Preface to Second Edition

Transfusion Ontario Programs (www.transfusionontario.org).

In 2001-2002, the Ontario Ministry of Health and Long-Term Care (MOHLTC) provided funding for a number of initiatives in the field of ‘blood conservation’, to promote rational use of blood components and products, and use evidence-based practices, including those directed at reducing ‘transfusion error’.

These initiatives included deploying ‘transfusion practitioners’ in 23 major hospitals that use the majority of blood components in the province, producing this Guide to Transfusion Medicine, and several other transfusion-related initiatives. Data supplied by the MOHLTC, illustrated below, show a temporal association between the introduction of this program in 2001-2002 and changes in the consumption of labile blood products. These changes include a reduction in the use of frozen plasma, reduction in the rate of increase in red cell use and stabilization in the rate of increase in platelet use.

YEAR-OVER-YEAR INCREMENTS (%) IN PRODUCTS ISSUED IN ONTARIO
ACKNOWLEDGEMENTS

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
Dr M A Blajchman, HAMILTON HEALTH SCIENCES CORP., HAMILTON – CHAIR
Dr R M Barr, LONDON HEALTH SCIENCES CENTRE, LONDON
Dr G Clarke, CANADIAN BLOOD SERVICES, EDMONTON
Ms J DiTomasso, MCMASTER UNIVERSITY, HAMILTON
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
Dr K Karkouti, UNIVERSITY HEALTH NETWORK, TORONTO – CHAIR
Dr G Batnagar, TRILLIUM HEALTH CENTRE, MISSISSAUGA
Dr G Bryson, OTTAWA HOSPITAL, OTTAWA
Dr L Burry, MOUNT SINAI HOSPITAL, TORONTO
Dr M Clairoux, CENTRE HOSP. UNIV. DE SHERBROOKE, HOPITAL FLEURIMONT
Dr N Colterjohn, HAMILTON HEALTH SCIENCES CORP., HAMILTON
Ms L Evans, UNIVERSITY HEALTH NETWORK, TORONTO
Dr B Feagan, LONDON HEALTH SCIENCES CENTRE, LONDON
Ms C Luke, ST MICHAEL’S HOSPITAL, TORONTO
Dr D Mazer, ST MICHAEL’S HOSPITAL, TORONTO
Dr S A McCluskey, UNIVERSITY HEALTH NETWORK, TORONTO
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
Dr V Bril, UNIVERSITY HEALTH NETWORK, TORONTO
Dr D Lane, CANADIAN BLOOD SERVICES, WINNIPEG
Dr C Laskin, UNIVERSITY HEALTH NETWORK, TORONTO
Ms A Lima, SUNNYBROOK AND WOMEN’S HSC, TORONTO
Dr A McGeer, MOUNT SINAI HOSPITAL, TORONTO
Dr M Nicolle, LONDON HEALTH SCIENCES CENTRE, LONDON
Dr L Ruben, ST MICHAEL’S HOSPITAL, TORONTO
Dr N Shear, SUNNYBROOK AND WOMEN’S HSC, TORONTO
Dr D Sutton, UNIVERSITY HEALTH NETWORK, TORONTO
Dr A Tinmouth, OTTAWA HOSPITAL, OTTAWA
Dr I Walker, HAMILTON HEALTH SCIENCES CORP., HAMILTON
Dr K Weber, MCMASTER UNIVERSITY, HAMILTON

ALBUMIN
Dr N Baig, TRILLIUM HEALTH CENTRE, MISSISSAUGA
Dr C Bell, ST MICHAEL’S HOSPITAL TORONTO
Dr A Cooper, SUNNYBROOK AND WOMEN’S HSC, TORONTO
Dr R Fowler, SUNNYBROOK AND WOMEN’S HSC, TORONTO
Dr D Irwin, UNIVERSITY OF TORONTO, TORONTO
Dr W Sibbald, SUNNYBROOK AND WOMEN’S HSC, TORONTO
Dr S Tobe, SUNNYBROOK AND WOMEN’S HSC, TORONTO
Dr F Wong, UNIVERSITY HEALTH NETWORK, TORONTO
Adapted from the WHO 1998 recommendations for the clinical use of blood:  

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. 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.

Important Notes

- This booklet is an educational tool to assist in providing care to patients.
- The recommendations are based on guidelines for ADULT patients only and may not apply to children.
- 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.

Disclaimer: While the advice and information in these guidelines are believed to be true and accurate at the time of publishing, neither the authors nor the publishers accept any legal responsibility or liability for any errors or omissions in the information provided, or for any of the recommendations made. Any decision involving patient care must be based on the judgement of the attending physician according to the needs and condition of each individual patient.
CONTENTS

1 Transfusion Basics ........................................... 10–15

2 Red Blood Cells .................................................. 16–21

3 Components ..................................................... 22–29
   • Platelets ......................................................... 22
   • Plasma .......................................................... 26
   • Cryoprecipitate ........................................... 29

4 Risk Charts ....................................................... 30–33
   ◆ Physician risk chart ........................................... 30
   ◆ Patient risk chart ............................................ 32

5 Transfusion Reactions ......................................... 34–65
   ◆ Reporting ......................................................... 34
   ◆ Reaction by symptom ........................................ 35
     • Fever .......................................................... 36
     • Dypsnea ...................................................... 43
     • Urticaria & Other Allergic Reactions/Anaphylaxis ... 49
     • Hypotension .................................................. 53
     • Hemolysis after transfusion ................................ 55
     • Cytopenias after transfusion ................................ 57
     • Virus, prion, and parasite infections ...................... 60
     • Complications of massive transfusion .................... 63

6 Blood Conservation in Surgical Patients .................. 66–83
   ◆ Good surgical technique .................................... 68
   ◆ Iron ............................................................. 70
   ◆ Preoperative Autologous Blood Donation ................ 72
   ◆ Acute Normovolemic Hemodilution ...................... 75
   ◆ Intraoperative Cell Salvage ................................ 77
   ◆ Erythropoietin in elective surgery ......................... 78
   ◆ Antifibrinolytics ............................................... 80
   ◆ DDAVP .......................................................... 82
   ◆ Regional Anesthesia .......................................... 82
   ◆ Other blood conservation strategies ....................... 83

7 Erythropoietin and Medical Patients ...................... 84–87
   ◆ General principles ............................................ 84
   ◆ Contraindications ............................................. 84
   ◆ Indications ..................................................... 84

8 Fractionated Blood Products .................................. 88–103
   ◆ Albumin ........................................................ 88
   ◆ IVIG ............................................................. 94

9 Sickle Cell Disease ............................................. 104–109

10 Appendices ..................................................... 110–121
   ◆ Price list ......................................................... 110
   ◆ Management of Jehovah’s Witnesses patients .......... 111
   ◆ References ...................................................... 112
**Overview**

**Who regulates**
- Health Canada regulates blood collection, testing, processing, and distribution.
- The Agency has expressed an intent to develop regulations for hospital transfusion practices (www.hc-sc.gc.ca/dhp-mps/index_e.html).
  - These regulations will be based in part on standards published by the Canadian Standards Association (www.csa.ca)

**Who collects**
- Canadian Blood Services (CBS), in all provinces and territories except Quebec.
- Héma-Québec in Quebec.

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

<table>
<thead>
<tr>
<th>DONOR UNITS TESTED FOR</th>
<th>SPECIFIC AGENTS</th>
<th>TESTS USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood groups</td>
<td>ABO and Rhesus (Rh) D Red cell alloantibodies</td>
<td>Blood group serology</td>
</tr>
<tr>
<td>Viruses</td>
<td>HIV 1 and 2 Hepatitis B Hepatitis C HTLV I and II West Nile Virus</td>
<td>Antibody and nucleic acid testing Surface antigen, core antibody Antibody and nucleic acid testing Antibody Nucleic acid testing</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Syphilis Bacterial contamination (Apheresis and buffy coat derived platelets)</td>
<td>Serology Bacterial culture</td>
</tr>
</tbody>
</table>

**Whole blood processing**
- Collect 490-500 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.
- White cells are removed (leukoreduction – white cells reduced by 4 logs $[10^{-4}]$ or more).
- Blood divided into separate components:
  - Red blood cells
  - Platelets*
  - Frozen plasma
  - Cryoprecipitate
- Certain groups of patients need irradiated blood components to prevent transfusion-associated graft vs host disease (TA-GvHD).
- CBS & Héma-Québec provide irradiated products on demand.
  - Refer to TA-GvHD (page 57) for list of patient groups that need irradiated blood

### Red Blood Cells and Components: Storage Conditions and Volumes

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>VOLUME</th>
<th>STORAGE LIMIT</th>
<th>STORAGE TEMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>280 mL</td>
<td>42 days</td>
<td>1 – 6 °C</td>
</tr>
<tr>
<td>Random donor platelets/unit</td>
<td>70 mL</td>
<td>5 days</td>
<td>20 – 24 °C</td>
</tr>
<tr>
<td>Buffy coat derived platelets</td>
<td>300 mL</td>
<td>5 days</td>
<td>20 – 24 °C</td>
</tr>
<tr>
<td>(from 4 units)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>300 mL</td>
<td>5 days</td>
<td>20 – 24 °C</td>
</tr>
<tr>
<td>Frozen plasma</td>
<td>250 mL</td>
<td>1 year</td>
<td>-18 °C or colder</td>
</tr>
<tr>
<td>Apheresis plasma</td>
<td>500 mL</td>
<td>1 year</td>
<td>-18 °C or colder</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>15 mL</td>
<td>1 year</td>
<td>-18 °C or colder</td>
</tr>
<tr>
<td>Autologous red blood cells*</td>
<td>280 mL</td>
<td>42 days</td>
<td>1 – 6 °C</td>
</tr>
<tr>
<td>Autologous frozen plasma**</td>
<td>250 mL</td>
<td>1 year</td>
<td>-18 °C or colder</td>
</tr>
<tr>
<td>Directed red blood cells</td>
<td>280 mL</td>
<td>42 days</td>
<td>1 – 6 °C</td>
</tr>
</tbody>
</table>

* Note: Pools of random donor platelets are being gradually superceded by pools of 4 buffy coat derived units of platelets.

* Autologous whole blood collected in CPDA1 has a storage limit of 35 days.
** Only on request and referral by patient’s physician.
**Preparation of Buffy Coat Derived Platelets**

1. **Whole Blood x 4**
   - 37°C
   - 20°C
   - Hard Spin

2. **Plasma**
   - Plasma x 1
   - Buffy coat x 4

3. **Pool**
   - 4 Buffy coats + 1 unit Plasma

4. **WBC**
   - Platelet Rich Plasma
   - Soft Spin

5. **Leuko-reduction filter**
   - Leuko-reduced pooled platelets

6. **Platelet Rich Plasma with pool of 4 donor platelets, leuko-reduced**

**Possible advantages of buffy coat derived platelets**

- Bacterial testing of pools earlier in storage
- Enhanced platelet recovery, allowing pools of 4 rather than 5 donations/dose
- Less collection injury and activation of platelets
- Improved plasma recovery for other purposes
- Possibility of extending the shelf-life

---

**ATTENTION**

- Random single donor platelets are being superceded by pools of 4 buffy coat derived units of platelets

---

**Informed Consent**

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

**What***
- Include in your discussion:
  - Description of blood or blood product
  - Benefits
  - Risks
  - Alternatives

- Give your patient the opportunity to ask questions.

