasculitides, paraneoplastic neurological syndromes and autism.

Rheumatology

IVIG IN RHEUMATOLOGY[258,263]

Diagnosis	Efficacy/Comment	Dose
Dermatomyositis	Benefit established. Option in combination with other agents for patients who have not responded to other immunosuppressive therapies. Use should be made in consultation with experts in neuromuscular disease.	Total dose of 2 g/kg divided over 2-5 days (adults) or 2 days (children); maintenance therapy should be individualized
Polymyositis [264,266]	Benefit uncertain; appropriate consultation advisable	Determine in consultation
Systemic lupus erythematosus [267,268,269]	Current evidence does not support use in routine management	Determine in consultation
Kawasaki disease [270]	Benefit established	2 g/kg x 1 day
Rheumatoid arthritis [267,271]	Ineffective	Not indicated
Inclusion body myositis [264,272]	Ineffective	Not indicated
Chronic Fatigue Syndrome [273]	Ineffective	Not indicated

* For immune thrombocytopenia associated with systemic lupus erythematosus, see **Hematology**.

Dermatology

IVIG IN DERMATOLOGY[258,274]

Diagnosis	Efficacy/Comment	Dose
Toxic epidermal necrolysis	Anecdotal evidence.[275] May be effective early in clinical course. Case control study did not show improvement in outcome.[276]	1 g/kg/day for 3 days
Pemphigus vulgaris and variants	Anecdotal evidence [277] supports use of IVIG as adjunctive or second-line treatment if conventional treatment is ineffective.	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized.
Epidermolysis bullosa acquisita	Anecdotal evidence [278] supports use of IVIG as adjunctive or second-line treatment if conventional treatment is ineffective.	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized.
Bullous pemphigoid	Anecdotal evidence [279] supports use of IVIG as second-line treatment if conventional treatment is ineffective.	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized.

Obstetrics and Gynecology

IVIG IN OBSTETRICS AND GYNECOLOGY [280]

Diagnosis	Efficacy/Comment	Dose
Anti-phospholipid syndrome	Uncertain benefit [281,282] may improve fetal outcomes when Aspirin® and heparin have been ineffective; appropriate consultation advisable	Determine in consultation with high-risk pregnancy unit and attending specialist
Recurrent spontaneous abortion	Ineffective [283]	Not indicated
In Vitro fertilization/ implantation procedures	Ineffective [284]	Not indicated

Infectious Diseases

IVIG IN BACTERIAL INFECTION [285]

Diagnosis	Efficacy/Comment	Dose
Septic/Toxic Shock Syndrome (Group A streptococcal sepsis with hypotension and multi-organ failure) [286,287,288,289]	Recommended as an adjunctive therapy when evidence of systemic inflammation and end organ hypoperfusion with fever, tachycardia, tachypnea and hypotension	1 g/kg on day one and 0.5 g/kg on days 2 and 3 or 0.15 g/kg per day over 5 days
Necrotizing fasciitis [290,291]	Possibly recommended for severe invasive group A streptococcal disease if other approaches have failed	Adjunctive treatment in rapidly progressing disease 1-2 g/kg over 6 hours
Sepsis in patients in critical care [285,286,287,292]	No large randomized controlled trials to confirm benefit	Not recommended for use

- HIV: see **Immunology.**
- Bone marrow transplant and red cell aplasia due to parvovirus B19: see **Hematology.**
- Specific hyper-immune globulins are not discussed.

Dosing of IVIG for Obese Patients [293]

Dose Calculator

http://www.transfusionontario.org/dose/

The dose of IVIG varies depending on the clinical condition. In general, the dose is based on the patient's weight. In the case of obese patients, the appropriate dosing regimen is unclear. It is suggested that patients weighing more than 100 kg and with a body mass index greater than 30 kg/m2 should have their IVIG dose calculated using an adjusted body weight. The adjusted weight takes into account the increased volume of distribution in these patients (because of increased body fluids) without accounting for the increase in weight from body fat.