*As advised in the Canadian “Report of the Expert Working Group”.3

**Of note**
- Confirm that you discussed consent with the patient, by noting it in the patient’s chart.
- 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, page 111).

**ATTENTION**

Refer to pages 30-32 for risk charts, to assist discussion of risks with patients.
Directed Blood Donations

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

Who
- Currently in Canada (other than Quebec), directed blood donations are available only for the following recipients:
  - Parent to minor child
  - Patients with rare red blood cell types
  - HLA-alloimmunized, thrombocytopenic patients requiring platelet transfusions
  - Neonatal allo-immune thrombocytopenia
- In Quebec, all recipients may have access to directed blood donations.

Where
- Directed blood donations are collected by Canadian Blood Services and Héma-Québec.

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.
**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)

1. **Transfusion PLANNED**
2. Surgery with > 10% risk of transfusion

**Group & Screen**

**Group & Screen & Crossmatch**

**Routine Transfusion Medicine Tests**

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

**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**

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

**ATTENTION**

Check the patient’s wristband before transfusing!
Failure to check is the major cause of acute hemolytic transfusion reactions.
## 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 at:

  ![Monitoring schedule](image)

- Transfuse slowly (50 mL/hr) for the first 15 minutes, where appropriate.
- Monitor the patient closely for the first 15 minutes.

### 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 hrs, but always within 4 hrs.
- 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.

### 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 57 (irradiated products) and page 61 (CMV-seronegative products).
**Indications for RBCs**

**ACUTE BLOOD LOSS**

- Maintain hemoglobin > 70 g/L during active bleeding.
  - 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:
  - Impaired pulmonary function
  - Increased oxygen consumption (fever, chills)
  - Coronary artery disease
  - Unstable or acute coronary syndromes
  - 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.

- In a patient with an acute coronary syndrome, there is controversy over where to maintain the hemoglobin level:
  - 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 transfusions 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, and possibly superior to, a liberal transfusion policy for critically ill patients.

**PERIOPERATIVE PATIENT**

- Manage patients undergoing elective surgery preoperatively, intraoperatively, and postoperatively with strategies to minimize the need for RBCs (see page 67).

- Administer RBCs one unit at a time in non-urgent settings.

- Assess patient prior to transfusing additional units (clinical exam & hemoglobin level).

- Follow guidelines for perioperative patient:

<table>
<thead>
<tr>
<th>HEMOGLOBIN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 g/L</td>
<td>Likely inappropriate except in exceptional circumstances.</td>
</tr>
<tr>
<td>70-100 g/L</td>
<td>Likely to be appropriate if there are signs or symptoms of impaired oxygen delivery.</td>
</tr>
<tr>
<td>&lt; 70 g/L</td>
<td>Likely to be appropriate.</td>
</tr>
<tr>
<td>&lt; 60 g/L</td>
<td>Transfusion highly recommended.</td>
</tr>
</tbody>
</table>

  - Young patients with low risk of ischemic cardiovascular disease can sometimes tolerate greater degrees of anemia.

**CHRONIC ANEMIA**

- Administer transfusions only when alternatives do not exist or have failed.

- Administer RBCs at intervals to maintain the hemoglobin just above the lowest concentration that is not associated with symptoms of anemia.

- Assess patients that are expected to have long-term transfusion-dependent survival for iron overload, and treat if appropriate.
COMPONENTS: Platelets

Basics

- Platelets come in 4 forms:
  - Pool of 4 units of buffy coat derived platelets
  - Pool of 5 units of random donor platelets
  - 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.
- The bleeding time is NOT useful in predicting which thrombocytopenic patients are at risk.\(^\text{11}\)
- Relative Contraindications:
  - Thrombotic thrombocytopenic purpura (TTP)
  - Heparin induced thrombocytopenia (HIT)
  - Post-transfusion purpura (PTP)

Monitor patient

- Check patient’s vital signs; vital signs should be assessed at:
  - 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 x 10^9/L.\(^\text{13}\)

Transfuse

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

Risks

- Risk of sepsis from a pool of random platelets is approximately 1 per 10,000 transfusions.\(^\text{14}\)

Follow-up

- Obtain post-transfusion platelet counts (10-60 min) after all transfusions to ensure adequate replacement and recognition of platelet refractoriness.\(^\text{15}\)
  - A pool of donor platelets should raise the platelet count of an average sized adult by at least 15 x 10^9/L
  - If increments in platelet count are NOT adequate, special measures are required. Refer to the algorithm on page 24.
Platelet Refractoriness Management Algorithm

1. Post-transfusion increment in platelet count > 15x10^9/L
   - Yes
   - No
     - Refractoriness not present
     - Use ABO identical platelets
     - Platelet count increment < 15x10^9/L
       - Yes
       - No
         - Monitor post-transfusion platelet count
           - Consider, and where present, manage other causes of refractoriness. If absent, test for HLA antibodies
           - Antibodies present
             - Yes
             - No
               - Determine patient’s HLA type
                 - Yes
                 - No
                   - Continued poor responses
                     - Select HLA-compatible apheresis donor and supply single donor irradiated platelets
                       - Yes
                       - No
                         - Post-transfusion increment in platelet count > 15x10^9/L
                           - Yes
                           - No

2. Procedures not associated with significant blood loss
   - 1 pool of platelets on hold, transfuse only if significant bleeding
   - 20-50
     - Procedures not associated with significant blood loss
       - 1 pool of platelets
         - > 15x10^9/L
           - Seek transfusion medicine consultation
             - Yes
             - No

3. Procedures associated with blood loss or major surgery (> 500 ml expected blood loss)
   - Transfuse 1 pool immediately before procedure
   - 50
     - Procedures associated with blood loss or major surgery
       - Transfuse 1 pool immediately before procedure
         - > 500 ml expected blood loss
           - Yes
           - No

4. Pre-neurosurgery or head trauma
   - Transfuse 1 pool of platelets
   - < 100
     - Pre-neurosurgery or head trauma
       - Transfuse 1 pool of platelets
         - Any
           - Platelet dysfunction and marked bleeding (e.g. post cardiopulmonary bypass, aspirin, antiplatelet agents)
             - Transfuse 1 pool of platelets

Indications & Infusion Recommendations

<table>
<thead>
<tr>
<th>PLT (x10^9/L)</th>
<th>CLINICAL SETTING</th>
<th>SUGGEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>Immune thrombocytopenia</td>
<td>Transfuse platelets only with serious bleeding</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Non-immune thrombocytopenia</td>
<td>Transfuse 1 pool of platelets</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Non-immune thrombocytopenia &amp; HLA-alloimmunized</td>
<td>Transfuse 1 unit of HLA-matched apheresis</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Non-immune thrombocytopenia and fever &gt; 38.5°C or coagulopathy</td>
<td>Transfuse 1 pool of platelets</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Procedures not associated with significant blood loss</td>
<td>Transfuse 1 pool of platelets</td>
</tr>
<tr>
<td>20-50</td>
<td>Procedures not associated with significant blood loss</td>
<td>1 pool of platelets on hold, transfuse only if significant bleeding</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Epidural anesthesia and lumbar puncture</td>
<td>Transfuse 1 pool immediately before procedure</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Procedures associated with blood loss or major surgery (&gt; 500 ml expected blood loss)</td>
<td>Transfuse 1 pool immediately before procedure</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>Pre-neurosurgery or head trauma</td>
<td>Transfuse 1 pool of platelets</td>
</tr>
<tr>
<td>Any</td>
<td>Platelet dysfunction and marked bleeding (e.g. post cardiopulmonary bypass, aspirin, antiplatelet agents)</td>
<td>Transfuse 1 pool of platelets</td>
</tr>
</tbody>
</table>
COMPONENTS: Frozen Plasma

Basics

- Frozen plasma (FP) can be derived from two sources:
  - Random donor plasma (250 mL)
  - Apheresis donors (500 mL)
    - equivalent to 2 units of random donor plasma

How

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

Dose

- 10-15 mL/kg
  - Small adult: 3 units
  - Large adult: 4 units

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.
  - The biological half-life of plasma coagulation proteins is different for each protein:
    - 3–6 hours for factor VII
    - 8–12 hours for factor VIII
    - 2–3 days for factors II and IX

Monitor patient

- Check patient’s vital signs; vital signs should be assessed at:
  - Transfuse slowly (50 mL/hr) for the first 15 minutes, where possible.
  - Monitor the patient closely for the first 15 minutes.
  - Check PT/INR and PTT after infusion (10–60 minutes).

Notes:

- ‘Frozen plasma’ (FP) frozen within 24 hours of collection is superseding ‘Fresh Frozen Plasma’ (FFP) frozen within 8 hours.
- Change required to accommodate buffy coat method for platelet preparation.
- There is no clinically significant change in the factor VIII content of FP compared with FFP.
- FFP and cryosupernatant will still be available for plasma exchange.
- Contains 400–900 mg fibrinogen per random donation.
1. **Emergency reversal of warfarin therapy** in a patient undergoing an emergency operative procedure or with potentially life-threatening bleeding.\(^3\)
   - Urgent reversal of warfarin therapy in a bleeding patient OR a patient about to undergo an invasive procedure should also include Vitamin K (10 mg i.v.)\(^{23,24}\)
   - Repeat PT/PTT after infusion of FP to ensure that replacement is adequate\(^{20}\)
   - After administration, Vitamin K effect can be detected after 2 hours and the INR should be normalized after 12-24 hours\(^{25}\)

**Note:26**
- Patients with INR > 5 due to warfarin without bleeding
  - With INR > 5 and < 9, bring within the therapeutic range with 1-2 mg of oral Vitamin K\(^{24}\)
  - With INR ≥ 9, use 5-10 mg of oral vitamin K\(^{24}\)
  - SC and IM NOT recommended; use intravenous formulation orally, if oral tablets are not readily available
  - These patients do NOT require frozen plasma

2. **Active bleeding/major surgery with PT/PTT more than 1.5 times normal\(^{10}\)**

3. **Microvascular bleeding or massive transfusion** AND patient’s clinical status precludes waiting 30-45 minutes for PT/PTT results\(^3\)

4. Patients with liver disease-related coagulopathy for certain invasive procedures (percutaneous liver biopsy, paracentesis, thoracentesis) and INR > 2.0 \(^3\)