A tool which assists with the calculation of the appropriate dose of IVIG based on the patient's gender, height and weight is available at www.transfusionontario.org/dose.

A Basics [294,295]

Prothrombin complex concentrates (PCCs) are coagulation factor concentrates that contain factors II, VII, IX, X. The amount of the individual coagulation factor levels varies with the specific preparations.

Manufacturing

- The factor concentrate is made from pools of 1000-2000 plasma donations.
- Plasma units are tested for HIV (1 and 2), hepatitis B, hepatitis C.
- Manufacturing processes include viral inactivation steps.

Products available

- PCCs are supplied by CBS and HQ.
- Two prothrombin complex concentrates are licensed in Canada: Octaplex® and Beriplex®.

COAGULATION FACTOR LEVELS (IU/ML) IN PCCS [295]

Product	Manufacturer	Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S	AT III	Heparin
Octaplex®	Octapharma	31.4	16.1	22.3	24.4	12.0	22.2	0.1	6.0
Beriplex®	CSL Behring	31.0	16.2	28.9	41.3	17.9	21.6	0.6	0.5

B Monitoring & Infusion Practices for Octaplex® and Beriplex® [294,296]

How

- Lyophilized powder must be reconstituted for administration.
- Final volume is 20 mLs per vial which contains 500 IU of factor IX.
- Can be prepared in syringe or minibag for intravenous infusion.
- Vitamin K 5-10 mg IV (**not** intramuscular or subcutaneously) should be administered immediately to avoid rebound anticoagulation.

ATTENTION

Vitamin K should be given intravenously at same time as PCCs to avoid rebound anticoagulation.

Dose

- For dosing instructions consult your hospital policy. In general, a dose of 1000 IU is sufficient for patients with weight between 50-90 kg and INR in the therapeutic range (< 3).
- The maximum dose should not exceed 3000 IU of Factor IX.

When

- Infusion rate should not exceed 2-3 mL/min for Octaplex® and 8 mL/min for Beriplex®.

Storage

- Store between +2 to +25°C for Octaplex® and room temperature (up to 25°C) for Beriplex®.
- Freezing and light exposure may affect product quality.

Monitor patient

- Check patient's vital signs prior to starting, 15 mins. after starting, at end of transfusion and if there are any transfusion reactions.
- Repeat INR immediately postinfusion to ensure adequate correction of INR.
- Effective half life of PCC is approximately 6 hours.

INDICATIONS FOR PCCS

1. For patients on warfarin or vitamin K deficiency with INR values > 1.5 AND
   a) life or limb threatening bleeding; or
   b) emergency surgery required within 6 hours
2. PCCs should NOT be administered if:
   - INR ≤ 1.5 as individual coagulation factors are not below the level needed to maintain hemostasis
   - Patients with coagulopathies not related to warfarin or Vitamin K deficiency as they are deficient in coagulation factors not contained in PCCs
   - Patients with known HIT (Beriplex® and Octaplex® both contain heparin)
   - Patient has received or will receive recombinant Factor VIIa

PCCs should not be given to correct coagulopathies other than warfarin.

If PCCs not effective in reversing warfarin, then other etiologies should be considered.

A Principles of Transfusion in Sickle Cell Disease

Patients with sickle cell disease:

- Have elevated blood viscosity which may be exacerbated by increases in hematocrit.
- Are more likely to experience delayed hemolytic transfusion reactions. Hence the indications for transfusion in patients with sickle cell disease differ significantly from other patients:
  - **Exacerbation of anemia:** in the absence of heart failure, dyspnea, hypotension or marked fatigue, transfusion should be avoided unless the hemoglobin has decreased to < 50 g/L.[297]
    - A rapid decrease in Hgb can be anticipated if the reticulocyte count falls below 250 x 10^9/L
  - **Treatment or prevention of sickle cell complications:** total hemoglobin (Hgb) should not be increased above 100-110 g/L.[298]
    - Augmentation of oxygen delivery in patients with sickle cell disease is achieved more efficiently through decreasing the HgbS% than by increasing the total Hgb level [299]

ATTENTION

Indications for transfusion in patients with sickle cell disease differ significantly from other patients.