---

**ATTENTION**

Frozen plasma is NOT indicated for reversal of heparin or low M-W heparin anticoagulation.\(^3\)

---

**Components: Cryoprecipitate**

**What**
- Cryoprecipitate contains factor VIII (8), fibrinogen, and von Willebrand’s 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.\(^{10}\)
- 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’s disease or Hemophilia A only:
   - when factor concentrates are unavailable (remote geographic region); and
   - DDAVP is unavailable or ineffective
<table>
<thead>
<tr>
<th>Risk of Event</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 10</td>
<td>Febrile non-hemolytic transfusion reaction per pool of 5 donor units of platelets (5 ‘donor exposures’) per unit of component</td>
</tr>
<tr>
<td>1 in 100</td>
<td>Minor allergic reactions (urticaria)</td>
</tr>
<tr>
<td>1 in 300</td>
<td>Febrile non-hemolytic transfusion reaction per unit of RBC (1 ‘donor exposure’)</td>
</tr>
<tr>
<td>1 in 700</td>
<td>Transfusion-associated circulatory overload per transfusion episode</td>
</tr>
<tr>
<td>1 in 5,000</td>
<td>Transfusion-related acute lung injury (TRALI)</td>
</tr>
<tr>
<td>1 in 7,000</td>
<td>Delayed hemolytic transfusion reaction</td>
</tr>
<tr>
<td>1 in 10,000</td>
<td>Symptomatic bacterial sepsis per pool of 5 donor units of platelets</td>
</tr>
<tr>
<td>1 in 40,000</td>
<td>Death from bacterial sepsis per pool of 5 donor units of platelets</td>
</tr>
<tr>
<td>1 in 40,000</td>
<td>ABO-incompatible transfusion per RBC transfusion episode</td>
</tr>
<tr>
<td>1 in 40,000</td>
<td>Serious allergic reaction per unit of component</td>
</tr>
<tr>
<td>1 in 82,000**</td>
<td>Transmission of hepatitis B virus per unit of component</td>
</tr>
<tr>
<td>1 in 100,000</td>
<td>Symptomatic bacterial sepsis per unit of RBC</td>
</tr>
<tr>
<td>1 in 500,000</td>
<td>Death from bacterial sepsis per unit of RBC</td>
</tr>
<tr>
<td>&lt; 1 in 1,000,000</td>
<td>Transmission of West Nile Virus</td>
</tr>
<tr>
<td>1 in 3,000,000</td>
<td>Transmission of HTLV per unit of component</td>
</tr>
<tr>
<td>1 in 3,100,000</td>
<td>Transmission of hepatitis C virus per unit of component</td>
</tr>
<tr>
<td>1 in 4,700,000</td>
<td>Transmission of human immunodeficiency virus (HIV) per unit of component</td>
</tr>
</tbody>
</table>

**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 3).**

### 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) – 2000-01.
  - 1 in 285,000 components possibly, probably or definitely related to patient death27
  - 1 in 192,231 components resulted in a death from transfusion28

### Serious Hazards of Transfusion (SHOT), United Kingdom
Major Adverse Events Reported 1996-2003 (2087 Reports)27

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect component</td>
<td>67%</td>
</tr>
<tr>
<td>Acute hemolysis</td>
<td>11%</td>
</tr>
<tr>
<td>Delayed hemolysis</td>
<td>10%</td>
</tr>
<tr>
<td>TRALI*</td>
<td>7%</td>
</tr>
<tr>
<td>PTP**</td>
<td>2%</td>
</tr>
<tr>
<td>Infections</td>
<td>2%</td>
</tr>
<tr>
<td>TA-GvHD†</td>
<td>1%</td>
</tr>
<tr>
<td>Unclassified &lt; 0.5%</td>
<td></td>
</tr>
</tbody>
</table>

* Transfusion-related acute lung injury (TRALI)
** Post-transfusion Purpura (PTP)
† Transfusion-associated Graft vs Host Disease (TA-GvHD)
### Risk of Event vs. Event

<table>
<thead>
<tr>
<th>Risk of Event</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 100</td>
<td>Hives (itchy skin rash)</td>
</tr>
<tr>
<td>1 in 300</td>
<td>Fever</td>
</tr>
<tr>
<td>1 in 700</td>
<td>Heart failure</td>
</tr>
<tr>
<td>1 in 5,000</td>
<td>Lung injury</td>
</tr>
<tr>
<td>1 in 7,000</td>
<td>Delayed hemolysis. Hemolysis is when your red blood cells are destroyed.</td>
</tr>
<tr>
<td>1 in 10,000</td>
<td>Symptomatic bacterial sepsis, per pool of platelets that you receive. Sepsis is when you get an infection in your bloodstream or tissue.</td>
</tr>
<tr>
<td>1 in 40,000</td>
<td>Death from bacterial sepsis, per pool of platelets that you receive.</td>
</tr>
<tr>
<td>1 in 40,000</td>
<td>Wrong ABO (blood) group, per unit of red blood cells that you receive.</td>
</tr>
<tr>
<td>1 in 40,000</td>
<td>Anaphylaxis, which is an extreme sensitivity to a drug or substance that can result in death.</td>
</tr>
<tr>
<td>1 in 82,000</td>
<td>Hepatitis B (HBV) transmission per unit of component. Hepatitis is an inflammation of the liver. Hepatitis B is caused by a virus and spread through contact with infected blood, blood products, and body fluids.</td>
</tr>
<tr>
<td>1 in 100,000</td>
<td>Symptomatic bacterial sepsis, per unit of red blood cells that you receive.</td>
</tr>
<tr>
<td>1 in 500,000</td>
<td>Death from bacterial sepsis, per unit of red blood cells that you receive.</td>
</tr>
<tr>
<td>&lt; 1 in 1,000,000</td>
<td>Transmission of West Nile Virus</td>
</tr>
<tr>
<td>1 in 3,000,000</td>
<td>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.</td>
</tr>
<tr>
<td>1 in 3,100,000</td>
<td>Hepatitis C (HCV) transmission, per unit of component. Hepatitis is an inflammation of the liver. Hepatitis C is caused by a virus and spread through injection drug use, tattooing, and body piercing.</td>
</tr>
<tr>
<td>1 in 4,700,000</td>
<td>Human Immunodeficiency Virus (HIV) transmission, per unit of component. HIV is the virus that causes AIDS. HIV attacks the immune system.</td>
</tr>
</tbody>
</table>

### Frequency of Non-Transfusion Associated Risks for Comparison with Risks of Complications of Blood Transfusion

<table>
<thead>
<tr>
<th>Hazard</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dying from lung cancer after smoking 1 pack a day for 30 years</td>
<td>1 in 10^{29}</td>
</tr>
<tr>
<td>Stroke within 30 days of cardiac surgery</td>
<td>1 in 60^{30}</td>
</tr>
<tr>
<td>Death associated with hip replacement surgery</td>
<td>1 in 100^{31}</td>
</tr>
<tr>
<td>Annual risk of death in a motor vehicle crash</td>
<td>1 in 10,000^{32}</td>
</tr>
<tr>
<td>Annual risk of being murdered in Canada</td>
<td>1 in 60,000^{32}</td>
</tr>
<tr>
<td>Death from anesthesia in fit patients</td>
<td>1 in 200,000^{33}</td>
</tr>
<tr>
<td>Death from oral contraceptives age &lt; 20 yrs</td>
<td>1 in 300,000^{34}</td>
</tr>
<tr>
<td>Annual risk of death from accidental electrocution in Canada</td>
<td>1 in 1,000,000^{32}</td>
</tr>
<tr>
<td>Annual risk of death from being struck by lightning in Canada</td>
<td>1 in 5,000,000^{32}</td>
</tr>
</tbody>
</table>
**Reporting**

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

**What**

- The transfusion service will investigate, assess and report the event to the Transfusion Transmitted Injuries Surveillance System (TTISS) at Public Health Agency of Canada*.

- Reactions relating to the quality of the product must be reported directly to CBS/Héma-Québec.

**How**

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

* [www.phac-aspc.gc.ca](http://www.phac-aspc.gc.ca) (click on Infectious Diseases; Blood Safety)

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

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

**Management Algorithm**

**Possible Reactions:**
- Bacterial sepsis
- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction

**Dyspnea**

- Management Algorithm
- Possible Reactions:
  - Transfusion-related acute lung injury (TRALI)
  - Transfusion-associated circulatory overload (TACO)
  - Anaphylaxis

**Urticaria & Other Allergic Reactions**

- Management Algorithm
- Possible Reactions:
  - Anaphylaxis
  - Minor allergic reaction – Urticaria

**Hypotension**

- Management Algorithm
- Possible Reactions:
  - Bradykinin mediated hypotension

**Hemolysis**

- Possible Reactions:
  - Acute hemolytic transfusion reaction
  - Hemolysis not related to RBC alloantibodies
  - Delayed hemolytic transfusion reactions

**Cytopenias**

- Possible Reactions:
  - Transfusion-associated graft vs host disease (TA-GvHD)
  - Post-transfusion purpura (PTP)
  - Transfusion-related alloimmune thrombocytopenia
  - Transfusion-related alloimmune neutropenia

**Virus, Prion, and Parasite Infection**

- Viruses
- Prions
- Other transfusion-transmissible agents
BACTERIAL SEPSIS OR CONTAMINATION

ETIOLOGY

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

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

<table>
<thead>
<tr>
<th>Gram-negative</th>
<th>Gram-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Klebsiella pneumoniae</td>
<td>• Staphylococcus aureus</td>
</tr>
<tr>
<td>• Serratia marcescens</td>
<td>• Staphylococcus epidermidis</td>
</tr>
<tr>
<td>• Pseudomonas species</td>
<td>• Bacillus cereus</td>
</tr>
<tr>
<td>• Yersinia enterocolitica</td>
<td></td>
</tr>
</tbody>
</table>

INCIDENCE

<table>
<thead>
<tr>
<th>BACTERIAL CONTAMINATION</th>
<th>SYMPTOMATIC SEPTIC REACTIONS</th>
<th>FATAL BACTERIAL SEPSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 units of platelets</td>
<td>1 in 1,000</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>1 unit of RBC</td>
<td>1 in 50,000</td>
<td>1 in 100,000</td>
</tr>
</tbody>
</table>

- 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
ACUTE HEMOLYTIC TRANSFUSION REACTION

ETIOLOGY

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

PREVENTION

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

CLINICAL PRESENTATION

■ Clinical features of transfusion-associated sepsis may include:36,40
  ◆ Rigors, fever, tachycardia, hypotension, nausea and vomiting, dyspnea, disseminated intravascular coagulation
■ It is usually possible to culture the offending organism from both the patient and the transfused product.
■ There may be no immediate clinical signs of bacterial infection after transfusion of bacterially-contaminated platelets, if the bacterial load is small.