ATTENTION

In the absence of symptoms, transfusion should be avoided unless the hemoglobin has decreased to < 50 g/L.

ATTENTION

Never transfuse a sickle cell patient to a hemoglobin > 100-110 g/L.

B Special Transfusion Requirements

- The following apply to patients with HgbSS, HgbSß-thalassemia or HgbSC. No special precautions are required for patients with HgbSA (sickle cell trait).
- Notify the hospital's Blood Transfusion Service whenever a patient with sickle cell disease presents, to allow sufficient time to prepare specialized blood products should the need for transfusion arise.

ATTENTION

Notify blood bank immediately.

Phenotypically-matched RBCs

- Determine extended phenotype (Rh, Kell, Duffy, Kidd and MNS blood groups) at first visit.
- In patients with no previous alloantibodies, select RBCs matched for the patient's Rh (D,C,c,E,e) and Kell (K1) antigens.
- If known alloantibodies, select RBCs that are matched for the patient's Rh (D, C, c, E, e), Kell (K1), Kidd (Jk^a, Jk^b), Duffy (Fy^a) and S (S,s) antigens, as well as any antigens to which the patient is immunized.[300]
  - Matching for Fyb in sickle cell patients with the Fy(a-b-) phenotype is rarely necessary
- If there is not sufficient time or resources to determine the patient's phenotype, contact other hospitals that may have transfused the patient previously. (In some regions of Canada, CBS maintains a phenotype registry of patients with sickle cell disease.)

ATTENTION

Life-saving transfusion should not be withheld if prophylactically phenotype-matched RBCs are not available.

Leukoreduced blood products

- As patients with sickle cell disease are at higher risk of harm from the effects of non-leukoreduced RBCs (febrile transfusion reactions, transmission of certain viruses and bacteria, alloimmunization to RBC, HLA and HPA antigens), only leukoreduced RBCs and platelets should be selected.[301]
  - As of 1999, all blood products in Canada are pre-storage leukoreduced

Sickledex®-negative blood

- RBC units which test positive by Sickledex® test are from donors with sickle cell trait (HgbSA). This blood is therefore safe to administer to patients with sickle cell disease, but it will confound post-transfusion measurements of the patient's HgbS% and should be avoided, if possible.[301]

C Exchange Transfusion

- Depending upon a patient's initial Hgb, it may not be possible to achieve a specific target HgbS% by top-up transfusion without exceeding a total Hgb of 100-110 g/L.
- Exchange transfusion may therefore be required for the traditional HgbS% goal of < 30% (HgbA% > 70%).
- Ensure patient is euvolemic before initiating an exchange.

Manual/partial exchange:

- A typical protocol (for children, smaller comparable volumes, e.g., 10 mL/kg):[298]
  1. Phlebotomize 1st 500 mL of whole blood (for patients who are very anemic at baseline [e.g., Hgb < 70 g/L], a top-up transfusion may be required before first phlebotomy)
  2. Bolus 500 mL of 0.9% normal saline
  3. Phlebotomize 2nd 500 mL of whole blood
  4. Transfuse 2 units of RBCs
  5. Repeat as necessary to achieve target HgbS% (typically a 1.5 blood volume exchange is necessary for first treatment; single cycles may be adequate for maintenance therapy). Note that for patients starting with Hgb near 100 g/L, step 4 should alternate between transfusion of 1 and 2 units in order to keep total Hgb from exceeding 110 g/L

Automated exchange/erythrocytopharesis

- Small aliquots of whole blood withdrawn under pressure, RBCs separated by centrifugation and discarded, plasma and platelets returned to patient accompanied by donor RBCs (usually through separate line).
- Cycle repeats until goal Hgb and HgbS% achieved.
- Automated exchanges are faster and more precise than manual exchanges but require specialized equipment and trained personnel.

D Transfusion Indications (first line)

THERAPEUTIC TRANSFUSION

Aplastic Crisis

- Most commonly due to parvovirus B19 infection, with profound reticulocytopenia following a viral illness.
- Due to decreased lifespan of sickle RBCs (16-20 days), significant fall in Hgb will occur before the reticulocyte count recovers.[302]
- Transfusion support may be required if symptomatic anemia, or if Hgb < 50 g/L.
- Due to a compensatory increase in plasma volume, transfuse slowly to avoid volume overload and consider pre-transfusion diuretic.

Sequestration crisis

- Trapping of sickle erythrocytes in splenic sinusoids resulting in massive, painful enlargement of spleen and severe anemia over a period of hours.
- If untreated, sequestration crises cause death from hypovolemic shock/anemia; immediate transfusion often required.
- Post-transfusion hemoglobin levels often higher than expected, suggesting autotransfusion as sequestered RBCs released back into circulation.
- To avoid accidental polycythemia and hyperviscosity, transfuse 1 unit at a time, reassessing Hgb level before administering more.

Pediatrics
In children, consider administering RBCs in smaller than normal aliquots (e.g., 3-5 mL/kg). Often a single transfusion is sufficient to reverse a sequestration crisis.[303]

- Less commonly, patients may present with hepatic sequestration crises, characterized by a rapidly enlarging liver accompanied by a decrease in hemoglobin, a rise in reticulocyte count, and a conjugated hyperbilirubinemia.
  - Transfusions should also be administered cautiously due to the risk of autotransfusion and hyperviscosity. Recurrences are common [297]

Acute chest syndrome

- A new infiltrate on CXR in a patient with sickle cell disease, associated with one or more symptoms of fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia.
- May progress rapidly to respiratory failure and be complicated by neurologic events.[304]
- May be triggered by infection or marrow embolism as complication of vaso-occlusive pain episode; specific cause not identified in ~60% of cases.[304]
- Empiric treatment with bronchodilators, incentive spirometry and antibiotics (e.g., macrolide or quinolone) advisable in all patients.
- RBC transfusion in setting of acute chest syndrome results in improved oxygenation.[304] Some studies have observed equivalent outcomes whether patients treated with exchange transfusion (HgbS% goal of 30%) or top-up transfusion (Hgb goal of 100 g/L).[304,305] However, other studies suggest that patients receiving top-up transfusions may progress to requiring exchange.[306]
- In absence of evidence from randomized controlled trials, most patients with acute chest syndrome should be transfused, with exchange transfusions reserved for patients with more severe or rapidly progressing disease [307] with concerning symptoms (see yellow box to the right).

Acute chest syndrome with the following suggest need for exchange transfusion rather than top-up transfusion:

- Altered mental status
- Persistent HR > 125 bpm, RR > 30/min, temp > 40°C, or hypotension
- Arterial pH < 7.35; SpO2% < 88% despite aggressive ventilatory support
- Serial decline in SpO2% or A-a gradient
- Fall in Hgb > 20 g/L
- Platelet count < 200/fL x 10^9/L
- Elevated troponin or brain natriuretic peptide (BNP)
- Evidence of multiorgan failure (e.g., renal or hepatic dysfunction)
- Pleural effusions or progressive pulmonary infiltrates

Progressive cholestasis

- Syndrome that may occur in absence of cirrhosis, marked by right upper quadrant pain, extreme elevation of bilirubin and alkaline phosphatase, and variable elevation in transaminases.
  - May be accompanied by renal failure, thrombocytopenia, and prolonged coagulation times
  - All survivors have been treated with RBC exchange transfusion [297]
- In contrast, benign cholestasis (unaccompanied by fever, abdominal pain, gastrointestinal symptoms, or hepatic synthetic failure) resolves within months without specific therapy.[297]

Acute ischemic stroke or retinal artery occlusion

- Transfusion recommended for adult patients without other obvious stroke etiology (e.g., cardioembolism).[303]