MANAGEMENT

■ If transfusion-transmitted bacterial infection is suspected:39
  ◆ 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 for culture (clamped) 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.
MANAGEMENT

■ Stop the transfusion!
■ Check if there is 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 (blood bank) to re-check ABO-group.
■ Return residual of blood product(s) and tubing (clamped) to the hospital transfusion service.
■ Provide supportive care.
■ Maintain good urine output.
■ Avoid fluid overload.
■ Manage DIC and hemorrhage as clinically indicated.

PREVENTION

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

INCIDENCE

■ 1 in 38,000 red cell transfusions are ABO-incompatible due to transfusing the wrong blood to a patient.\(^4^2\)
■ Less than 10% of ABO-incompatible transfusions result in a fatal outcome.\(^4^2\)
■ Over 50% of patients have no morbidity from an ABO-incompatible transfusion.
■ Risk of death correlates with the amount of incompatible blood transfused.\(^4^3\)
■ 13% of major morbidities from RBC transfusions are the result of an acute hemolytic reaction from non-ABO group antigens.\(^2^7\)

CLINICAL PRESENTATION\(^4^4\)

■ 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.

RBC alloantibodies (non-ABO)

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

ATTENTION

Stop transfusion immediately if acute hemolytic reaction suspected.
Dyspnea
(Anaphylaxis is described under Allergic Reactions/Anaphylaxis)

MANAGEMENT ALGORITHM

**Dyspnea**

**Immediately Management:**
1. Stop transfusion & maintain IV access with 0.9% saline
2. Take patient’s vital signs
3. Re-check identification of patient & blood product
4. Notify physician
5. Notify hospital transfusion service (blood bank)
6. Return clamped blood unit & tubing attached

**Consider:**
- **TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**
- **TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)**
- **ANAPHYLAXIS**
  - If TRALI is suspected, notify 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

**FEBRILE NON-HEMOLYTIC TRANSFUSION REACTION (FNHTR)**

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

**INCIDENCE**

<table>
<thead>
<tr>
<th>Component</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cells</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Platelet pool</td>
<td>1 in 10</td>
</tr>
</tbody>
</table>

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

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

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

**TRANSFUSION REACTIONS**

**Dyspnea**

Immediate Management:
1. Stop transfusion & maintain IV access with 0.9% saline
2. Take patient’s vital signs
3. Re-check identification of patient & blood product
4. Notify physician
5. Notify hospital transfusion service (blood bank)
6. Return clamped blood unit & tubing attached

**Consider:**
- **TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**
- **TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)**
- **ANAPHYLAXIS**
  - If TRALI is suspected, notify 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)\textsuperscript{49,50}

**DEFINITION OF ACUTE LUNG INJURY (ALI)**
- Acute onset
- Hypoxemia
  - PaO\textsubscript{2}/FiO\textsubscript{2} < 300 mm Hg OR
  - Oxygen saturation is < 90% on room air OR
  - Other clinical evidence
- Bilateral lung infiltration on the chest radiograph
- No evidence of circulatory overload

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

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

**ETIOLOGY**
- Presently not fully defined. Two postulated mechanisms have been implicated:
  1. Passive transfer of HLA or granulocyte antibodies from donor to blood product recipient; or, less commonly, HLA or granulocyte antibodies in the recipient (antibodies detected in donor or recipient in 75% of cases)\textsuperscript{51}
     - Antibodies are most common in multiparous female donors as a consequence of prior pregnancies
  2. Biologically active lipids in transfused component\textsuperscript{52}

**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.\textsuperscript{51,53}
- TRALI is known to be under-diagnosed and under-reported.
PREVENTION
- Deferral of donors confirmed to be implicated in an episode of TRALI, and with either antibodies or implicated in multiple episodes.
- Adherence to evidence-based transfusion guidelines.

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)

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

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

CLINICAL PRESENTATION
- Clinical presentation includes: dyspnea, orthopnea, cyanosis, tachycardia, increased venous pressure, and hypertension.
Urticaria & Other Allergic Reactions/Anaphylaxis

MANAGEMENT ALGORITHM

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

**Immediate Management:**
1. **Interrupt the transfusion** & maintain IV access with 0.9% saline
2. Take the patient’s vital signs
3. Re-check name of patient & name on blood product
4. Notify patient’s physician
5. Notify 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 > 2/3rds body

**No**

- Consistent with minor allergic reaction
  - Give diphenhydramine 25-50 mg IV/po
  - Continue transfusion cautiously
  - Stop transfusion if patient develops any of the above symptoms

**Yes**

- **DO NOT RESTART TRANSFUSION**
  - Notify the patient’s physician **STAT**
  - Notify the hospital transfusion service (blood bank) immediately

- **SUSPECT ANAPHYLACTIC REACTION OR SEVERE ALLERGIC REACTION**

**PREVENTION**
Pre-transfusion assessment is important to identify patients at risk and management should be adjusted accordingly.

Preventative measures include:
- Transfuse over longer periods (maximum 4 hours)
- Pre-emptive diuretics
- Components can be split into smaller aliquots to further reduce the speed of infusion without wasting product or increasing donor exposure

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

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

**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.

**ALLERGIC REACTIONS/ANAPHYLAXIS**

**MANAGEMENT**
- 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:
  - 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

**TRANSFUSION REACTIONS**

![Image of a transfusion reaction management chart](https://via.placeholder.com/150)
ANAPHYLAXIS

ETOLOGY\textsuperscript{59}
- 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, and 1 in 1,200 blood donors have anti-IgA, but most are NOT at risk of an anaphylactic transfusion reaction (reasons are not clear at this time).\textsuperscript{60}
- Haptoglobin deficiency is not uncommon in Asian patients (1 in 1,000) and has been associated with anaphylactic reactions.\textsuperscript{61}

INCIDENCE
- Transfusion-associated anaphylactic shock is rare.\textsuperscript{62}

CLINICAL PRESENTATION\textsuperscript{59}
- 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 (about 3% of cases).
- Potentially life-threatening.

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

PREVENTION OF RECURRENT ANAPHYLAXIS
- Pre-medication with intravenous steroids and diphenhydramine.
- If a patient is found to be IgA-deficient with anti-IgA, the following products are recommended:
  - RBC-washed (3L normal saline in 6 wash cycles\textsuperscript{63})
  - Plasma products: IgA-deficient plasma from IgA-deficient donors, available from Canadian Blood Services and Héma-Québec

MINOR ALLERGIC REACTION – URTICARIA

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

INCIDENCE
- 1 in 100 mild urticarial reactions with plasma-containing components.\textsuperscript{64}

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.
**Hypotension**

> 30 mmHg drop in systolic or diastolic blood pressure

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

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

**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
Hemolysis after Transfusion

HEMOLYSIS NOT RELATED TO RBC ALLOANTIBODIES

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

TRANSFUSION-ASSOCIATED GRAFT VS HOST DISEASE (TA-GvHD) 68

ETIOLOGY

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

INCIDENCE

- Unknown; there were 13 cases reported in the UK SHOT program over 7 years. Incidence reduced following universal leukoreduction.27

PATIENTS AT RISK, REQUIRING IRRADIATED PRODUCTS

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

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, Jkα, C, Fyα, K.66
- Delayed hemolysis may occur with transfusion-transmitted malaria and babesiosis.

INCIDENCE

- 1 in 6715 units of RBCs transfused are associated with a delayed hemolytic transfusion reaction.66

CLINICAL PRESENTATION

- 3 days to 2 weeks after transfusion, the patient presents with hemolytic anemia (low hemoglobin, high bilirubin, reticulocytosis, spherocytosis, high LDH, positive antibody screen, and a positive direct anti-globulin test (formerly Coombs’ Test)).67

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-Jkα, then the transfusion service will provide units that do not carry the Jkα antigen).

PREVENTION

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

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

TREATMENT

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

PREVENTION

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

POST-TRANSFUSION PURPURA (PTP)69

ETIOLOGY

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

INCIDENCE

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

CLINICAL PRESENTATION

- There are 5 times as many female transfusion recipients with PTP as males, as a consequence of sensitization in previous pregnancy.70
- Occurs post-transfusion by a median of nine days (range 1 to 24).

- Platelet count is less than 10 x 10^9/L in 80% of cases.
- Mortality is 8% and the majority of deaths are from intracranial hemorrhage.
- Transfusions are frequently associated with fever, chills, rigors, and bronchospasm.
- Differentiation from straightforward platelet alloimmunization is problematic.
  - *PTP should be considered when a platelet refractory patient fails to respond to HLA-matched platelets*

TREATMENT

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

PREVENTION

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

WARNING

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

TRANSFUSION-RELATED ALLOIMMUNE THROMBOCYTOPENIA

- Uncommon cause of thrombocytopenia
- Due to platelet specific donor alloantibodies to patient platelet antigens71

TRANSFUSION-RELATED ALLOIMMUNE NEUTROPENIA72

- Rare cause of neutropenia

ATTENTION

- Immunocompromised patients must receive irradiated blood.

Patients affected by PTP are at risk of NAIT.
Cytomegalovirus (CMV):\textsuperscript{80,81}

- 40% of Canadian blood donors have antibodies to and harbour CMV in their white cells, but without clinical consequences.
- Transmission is vertical from mother to child, or by body fluids, sexual activity, transfusion, or transplantation.
- CMV-seronegative units are available from CBS and HQ for restricted use only. The most commonly recommended indications for CMV-seronegative products are:
  1. CMV-seronegative pregnant women
  2. Intrauterine transfusions
  3. CMV-seronegative allogeneic bone marrow transplant recipients
- Leukoreduction removes most, but not all CMV from blood components.\textsuperscript{82}
- 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 known cases in Canada since nucleic acid testing of donations began in July 2003.\textsuperscript{83}
- In the USA in 2003, there were 6 confirmed cases of transfusion-transmitted West Nile Virus from 6 million donations.\textsuperscript{84}
- 1 case in the USA in 2004.\textsuperscript{75}
- Facts about transfusion-transmitted West Nile Virus:
  - The virus can be transmitted through RBCs, platelets, plasma, and cryoprecipitate, but not through manufactured blood products (e.g. albumin, IVIG, clotting factor concentrates)
  - The onset of symptoms post-transfusion has ranged from 3 to 13 days (median 7 days)
  - Symptomatic recipients were primarily immunocompromised patients; however, post-partum and post-operative patients have been affected

Virus, Prion, and Parasite Infection

(Bacterial contamination is described under Fever)

VIRUSES

Risks

- Donating blood in the ‘window period’ – the interval between the time of infectivity and the appearance of detectable disease markers such as specific antibodies or viral nucleic acid sequences.
- Current ‘window period’ estimates are:\textsuperscript{73}
  - 11 days for HIV
  - 10 days for HCV
  - 59 days for HBV
- Figures in chart below are risk per donor exposure: (i.e. 1 unit of RBC)