Pediatrics

Transfusion recommended for all pediatric patients. Within 3 hours of the first unit of transfused RBCs, MCA flow velocity decreases by 20%.[308] Exchange transfusion associated with lower recurrence rate than top-up transfusion.[309]

Note: Most strokes in young adult patients with sickle cell disease are hemorrhagic for which the role of transfusion therapy remains unclear.[310]

PROPHYLACTIC

Perioperative

- Due to high rates of perioperative complications (e.g., 10% rate of acute chest syndrome), aggressive supportive care and close observation is indicated for all patients with sickle cell disease undergoing surgical procedures.[311,312]
  - Avoid surgery during vaso-occlusive episodes
  - Assure ≥ 8 hrs pre-procedure hydration (admission to hospital 12-24 hours pre-operatively and monitoring for 48 hours post-operatively should be considered)
  - Avoid hypothermia
  - Avoid use of tourniquets
  - Favour laparoscopic approaches
  - Post-operative prophylaxis for deep venous thrombosis
  - Periprocedure incentive spirometry
  - Aggressive control of pain
  - Early remobilization
- Pre-operative transfusion support requires assessment of both surgical and patient risk:
  - Low-risk procedures (e.g., skin, ENT, dental, perineal, inguinal or distal extremity surgery): transfusion likely not required [303,313]
  - Intermediate-risk procedures (e.g., abdominal or orthopedic surgery): pre-op transfusion advised on basis of observational studies.[314] A large randomized controlled trial[311] has demonstrated that top-up transfusion to Hgb 100 g/L (approx. HgbS% of 60%) is equivalent to exchange transfusion (HgbS% goal of 30%) in preventing post-operative complications, and decreases transfusion-related adverse events
  - High-risk procedures (e.g., intracranial, cardiovascular, or intrathoracic procedures; pars plana vitrectomy or scleral buckling) or intermediate-risk procedures in patients with significant comorbidities (e.g., chronic pulmonary disease): although little supporting data, exchange transfusion (HgbS% goal of 30%) should be considered [313,315]
  - Exchange transfusion should also be considered for patients undergoing intermediate risk procedures whose Hgb level is ~100 g/L at baseline

Surgical Procedure
Low-risk: skin, ENT, dental, perineal, inguinal or distal extremity surgery
Intermediate-risk: abdominal or orthopedic surgery
High-risk: intracranial, cardiovascular, or intrathoracic procedures; pars plana vitrectomy or scleral buckling

High Stroke Risk

- In children, transfusion indicated for secondary prevention of ischemic stroke and for primary prevention in patients with high-risk features (e.g., high middle cerebral artery or internal carotid blood flow by pediatric transcranial ultrasound).
  - In the latter group, maintaining HgbS < 30% while keeping total Hgb < 120 g/L results in a 92% reduction in stroke incidence [316]
- Transfusions should be continued indefinitely as discontinuation is associated with high risk of stroke recurrence.[317]
  - It is likely safe to relax HgbS% goal to 50% for patients who have been free of neurologic events after 3-5 years of transfusion support [318]
- Little evidence to guide initiation of transfusions for stroke prophylaxis in adults, or following primary hemorrhagic strokes.
  - The underlying pathophysiology for both thrombotic and hemorrhagic strokes in sickle cell disease is likely the same [319]

Transfusion Indications (second line)

Initial therapeutic goal for the following indications should be HgbS% < 30% by exchange transfusion. Several months after condition stabilizes, may attempt gradual transition to higher HgbS% target by either decreasing quantity of RBCs transfused, or increasing interval between transfusion.

1. Recurrent pain episodes/acute chest syndrome

- In patients who have failed an adequate trial of hydroxyurea, chronic transfusion support may be considered as means of decreasing recurrence of vaso-occlusive pain episodes or acute chest syndrome.[320,321]
- Transfusion not indicated as treatment of uncomplicated acute vaso-occlusive pain episodes, or for treatment of chronic pain syndromes (e.g., avascular necrosis, osteomyelitis, neuropathic pain).[303,322]

2. Priapism

- Transfusion may be of benefit for episodes lasting > 4 hours, unresponsive to aspiration of blood from the corpora cavernosa and irrigation with dilute epinephrine.[323,324]

3. Malleolar ulcers

- Transfusion may speed healing if no response to bed rest, wound care, antibiotics, hyperbaric oxygen.[326]

ATTENTION

Be vigilant for ASPEN syndrome (Association of Sickle Cell Disease, Priapism, Exchange Transfusion, and Neurologic events).[325]

4. Pregnancy

- Transfusion not of benefit for uncomplicated pregnancy if adequate pre-natal care provided (e.g., bi-weekly obstetrics assessment, weekly in last month).[321]
- Transfusion support may be considered for pregnant patients with:[303]
  - Significant comorbidities
  - Chronic renal, pulmonary or hepatic disease
  - History of recurrent fetal loss
  - Multigestational pregnancy or evidence of chronic fetal distress/intrauterine growth retardation

5. Pulmonary hypertension

- Confirm pulmonary arterial hypertension by right-heart catheterization in patients with tricuspid regurgitant jet > 2.5 m/s or RVSP > 30 mmHg on echocardiogram.
- Consider transfusion therapy if no response to, or intolerance of, hydroxyurea or vasodilators (e.g., inhaled nitric oxide).[327]

Note: Priapism, pulmonary hypertension and malleolar ulcers may represent complications of chronic intravascular hemolysis (e.g., nitric oxide depletion) rather than acute vaso-occlusion.[328]

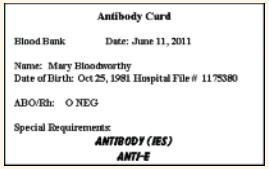
F Transfusion Complications

Delayed hemolytic transfusion reactions

- Without prophylactic phenotypic matching, 30% of transfused patients with sickle cell disease will develop alloantibodies, two thirds of them directed towards C, E and K1 antigens.[329]
  - Alloimmunization due in part to genetic differences in the antigens expressed on red blood cells in the donor population (primarily Caucasians) and recipients
- 30-50% of antibodies will be undetectable on retesting within the year; patients may be inadvertently re-challenged with subsequent transfusions, resulting in high rate of delayed hemolytic transfusion reactions.[301]
- Prophylactic matching for antigens therefore advised when selecting RBCs for sickle cell patients; advance notification of blood bank required.
- Delayed hemolysis manifests 1 week to 1 month after transfusion by worsening of hemolytic indices (increased indirect bilirubin and lactate dehydrogenase) accompanied by new alloantibody in patient plasma (detected by blood group and screen) and/or on patient's RBCs (detected by direct antiglobulin test).
- Patients often present with symptoms typical of a vaso-occlusive pain episode. In some cases, delayed hemolytic transfusion reactions may progress to hyperhemolysis (see next section).

ATTENTION

Alloimmunized sickle cell patients require antibody card.


Antibody Card

Blood Bank Date: June 11, 2011

Name: Mary Bloodworthy
Date of Birth: Oct 25, 1981 Hospital File # 1175380

ABO/Rh: O NEG

Special Requirements:
ANTIBODY (IES)
ANTI-E

Hyperhemolysis

- Defined as post-transfusion RBC destruction accompanied by fall in Hgb to below pre-transfusion levels.
  - Hemolytic indices increased from baseline, occasionally accompanied by relative reticulocytopenia [330]
  - Acute: occurs less than 7 days after transfusion, often with no new antibodies detectable
  - Delayed: occurs between 1 and 4 weeks following transfusion and often accompanied by new RBC antibodies
- Enhanced hemolysis appears to involve both transfused and autologous RBCs, and may be exacerbated by further transfusion of even crossmatch compatible/antigen-negative RBCs.
- **Avoid further transfusions, if at all possible**:
  - Treat with IVIG 2 g/kg over 2-5 days
  - Accompany by high dose steroids (e.g., prednisolone 1 mg/kg/d x 7 days)
  - Consider brief course of erythropoietin if relative reticulocytopenia [331]