<table>
<thead>
<tr>
<th>Virus</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 4.7 million\textsuperscript{74}</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>1 in 3.1 million\textsuperscript{74}</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>1 in 82,000\textsuperscript{74}</td>
</tr>
<tr>
<td>Human T-cell lymphotropic virus</td>
<td>1 in 3 million\textsuperscript{74}</td>
</tr>
<tr>
<td>West Nile Virus (WNV)</td>
<td>&lt; 1 in 1 million\textsuperscript{75}</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Virus</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>50% risk of developing AIDS within 7 years, with older recipients showing shorter latency periods.\textsuperscript{76}</td>
</tr>
<tr>
<td>HCV</td>
<td>50-70% of recipients develop chronic hepatitis, about 30 to 50% of which proceed to cirrhosis, usually indolent, and an uncertain proportion of these develop hepatocellular carcinoma.\textsuperscript{77}</td>
</tr>
<tr>
<td>HBV</td>
<td>60% of HBV-infected individuals develop evidence of hepatitis (incubation period of 11-12 wks). The vast majority of cases resolve by developing immunity. In less than 5% of cases, HBsAg persists beyond 6 months, indicating chronic infection with the likelihood of chronic liver disease. Rarely, hepatitis B presents as acute fulminant hepatitis.\textsuperscript{78}</td>
</tr>
<tr>
<td>HTLV</td>
<td>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.\textsuperscript{79}</td>
</tr>
</tbody>
</table>

Transfusion Reactions

VIRUS, PRION, AND PARASITE INFECTION

(Fever)

Bacterial contamination is described under Fever.

Cytomegalovirus (CMV)\textsuperscript{80,81}

- 40% of Canadian blood donors have antibodies to and harbour CMV in their white cells, but without clinical consequences.
- Transmission is vertical from mother to child, or by body fluids, sexual activity, transfusion, or transplantation.
- CMV-seronegative units are available from CBS and HQ for restricted use only. The most commonly recommended indications for CMV-seronegative products are:
  1. CMV-seronegative pregnant women
  2. Intrauterine transfusions
  3. CMV-seronegative allogeneic bone marrow transplant recipients
- Leukoreduction removes most, but not all CMV from blood components.\textsuperscript{82}
- 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 known cases in Canada since nucleic acid testing of donations began in July 2003.\textsuperscript{83}
- In the USA in 2003, there were 6 confirmed cases of transfusion-transmitted West Nile Virus from 6 million donations.\textsuperscript{84}
- 1 case in the USA in 2004.\textsuperscript{75}
- Facts about transfusion-transmitted West Nile Virus:
  - The virus can be transmitted through RBCs, platelets, plasma, and cryoprecipitate, but not through manufactured blood products (e.g. albumin, IVIG, clotting factor concentrates)
  - The onset of symptoms post-transfusion has ranged from 3 to 13 days (median 7 days)
  - Symptomatic recipients were primarily immunocompromised patients; however, post-partum and post-operative patients have been affected

Virus, Prion, and Parasite Infection

(Bacterial contamination is described under Fever)
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.90

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

1. **Dilutional coagulopathy**
   - 50% of massively-transfused patients develop an INR > 2.0 and about 33% have thrombocytopenia with a platelet count < 50 x 10^9/L.91
   - Number of RBCs transfused does not accurately predict the need for a platelet and FP transfusion; use laboratory values to determine when these products should be transfused.91

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):92
     - < 34°C - 40%
     - < 33°C – 69%
     - < 32°C – 100%
Transfusion Reactions

3. Hypocalcemia/Hypomagnesemia/Citrate toxicity

- Risk of clinically important hypothermia is significantly increased by infusion of 5 or more units of blood.\(^9^2\)
- Consequences of hypothermia:
  - Platelet dysfunction
  - Reduced clearance of citrate
  - Decreased cardiac output
  - Hypotension
  - Arrhythmias (especially if cold blood is transfused rapidly through a central line)
  - ECG changes: prolonged PR, QRS, QT; T-wave inversion; J (Osborne) waves

- Risk of clinically important hypothermia is significantly increased by infusion of 5 or more units of blood.\(^9^2\)

- Consequences of hypothermia:
  - Platelet dysfunction
  - Reduced clearance of citrate
  - Decreased cardiac output
  - Hypotension
  - Arrhythmias (especially if cold blood is transfused rapidly through a central line)
  - ECG changes: prolonged PR, QRS, QT; T-wave inversion; J (Osborne) waves

3. Hypocalcemia/Hypomagnesemia/Citrate toxicity

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

4. Metabolic acidosis

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

5. Hyperkalemia

- Release of potassium from stored RBCs increases with storage time and after irradiation.
- After 28-days storage in citrate, a unit of RBCs contains approximately 6 mmol of potassium per unit.\(^9^3\)

Note: For discussion of the changes in electrolytes and acid-base balance with massive transfusion, see Wilson et al.\(^9^4\)

TIPS DURING MASSIVE TRANSFUSION/BLEEDING

- Monitor core temperature.
- Prompt use of measures to prevent hypothermia, including use of a blood warmer for all IV fluids and blood components.
- Watch for dilutional coagulopathy.
  - While patient is actively bleeding:
    - Transfuse to keep platelet count > 50x10^9/L (with head injury > 100x10^9/L), INR < 1.5, and fibrinogen > 1.0 g/L with blood components
  - Watch for hypocalcemia.
- Use SQ40 Pall® filter with blood tubing to minimize the number of times the blood tubing has to be changed.
  - Change blood tubing q4-q24h with SQ40 filter
  - Change blood tubing q2-4 units of RBCs if SQ40 Pall® not used
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 and offered a blood conservation alternative at least 28 days prior to surgery.
  - As use varies from institution to institution and surgeon to surgeon for the same procedure, each institution must determine its own requirements for transfusion.

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.

Blood Conservation Strategies

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

<table>
<thead>
<tr>
<th>Time until Surgery</th>
<th>Blood Conservation Strategies Available</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 35 days</td>
<td>- Investigate and treat anemia</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>- Delay surgery until anemia corrected</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>- Iron</td>
<td>70</td>
</tr>
<tr>
<td>14–35 days</td>
<td>- Delay surgery until anemia corrected</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>- Autologous blood donation</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>- Erythropoietin weekly dosing regimen</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>- Iron</td>
<td>70</td>
</tr>
<tr>
<td>10–13 days</td>
<td>- Delay surgery until anemia corrected</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>- Erythropoietin daily dosing regimen</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>- Iron</td>
<td>70</td>
</tr>
<tr>
<td>&lt; 10 days</td>
<td>- Delay surgery until anemia corrected</td>
<td>–</td>
</tr>
<tr>
<td>before surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>- Attention to surgical hemostasis</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>- Antifibrinolytics and DDAVP</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>- Intraoperative cell salvage</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>- Regional anesthesia</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>- Other measures, mainly investigational</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>- Adherence to strict transfusion guidelines</td>
<td>21</td>
</tr>
</tbody>
</table>
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 thrombogenic agents
  - Prevent and treat coagulopathy associated with massive transfusion

Stop using anti-platelet agents and anti-coagulants before major surgery

- **Acetylsalicylic Acid (Aspirin®)**
  - 48 hours minimum, 7 days preferable

- **Clopidroge (Plavix®)**
  - 5 days minimum, 7 days preferable

**NSAIDs**

- Stopping times are variable depending on the drug half-life
- Stop 5 half-lives prior to surgery (drug virtually eliminated at 5-half-lives)
- Refer to chart below for recommended stopping time; refer to individual product monograph for more details

Minimize blood sampling and loss

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

---

**Blood Conservation**

**NSAID**

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Brand Name</th>
<th>Half-Life (hours)</th>
<th>Stopping Time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Celebrex™</td>
<td>11*</td>
<td>3</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Arthrotec®</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Diflusinol</td>
<td>8–12</td>
<td>3</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Ultradol™</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Nalfon®</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Ansaid®</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil®</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Rhovail®</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Toradol®</td>
<td>4–9</td>
<td>2</td>
</tr>
<tr>
<td>Mefenamic Acid</td>
<td>Ponstan™</td>
<td>3–4</td>
<td>1</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Mobicox™</td>
<td>15–20</td>
<td>4</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Relafen®</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Nalsyn®</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Oxaaprozin</td>
<td>Daypro®</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene™</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>Tenoxicam</td>
<td>72</td>
<td>15</td>
</tr>
<tr>
<td>Tiaprofenic Acid</td>
<td>Surgam®</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tolmetin Sodium</td>
<td>Tolectin®</td>
<td>1–3</td>
<td>1</td>
</tr>
</tbody>
</table>

* Does not inhibit platelet aggregation at usual doses

**Preoperative patients on Warfarin:**

- If low risk of thromboembolic events (e.g. primary prophylaxis of atrial fibrillation):
  - Stop warfarin 4 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 hematologist on timing and preferred regimen
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 is helpful for patients with low preoperative hemoglobin levels (expected rise in hemoglobin of 11 g/L from preoperative iron)\(^98\)
  - Preoperative iron therapy for non-anemic patients MAY reduce the post-operative fall in hemoglobin level, but data are limited\(^98\)
  - 4 randomized trials failed to confirm a benefit of post-operative iron therapy in patients that were not anemic preoperatively\(^99,100,101,102\)

Dosage

- 150-200 mg of elemental iron/day.

Commonly Used Iron Replacement Therapies

**ELEMENTAL IRON**

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DOSE MG</th>
<th>ELEMENTAL MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous gluconate</td>
<td>300</td>
<td>35</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>300</td>
<td>60</td>
</tr>
<tr>
<td>Ferrous fumarate (Palafer(^{®}))</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>Polysaccharide-iron complex (Triferex(^{®}))</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

Common Adverse Events*

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

* See product monograph for details

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.).

ATTENTION

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

VITAMIN C

- Vitamin C (ascorbic acid) as an adjunct to increase iron absorption is not recommended if the elemental iron dosage is > 60 mg.\(^{103}\)

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.
- 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.

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

ATTENTION

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

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

### Cost-effectiveness of Autologous Blood Donation
- Studies suggest poor cost-effectiveness 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)

### Preoperative Autologous Blood Donation (PAD)

**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:
  - cardiac surgery
  - major vascular surgery
  - revision hip replacement
  - major spine surgery
  - radical prostatectomy
  - hepatic resection

**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**
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 Donations**
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).
2. Iatrogenic anemia – average 10 g/L hemoglobin drop per unit donated.
3. Unit lost, damaged, or prematurely discarded.
4. Surgery cancelled, resulting in outdated autologous unit.