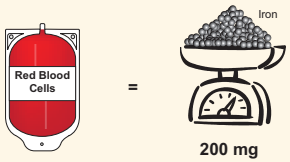
Hyperviscosity

- Sudden onset hypertension during or shortly after transfusion, accompanied by signs of congestive heart failure and profound alterations in mental status, including stupor, coma, seizures, or features of intra-cerebral infarct or hemorrhage.[332]
- Risk increases if Hgb transfused above 100-110 g/L in patients with SCD and HgbS% > 25%, particularly if patient dehydrated and hypoxemic.[299]
  - May also occur secondary to auto-transfusion following transfusion support of sequestration crises
- Manage with emergency phlebotomy.

ATTENTION

Never transfuse a sickle cell patient > 100-110 g/L

Transfusional iron overload



- Each transfused unit of RBCs delivers 200 mg of iron.
- Significant iron overload therefore likely after repeated top-up transfusions: may eventually result in hepatic, cardiac or endocrine dysfunction.
- Selecting fresh RBCs (< 7 days old) may slow iron loading in chronically transfused patients to a small degree.
- Exchange transfusions can more effectively mitigate or even reverse iron loading.[333]
- Iron chelation therapy indicated once hepatic iron concentration > 7 mg/g dry weight, as assessed by either biopsy or calibrated MRI scan.[334]
  - This degree of iron loading can be anticipated after the transfusion of more than 100 mg/kg of iron (in adult patients, approximately 20-30 RBC units)
  - Iron overload correlates poorly with serum ferritin in sickle cell patients but is likely present if serum ferritin persistently > 3000 ng/mL [335]
- Iron chelators licensed for use in Canada include deferoxamine and deferasirox (deferiprone also available through Health Canada's Special Access Program).
  - Referral to a centre with expertise in iron chelation therapy advised prior to initiation of treatment

Appendix A

Price List

Item	Price
Red blood cells*	$419
Autologous (whole) blood	$419
4 units buffy coat derived platelets	$286
1 unit single donor (apheresis) platelets	$619
1 unit HLA-matched single donor (apheresis) platelets	$1,250
Apheresis fresh frozen plasma	$360
4 units frozen plasma	$156
8 units cryoprecipitate	$1,080
Tranexamic acid 6 g	$247.20
IVIG *per gram*	$63
Albumin *5% 500 mL*	$65
Pentaspan® *per 500 mL*	$55
Voluven® *per 500 mL*	$55
Blood group (ABO, Rh D)	$10
Antibody screen	$30
Crossmatch (no antibody)	$12
Crossmatch (antibody positive patient)	$30
Octaplex® 1,000 IU	$720
Recominant Factor VIIa/mg	$1,163
Anti-D 120 mcg	$33
Anti-D 300 mcg	$82

* This cost refers only to the acquisition cost of a unit of RBC. The cost of delivery of a unit of blood to a patient ranges from $522 to $1183 (US).[336]

Appendix B

Information for Physicians Treating Patients Who Are Jehovah's Witnesses

Jehovah's Witnesses refuse transfusion of allogeneic blood based on their understanding of several Biblical passages, which they view as **prohibiting** the use of:

- Whole blood, including predonated autologous blood (predeposit)
- Red blood cells
- White blood cells
- Platelets
- Plasma

Their religious understanding **may permit** the use of products containing fractions of plasma or cellular components, such as:

- Cryoprecipitate
- Clotting factor concentrates
- Albumin
- Intravenous immunoglobulin
- Fibrin glue
- Hemoglobin-based oxygen carriers
- Recombinant factor VIIa
- Autologous blood obtained by acute normovolemic hemodilution or by cell salvage

Witness patients will accept most surgical and anesthesiological procedures (e.g., hemostatic surgical instruments, hypotensive anesthesia), most diagnostic and therapeutic procedures (e.g., phlebotomy for laboratory testing, angiographic embolization), pharmacologic agents to enhance hemostasis (e.g., topical and systemic hemostatic agents) and therapeutic agents to stimulate hematopoiesis (including recombinant products) that do not contain blood derivatives, synthetic oxygen therapeutics, and non-blood volume expanders.