**Risks at Transfusion**
1. Bacterial contamination – 1 in 100,000 RBC units
2. ABO-incompatible transfusion (wrong blood given to the patient) – 1 in 40,000 risk
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.\(^{112}\)

DAYS UNTIL SURGERY WHEN 1ST UNIT COLLECTED

<table>
<thead>
<tr>
<th>Days</th>
<th>35</th>
<th>28</th>
<th>21</th>
<th>14</th>
<th>6</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units of RBC regenerated after 2 units collected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STORAGE

- Current Canadian standards allow that autologous red blood cells can be stored for 42 days as RBC (see page 11) or 35 days as whole blood in CPDA1.
- 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\(^{113}\)

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

ATTENTION

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

ACUTE NORMOVOLEMIC HEMODILUTION (ANH)\(^{114}\)

Principles

- 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
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):
  - 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
  - ANH may be an acceptable alternative for some Jehovah’s Witnesses

**Safety**
- The safety of the procedure is not proven

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

### INTRAOPERATIVE CELL SALVAGE

**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

**Indication**
- Meta-analysis of 27 studies:
  - Cell salvage in orthopedic surgery (all types of salvage devices, washed and unwashed)
    - Relative risk of transfusion 0.35-0.39
  - Cell salvage in cardiac surgery (unwashed only)
    - Relative risk of transfusion 0.85
  - No increase in adverse events in treatment group
  - Consider in the setting of: trauma, hepatic resection, major orthopedic and spine surgery, or ruptured aneurysm with appropriate quality assurance
  - Two recent randomized controlled trials show significant reduction in transfusion in cardiovascular surgery by the use of intraoperative cell salvage
  - May be an acceptable alternative for some Jehovah's Witnesses (see Appendix B)

**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

**Contraindications**
- Malignant cells in operative field.
- Bacterially-contaminated operative fluid, ascitic fluid, or amniotic fluid in operative field.
ERYTHROPOIETIN IN ELECTIVE SURGERY

Principles

- Erythropoietin stimulates erythropoiesis 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.\(^{121}\)
  - Expected rise in hemoglobin is 10-20 g/L
  - Odds ratio (OR) for allogeneic transfusion for patients undergoing orthopedic surgery after erythropoietin is 0.36 compared with no erythropoietin\(^{122}\)
- Erythropoietin can be administered to enhance the collection of autologous blood (PAD).\(^{122,123}\)
  - Combined use only recommended for patients with very high likelihood of allogeneic blood exposure and high expected blood loss (e.g. major spine surgery)
  - Odds ratio for allogeneic transfusion for patients combining erythropoietin and PAD is 0.25\(^{122}\)

Eligibility

- Patients with a hemoglobin < 130 g/L and a probability of requiring a blood transfusion of 10% or greater;\(^{121,124,125}\)

Dosage

- Preferred dose: 600 U/kg sc qwk for up to 4 doses commencing 28 days before surgery;\(^{126,127,128}\)
  - 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;\(^{129}\)
  - e.g. 20,000 U sc qd x 15 days, start day 10 pre-op
- Supplemental iron advised;\(^{123,130}\)

Supplied

- See product monograph, available in:
  - Pre-filled syringes
  - Multi-dose vials containing human serum albumin
  - 1,000 IU 20,000 IU
  - 2,000 IU
  - 3,000 IU
  - 4,000 IU
  - 5,000 IU
  - 6,000 IU
  - 8,000 IU
  - 10,000 IU
  - 40,000 IU

Contraindications (in elective surgery patients)

- Uncontrolled hypertension.
- Hypersensitivity to mammalian-derived cell products, albumin, or other components of the product.
- Cardiac, peripheral vascular, or cerebrovascular disease.
  - For more details, refer to product monograph.

Adverse Effects

- In clinical trials of patients undergoing elective surgery, there were no differences in side effects in the treatment group compared to placebo treated group.
  - No increased risk of venous thromboembolism seen in randomized clinical trials if Hb does not exceed 130 g/L.
  - For more details, refer to product monograph.
ANTIFIBRINOLYTICS

General Principles
- Antifibrinolytics are administered to prevent/treat increased fibrinolysis during surgery, particularly cardiac surgery.
- There are two commonly-used antifibrinolytics:
  1. Aprotinin – a proteinase inhibitor derived from bovine lung that inhibits plasmin
  2. Tranexamic acid – an inhibitor of plasminogen

Indications
1. Antifibrinolytics in Cardiac Surgery
   - Prophylactic administration is preferred rather than at time of marked hemorrhage.
   - Aprotinin and tranexamic acid show similar effects on blood loss and need for allogeneic transfusion in primary elective cardiac surgery with bypass.\textsuperscript{131,132}
   - Aprotinin significantly reduced the likelihood of reoperation for bleeding.\textsuperscript{132}
   - Tranexamic acid is very much less expensive than aprotinin.
   - Use of these agents does not appear to increase the rate of non-fatal MI, stroke, DVT, or any thrombosis.\textsuperscript{132}

   \begin{center}
   \textbf{ATTENTION}
   \end{center}
   \textbf{Antifibrinolytics decrease RBC transfusion by one-third.}

2. Antifibrinolytics in Non-cardiac Surgery\textsuperscript{132}
   - Preliminary evidence suggests that antifibrinolytics may reduce allogeneic blood exposure without adverse events in patients undergoing non-cardiac surgery.
   - There are 7 randomized aprotinin trials and 3 randomized tranexamic acid trials involving 649 non-cardiac surgery patients (e.g. major orthopedic surgery, liver resection, liver transplantation).
     - There was considerable heterogeneity in these studies
     - In the aprotinin trials, there was a non-significant 27\% relative risk reduction in allogeneic transfusion
     - In the tranexamic acid trials, there was a significant 48\% relative risk reduction in allogeneic transfusion

Dosage
- Variable dosage with different surgical procedures.
  - Review medical literature prior to using antifibrinolytics in non-cardiac surgery patients to determine dosage

Adverse Effects
- Aprotinin: \textit{hypersensitivity reactions}.
  - Reactions vary from skin flushing to severe circulatory depression; higher risk on second exposure\textsuperscript{133}
  - May increase possibility of renal dysfunction in cardiac patients with, or at risk for, renal disease\textsuperscript{134}
- Tranexamic acid: GI upset.

\begin{center}
\textbf{DOSAGE IN CARDIAC SURGERY}
\end{center}

\begin{tabular}{|l|l|}
\hline
\textbf{Aprotinin*} & 1 mU bolus, then 0.25 mU/hr for duration of surgery, and 1 mU added to pump prime \\
\hline
\textbf{Tranexamic acid} & 50-100 mg/kg ± 2-4 mg/kg/hr for duration of surgery \\
\hline
\end{tabular}

* Note: In high-risk patients (e.g. re-do cardiac surgery), the majority of the trials used double dose aprotinin (2 mU bolus, then 0.5 mU/hr infusion, plus 2 mU to the pump prime)\textsuperscript{132}
**Contraindications**\(^{135}\)
- Aprotinin – hypersensitivity to aprotinin, pregnancy.
- Tranexamic acid – patients at elevated risk of thrombosis, pregnancy, hematuria; dose adjustment required in renal failure.

Refer to product monograph for more details

**DDAVP**
- There is no convincing evidence that DDAVP minimizes perioperative allogeneic RBC transfusion in patients who do not have congenital bleeding disorders.\(^{136,137}\)
- The use of DDAVP in cardiac surgery may increase the risk of myocardial infarction.\(^{137}\)
- DDAVP is ineffective in reducing bleeding after cardiopulmonary bypass surgery in patients receiving Aspirin\(^{\circledR}\).\(^{138}\)
- Use of DDAVP should be restricted to management of suitable cases of Hemophilia A and von Willebrand’s syndrome.

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

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

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

**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
    - May reduce the need for RBC transfusion in the treatment of blunt trauma\(^{140}\)
    - Does not increase the incidence of thrombo-embolic events in blunt or penetrating trauma\(^{141}\)
    - Significant reduction in mortality and morbidity from intracranial hemorrhage if given within 4 hours of onset\(^{142}\)
    - Possible role in patients with massive, INTRACTABLE bleeding\(^{143}\)
    - Does not improve mortality from upper gastro-intestinal bleeding in patients with hepatic cirrhosis\(^{144}\)
    - No reduction in transfusion in major liver resection\(^{145}\)
    - *Note*: Expensive. A single dose of 100 uG/kg for a 70 kg patient costs $7,000
  - Hypervolemic hemodilution
  - Controlled hypotension
**General Principles**

- 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**

- Uncontrolled hypertension.
- Hypersensitivity to mammalian-derived cell products, albumin, or other components of the product.
- Loss of efficacy due to development of antibodies to erythropoietin (including pure red cell aplasia).
  
  Refer to product monograph for more details

**Indications**

- Chronic renal failure
- Anemia associated with malignancy
- HIV infection
- Critical care

**CHRONIC RENAL FAILURE (CRF)**

- **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 < 110 g/L or less should be considered
- Usually erythropoietin is required when the creatinine clearance is < 30 mL/min/1.73 m²
- Other causes of anemia must be excluded or successfully treated; causes include:
  - Nutritional deficiencies: Iron, B12, folate
  - Hyperparathyroidism
  - GI bleeding
  - Inflammatory diseases

**Target therapeutic outcome**

- To maintain the hemoglobin in the range of 110 – 120 g/L

**Iron**

- If the serum ferritin is < 100 ug/L or transferrin saturation is < 20% with serum ferritin < 400 ug/L:
  - trial of oral iron therapy (see page 70 for details)
  - if this fails, 1 gram of intravenous iron in 10 divided doses is recommended
  
  Refer to intravenous iron product monographs for more details
- All other patients should receive oral iron supplements (see page 70 for details)
- Patients should be monitored to prevent iron overload
  - Stop iron if ferritin > 1000 ug/L

**Dosage**

- Starting dose: EPO (Eprex®) 300 u/kg subcutaneously (sc) once per week or darbropoietin (Aranesp™) 0.45 ug/kg once per week
- Maintenance dose: adjust dose to maintain a hemoglobin level of 110 to 120 g/L
  
  Once per week dosage likely equivalent
  
  Adjust dose per product monograph to avoid major fluctuations in hemoglobin level
Erythropoietin and Medical Patients

- Where inadequate responses occur, re-examine for other causes of anemia
- If refractoriness develops, consider the possibility of inhibitors (pure red cell aplasia)\(^{149}\)

**ANEMIA ASSOCIATED WITH MALIGNANCY**

- **Eligibility**\(^{155,156,157,158}\)
  - Patients with malignancies; AND
  - Hemoglobin < 100 g/L and/or requiring red cell transfusions
    - Other contributing causes of anemia must be excluded or successfully treated
    - No dependable predictors of response have been identified, although patients with serum erythropoietin < 500 u/L tend to have better responses\(^{155}\)

- **Target outcome**
  - To maintain the hemoglobin in the range 110-120 g/L without transfusions

- **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:
    - 150 U/kg sc 3 times/week; if the response is inadequate after 4 weeks, increase dose to 300 U/kg\(^{159}\) sc 3 times/week; or
    - 40,000 units sc once weekly with dose increase to 60,000 units after 4 weeks if the response is inadequate\(^{160}\)
  - If the response remains inadequate after 4 weeks at the increased dose, erythropoietin therapy is likely to be ineffective and should be discontinued

**HIV INFECTION**

- **Eligibility**
  - Erythropoietin was originally indicated for patients with anemia taking zidovudine
  - Similar responses to erythropoietin are obtained in zidovudine- and non-zidovudine-treated patients\(^{161,162,163}\)
  - Erythropoietin is unlikely to produce a response in patients with serum erythropoietin > 500 u/L\(^{164,165}\)
  - Other contributing causes of anemia must be excluded or successfully treated\(^{166}\)

- **Target therapeutic outcome**
  - To maintain hemoglobin in the range 110-120 g/L without red cell transfusions\(^{165}\)

- **Therapeutic regimen**
  - Iron supplementation should be used with caution, as it may be associated with accelerated progression of disease\(^{165}\)
  - Start erythropoietin with a dose of either:
    - 100 U/kg sc 3 times/week; if inadequate response after 4 weeks, increase dose to 200 U/kg\(^{167}\) or 300 U/kg\(^{165}\) sc 3 times/week; or
    - 40,000 units sc once weekly with dose increase to 60,000 U sc after 4 weeks if response is inadequate\(^{163,168}\)

- If the response remains inadequate after 4 weeks at the increased dose, erythropoietin therapy is likely to be ineffective and should be discontinued

**CRITICAL CARE**\(^{169,170}\)

- Randomized controlled trials of erythropoietin in critical care show a variable decrease in RBC transfusion in erythropoietin-treated groups
- No beneficial effect on mortality is obtained
- A dosage schedule has not been established
- Routine use in critical care setting is not recommended
FRACTIONATED BLOOD PRODUCTS: Albumin

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).\(^1\)
- 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 2003-2004, 5.4 million grams of albumin were used in Canada, at a cost of about $18.2 million dollars.

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:

<table>
<thead>
<tr>
<th>Volume (mL)</th>
<th>5% Albumin</th>
<th>25% Albumin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mL</td>
<td>= 25 grams of albumin</td>
<td>= 25 grams of albumin</td>
</tr>
<tr>
<td>100 mL</td>
<td>250 mL increase in intravascular volume (250 mL from interstitial pool)</td>
<td></td>
</tr>
<tr>
<td>450 mL</td>
<td>350 mL increase in intravascular volume (350 mL from interstitial pool)</td>
<td></td>
</tr>
</tbody>
</table>

*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!

Per Capita Use of Albumin (Per 1,000 Persons; 2000):

- USA – 377 g
- Ontario – 158 g
- UK – 88 g

Attention

Albumin is a blood product. Consent required.

Adverse reactions / Risks

- Anaphylaxis – rare
- Circulatory overload
- Hypotension – rare case reports of transient hypotension in patients on angiotensin-converting enzyme inhibitors\(^3\)
- 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\(^4\))
   - 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

<table>
<thead>
<tr>
<th>Volume of Ascites</th>
<th># Vials of 100 mL 25% Albumin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 L</td>
<td>0</td>
</tr>
<tr>
<td>5–8 L</td>
<td>2</td>
</tr>
<tr>
<td>8–12 L</td>
<td>3</td>
</tr>
<tr>
<td>12–15 L</td>
<td>4–5</td>
</tr>
</tbody>
</table>

* 8 grams albumin per L of fluid removed for paracentesis > 5 L\(^5\)

- One randomized study (n=60) suggests that starch (20 mL/kg; e.g. 1000-1500 mL pentastarch) may be an effective alternative to albumin.\(^6\)
- Malignant ascites – there is insufficient data in the medical literature to guide 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, range 1.0 to 20.9).\textsuperscript{178}
   - 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\textsuperscript{179} or midodrine/ocntreotide\textsuperscript{180} may be effective in salvaging some patients with type 1 hepatorenal syndrome who are candidates for liver transplantation.
   - **Dosage**: 100 mL of 25% albumin daily with above agents.\textsuperscript{180}

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 fresh frozen plasma.
   - Preliminary trials suggest that 10% pentastarch can be used for the first half of replacement (to a maximum of 28 mL/kg/day) and 5% albumin thereafter\textsuperscript{181,182}
   - A single trial suggests that pentastarch can be used instead of albumin up to 41 mL/kg in therapeutic plasma exchange\textsuperscript{183}

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:

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (OR)</th>
<th>OR Range</th>
<th>% Increase in Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Injuries Group\textsuperscript{184}</td>
<td>1.69</td>
<td>1.07–2.67</td>
<td>69% (7 to 167%)</td>
</tr>
<tr>
<td>Wilkes et al\textsuperscript{185}</td>
<td>1.59</td>
<td>0.91–2.78</td>
<td>59% (-9 to 178%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Odds Ratio (OR)*</th>
<th>OR Range</th>
<th>% Increase in Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Injuries Group(^\text{184})</td>
<td>2.40</td>
<td>1.11–5.19</td>
</tr>
<tr>
<td>Wilkes et al(^\text{185})</td>
<td>1.76</td>
<td>0.97–3.17</td>
</tr>
</tbody>
</table>

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\(^\text{187}\)
  - A small RCT concluded that 5% albumin was no more effective than normal saline for the treatment of hypotension during dialysis\(^\text{188}\)

5. Cardiac surgery\(^\text{189}\)
- 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.

**Alternatives**

<table>
<thead>
<tr>
<th>Approximate Cost Per 500 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin 5%</td>
</tr>
<tr>
<td>Pentaspan(^\text{®})</td>
</tr>
<tr>
<td>Hextend(^\text{®})</td>
</tr>
<tr>
<td>Saline (IL)</td>
</tr>
</tbody>
</table>

**Starch Polymers\(^\text{190,191}\)**

**What?**
- Pentastarch (Pentaspan\(^\text{®}\)) is the only available starch volume expander supplied by CBS.
- Hetastarch (Hextend\(^\text{®}\), BioFine Inc.) not supplied by CBS nor by Héma-Québec.
- NOT blood products.

**Indications**
- Plasma volume expander for patients for whom resuscitation with crystalloid alone is problematic or not feasible.

**Contraindications**
- Hypersensitivity to hydroxyethyl starch, bleeding disorders, congestive heart failure (volume overload).
- Do not use hetastarch in patients with lactic acidosis.

**Dosage**

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentastarch (Pentaspan(^\text{®}))</td>
<td>Up to 2000 mL/day or 28 mL/kg/day</td>
<td>250 or 500 mL bags</td>
</tr>
<tr>
<td>Hetastarch (Hextend(^\text{®}))</td>
<td>Up to 1500 mL/day or 20 mL/kg/day</td>
<td>500 mL bag</td>
</tr>
</tbody>
</table>

**Adverse Effects**
- Fluid overload
- Increased bleeding
- Hypersensitivity
- Renal insufficiency

Refer to product insert for complete details.
AVAILABILITY & CONSUMPTION
- Less than 30% of the IVIG used in Canada is derived from Canadian plasma, which is processed separately from other source plasma.
- The rest is derived from paid U.S. donors.
- Canada has the highest per capita consumption of IVIG in the world.

COMPARISON OF IVIG IN SELECTED COUNTRIES

<table>
<thead>
<tr>
<th>Country</th>
<th>IVIG Use</th>
<th>Canada</th>
<th>USA</th>
<th>Australia</th>
<th>Finland</th>
<th>New Zealand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grams per 1,000 population</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

IVIG USAGE IN ONTARIO (PER 1,000 POPULATION)

In 2004–2005
Canada spent more than $160 million on IVIG.

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

PRODUCTS AVAILABLE
- Products are supplied by CBS or Héma-Québec.
- Informed consent is required as for any blood component or product.

Refer to product’s package insert for further details.

IVIG PRODUCTS LICENSED IN CANADA*

<table>
<thead>
<tr>
<th>Product</th>
<th>CBS IVIG</th>
<th>GAMUNEX®</th>
<th>GAMMAGARD® SD®</th>
<th>IVEEGAM IMMUNO®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Bayer</td>
<td>Bayer</td>
<td>Baxter</td>
<td>Baxter</td>
</tr>
<tr>
<td>IgG (g/L)</td>
<td>98 ± 20</td>
<td>100 ± 10</td>
<td>&gt; 90</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>IgA (mg/L)</td>
<td>270</td>
<td>46</td>
<td>3.7</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Sugar content</td>
<td>None</td>
<td>None</td>
<td>20 g/L</td>
<td>50 g/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>274 mOsm/L</td>
<td>258 mOsm/L</td>
<td>5% 636 mOsm/L</td>
<td>10% 1250 mOsm/L</td>
</tr>
<tr>
<td>Form</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
</tr>
</tbody>
</table>

* 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 1g/kg each day for 2 days, costs $8,000-$10,000.

In 2004–2005
Canada spent more than $160 million on IVIG.
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 blood products.
- Steps in manufacturing are believed to reduce the risk of transmission of prion disease.196

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

IVIG INFUSION RATES*

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>INITIAL RATE</th>
<th>MAXIMUM RATE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS IVIG</td>
<td>0.6-1.2 mL/kg/hour (0.01-0.02 mL/kg/minute) for 30 minutes</td>
<td>Increase gradually to a maximum rate of 3.6 mL/kg/hour if initial dose is tolerated</td>
<td>Time to infuse 70 g is approximately 3 hours</td>
</tr>
<tr>
<td>GAMMAGARD® SD™</td>
<td>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</td>
<td>Increase gradually to a maximum rate of 4 mL/kg/hour if initial dose is tolerated</td>
<td>Use of ante-cubital vein is recommended, especially for 10% solution. See package insert for reconstitution procedure</td>
</tr>
</tbody>
</table>

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 IVIG197,198,199

<table>
<thead>
<tr>
<th>REACTION</th>
<th>SEVERITY</th>
<th>FREQUENCY*</th>
<th>COMMENT/TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, chills/fever, rash, flushing, headache, chest, back or abdominal pain, nausea/vomiting, tachycardia, hypop or hypertension</td>
<td>Mild-moderate</td>
<td>Common</td>
<td>Slow or pause IVIG treatment. Symptomatic treatment. Recurrent reactions – pre-medicate and/or change to another manufacturer’s IVIG product</td>
</tr>
<tr>
<td>Aseptic Meningitis</td>
<td>Moderate</td>
<td>Rare</td>
<td>Stop infusion. Administer analgesics. Usually resolves spontaneously in 24-48 hours</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Severe</td>
<td>Rare</td>
<td>Stop infusion. May require epinephrine promptly. Often reaction to IgA in an IgA-deficient patient</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Severe</td>
<td>Rare (120 cases reported to FDA in 13 years)</td>
<td>Usually with sucrose-containing product (none currently licensed in Canada). Predisposing factors: age &gt; 65, diabetes mellitus, pre-existing renal insufficiency</td>
</tr>
<tr>
<td>Thrombo-embolic events200</td>
<td>Severe</td>
<td>Rare (anecdotal reports)</td>
<td>Causative relationship not clearly established. Possibly related to increases in viscosity</td>
</tr>
<tr>
<td>Viral transmission</td>
<td>Severe</td>
<td>No reported case since HCV in 1995201</td>
<td>Modern viral reduction measures are robust. Prion (vCJD) transmission remains an entirely theoretical risk</td>
</tr>
</tbody>
</table>

* Reactions are more likely with faster rates of infusion.