A valuable and detailed discussion of the position of Jehovah's Witnesses on blood transfusion and related interventions is available.[337]

Physicians should **discuss the options with individual patients** because each person must make personal decisions according to their conscience regarding the acceptance of blood derivatives and autologous blood management options.

Jehovah's Witnesses have established a network of **Hospital Liaison Committees** (HLC) across Canada. On call local HLC members can be contacted through the hospital switchboard or by contacting the **Hospital Information Services for Jehovah's Witnesses**. This service is available 24 hours a day at **1-800-265-0327**.

Appendix C

Original Advisory Panels for Bloody Easy, Version 1

BLOOD PRODUCTS ADVISORY PANEL

Dr S A McCluskey, UNIVERSITY HEALTH NETWORK, TORONTO – **CHAIR**
Dr R Arrelano, QUEEN ELIZABETH II HSC, HALIFAX
Dr M Chapman, SUNNYBROOK & WOMEN'S HSC, TORONTO
Dr D Cheng, UNIVERSITY OF WESTERN ONTARIO, LONDON
Mr A Coovadia, SUNNYBROOK & WOMEN'S HSC, TORONTO
Dr C Cruise, TRILLIUM HEALTH CENTRE, TORONTO
Dr D Fergusson, OTTAWA HEALTH RESEARCH INSTITUTE, OTTAWA
Dr I Fleming, UNIVERSITY HEALTH NETWORK-MOUNT SINAI, TORONTO
Dr B Hannach, CANADIAN BLOOD SERVICES, TORONTO
Dr G Hare, ST MICHAEL'S HOSPITAL, TORONTO
Dr H Hume, CANADIAN BLOOD SERVICES, OTTAWA
Dr R McLean, HAMILTON HEALTH SCIENCES CORP., HAMILTON
Dr B McDonald, OTTAWA HOSPITAL, OTTAWA
Dr T M Yau, UNIVERSITY HEALTH NETWORK, TORONTO

TRANSFUSION REACTIONS ADVISORY PANEL

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Dr G Clarke, CANADIAN BLOOD SERVICES, EDMONTON
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Dr J Freedman, ST MICHAEL'S HOSPITAL, TORONTO
Ms N Heddle, MCMASTER UNIVERSITY, HAMILTON
Dr S Kleinman, UNIVERSITY OF BRITISH COLUMBIA, VICTORIA
Ms R Koen, ST MICHAEL'S HOSPITAL, TORONTO
Dr D H Lee, QUEEN'S UNIVERSITY, KINGSTON
Ms A Lima, SUNNYBROOK AND WOMEN'S HSC, TORONTO
Ms S McMillan, NIAGARA HEALTH SYSTEM, ST CATHARINES

BLOOD CONSERVATION ADVISORY PANEL

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Dr L Burry, MOUNT SINAI HOSPITAL, TORONTO
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Dr D Mazer, ST MICHAEL'S HOSPITAL, TORONTO
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Dr B Muirhead, WINNIPEG HEALTH SCIENCES CENTRE, WINNIPEG
Dr J Murnaghan, SUNNYBROOK AND WOMEN'S COLLEGE HSC, TORONTO
Dr M Oliver, SUNNYBROOK AND WOMEN'S COLLEGE HSC, TORONTO
Dr G Piliotis, TORONTO-SUNNYBROOK REGIONAL CANCER CENTRE, TORONTO
Dr D Towns, CANADIAN BLOOD SERVICES, CALGARY

FRACTIONATED BLOOD PRODUCTS ADVISORY PANEL

IVIG

Dr G A Rock, OTTAWA HOSPITAL, OTTAWA – **CHAIR**
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Dr F Wong, UNIVERSITY HEALTH NETWORK, TORONTO

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