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

**IVIG IN IMMUNOGLOBULIN DEFICIENCY**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary immune deficiencies, combined immunodeficiency syndromes, IgG subclass deficiencies, hyper-IgM syndrome</td>
<td>Benefit established</td>
<td></td>
</tr>
<tr>
<td>Acquired hypogamma-globulinemia, e.g. in chronic lymphocytic leukemia, multiple myeloma</td>
<td>Benefit established</td>
<td>As above</td>
</tr>
<tr>
<td>Patients with advanced HIV and recurrent serious infections unresponsive to antiviral therapy</td>
<td>Benefit established</td>
<td>As above</td>
</tr>
</tbody>
</table>

**HEMATOLOGY**

**IVIG IN HEMATOLOGICAL DISORDERS**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy</th>
<th>Comment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic Thrombotic Purpura (ITP) refractory to standard treatment, platelet count &lt; 20x10^9/L</td>
<td>Benefit established</td>
<td></td>
<td>1 g/kg</td>
</tr>
<tr>
<td>ITP with persistent or life-threatening bleeding and platelet count &lt; 50x10^9/L</td>
<td>Benefit established</td>
<td></td>
<td>1 g/kg</td>
</tr>
<tr>
<td>Thrombocytopenia associated with HIV unresponsive to antiviral therapy, platelet count &lt; 20x10^9/L or &lt; 50x10^9/L with bleeding</td>
<td>Benefit established</td>
<td></td>
<td>1 g/kg for 2 days</td>
</tr>
<tr>
<td>ITP in pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- platelet count &lt; 10x10^9/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- platelet count 10-30x10^9/L in 2nd or 3rd trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- platelet count &lt; 30x10^9/L and bleeding at any stage in pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post–transfusion purpura</td>
<td>Anecdotal evidence suggests IVIG is the preferred treatment</td>
<td></td>
<td>1 g/kg for 2 days</td>
</tr>
<tr>
<td>Allo-immune fetal thrombocytopenia (treatment of mother or fetus)</td>
<td>Probable benefit; appropriate consultation advisable with high-risk pregnancy unit</td>
<td>Determine in consultation with high-risk pregnancy unit</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>Anecdotal evidence only; use only after failure of other treatments</td>
<td></td>
<td>1 g/kg for 2 days</td>
</tr>
<tr>
<td>Allogeneic bone marrow/stem cell transplant</td>
<td>No advantage over placebo in HLA-identical sibling donors. Not recommended for routine prophylaxis</td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td>Autologous bone marrow/stem cell transplant</td>
<td>No benefit</td>
<td>Not indicated</td>
<td></td>
</tr>
</tbody>
</table>
### NEUROLOGY

**IVIG IN NEUROLOGICAL DISORDERS**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy/Comment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barre Syndrome</td>
<td>Benefit established (equivalent to plasma exchange; plasma exchange after IVIG is of no added benefit&lt;sup&gt;217,218&lt;/sup&gt;)</td>
<td>2 g/kg over 2-5 days. Evaluate response at 4 weeks</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculopathy</td>
<td>Benefit established; probably equivalent to plasma exchange or corticosteroids&lt;sup&gt;219,220&lt;/sup&gt;</td>
<td>2 g/kg over 2-5 days; maintenance therapy should be individualized</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>Benefit established; probably treatment of choice&lt;sup&gt;221,222&lt;/sup&gt;</td>
<td>2 g/kg over 2-5 days: maintenance therapy should be individualized</td>
</tr>
<tr>
<td>Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)</td>
<td>Effective and useful in selected circumstances&lt;sup&gt;214,223,224,225&lt;/sup&gt;; appropriate consultation advisable</td>
<td>2 g/kg over 2-5 days: maintenance therapy should be individualized</td>
</tr>
<tr>
<td>Stiff person syndrome</td>
<td>Effective in the short term&lt;sup&gt;226&lt;/sup&gt;; long term outcomes unknown</td>
<td>2 g/kg over 2 days</td>
</tr>
<tr>
<td>Lumbo-sacral diabetic plexopathy</td>
<td>Uncertain value; appropriate consultation advisable</td>
<td>Determined in consultation</td>
</tr>
<tr>
<td>Multiple sclerosis (relapsing-remitting)</td>
<td>Possible benefit on relapse rate&lt;sup&gt;227&lt;/sup&gt; but efficacy compared to other agents not known</td>
<td>2 g/kg over 2-5 days; maintenance therapy should be individualized</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Ineffective</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Ineffective</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

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

### RHEUMATOLOGY

**IVIG IN RHEUMATOLOGY**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy/Comment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatomyositis&lt;sup&gt;214,229,230&lt;/sup&gt;</td>
<td>Benefit established; use in patients resistant to or intolerant of corticosteroids or immunosuppressives</td>
<td>2 g/kg over 2 days; maintenance therapy should be individualized</td>
</tr>
<tr>
<td>Polymyositis&lt;sup&gt;214,231&lt;/sup&gt;</td>
<td>Benefit uncertain; appropriate consultation advisable</td>
<td>Determine in consultation</td>
</tr>
<tr>
<td>Systemic lupus erythematosus&lt;sup&gt;228,232,233&lt;/sup&gt;</td>
<td>Current evidence does not support use in routine management</td>
<td>Determine in consultation</td>
</tr>
<tr>
<td>Rheumatoid arthritis&lt;sup&gt;228,234&lt;/sup&gt;</td>
<td>Ineffective</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Inclusion body myositis&lt;sup&gt;214,239&lt;/sup&gt;</td>
<td>Ineffective</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome&lt;sup&gt;235&lt;/sup&gt;</td>
<td>Ineffective</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

### DERMATOLOGY

**IVIG IN DERMATOLOGY**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy/Comment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>Anecdotal evidence&lt;sup&gt;237&lt;/sup&gt;. May be effective early in clinical course. Case control study did not show improvement in outcome&lt;sup&gt;238&lt;/sup&gt;</td>
<td>1 g/kg for 3 days</td>
</tr>
<tr>
<td>Pemphigus vulgaris and variants</td>
<td>Anecdotal evidence&lt;sup&gt;239&lt;/sup&gt; supports use of IVIG as adjunctive or second-line treatment if conventional treatment is ineffective</td>
<td>2 g/kg over 3-5 days. Maintenance treatment should be individualized</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td>Anecdotal evidence&lt;sup&gt;240&lt;/sup&gt; supports use of IVIG as adjunctive or second-line treatment if conventional treatment is ineffective</td>
<td>2 g/kg over 5 days. Maintenance treatment should be individualized</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Anecdotal evidence&lt;sup&gt;241&lt;/sup&gt; supports use of IVIG as second-line treatment if conventional treatment is ineffective</td>
<td>2 g/kg over 2-5 days. Maintenance treatment should be individualized</td>
</tr>
</tbody>
</table>
### IVIG IN OBSTETRICS AND GYNECOLOGY

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy/Comment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-phospholipid syndrome</td>
<td>Uncertain benefit(^{243,244}) may improve fetal outcomes when Aspirin® and heparin have been ineffective; appropriate consultation advisable</td>
<td>Determine in consultation with high-risk pregnancy unit and attending specialist</td>
</tr>
<tr>
<td>Recurrent spontaneous abortion</td>
<td>Ineffective(^{245})</td>
<td>Not indicated</td>
</tr>
<tr>
<td>In Vitro fertilization/implantation procedures</td>
<td>Ineffective(^{246})</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

### IVIG IN INFECTIOUS DISEASES

#### IVIG IN BACTERIAL INFECTION\(^{247}\)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Efficacy/Comment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic/Toxic Shock Syndrome (Group A streptococcal sepsis with hypotension and multi-organ failure)(^{248,249,250,251})</td>
<td>Anecdotal reports, an observational study and a small RCT suggest some value</td>
<td>Adjunctive treatment in selected cases 1-2 g/kg over 6 hours</td>
</tr>
<tr>
<td>Necrotizing fasciitis(^{252,253})</td>
<td>Uncertain benefit</td>
<td>Adjunctive treatment in rapidly progressing disease 1-2 g/kg over 6 hours</td>
</tr>
<tr>
<td>Sepsis in patients in critical care(^{247,248,249,254})</td>
<td>No large randomized controlled trials to confirm benefit</td>
<td>Not recommended for use</td>
</tr>
</tbody>
</table>

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

Special Transfusion Requirements

- Identify patients with sickle cell disease (SCD) prior to transfusion, so that special transfusion precautions can be taken.
  - Physician/nurse must identify these patients to blood bank or hematology service at the time of admission.

- Consider the following guidelines when selecting blood for transfusion:

  1. **Sickledex negative blood**
     - Time permitting, Sickledex negative blood should be provided (i.e. avoid transfusing blood containing HbS, e.g. sickle cell trait).
  2. **Red cells < 14 days old**
     - Use red blood cells less than 14 days from collection whenever possible.
  3. **Phenotypically-matched RBC**
     - Determine and record extended phenotype [Rh (D,C,E), Kell (K1), Fy, Jk]
     - Register the patient’s antibody status and RBC phenotyping at CBS (if available) *(In some geographic regions, CBS has registries for patients with SCD)*
     - Match RBC prophylactically, where time allows, for:
       1. Rh (D,C,E)
       2. Kell (K1)

### Simple Transfusion

- **Acute anemia**
- **Splenic sequestration**
- For preoperative patients, transfused to a hemoglobin of 100 g/L prior to general anesthesia or eye surgery to prevent perioperative complications.
  - Transfusion above a hemoglobin of 100 g/L should be avoided due to concerns of increasing blood viscosity.

### Exchange Transfusion

- Red blood cell exchange is designed to reduce the level of hemoglobin S to less than 30%.
- Indications for exchange transfusion may include the following:
  - ischemic stroke
  - hemorrhagic stroke
  - severe acute chest syndrome
  - acute multiple organ damage syndrome
  - retinal artery occlusion
  - priapism – second-line therapy (first-line – aspiration of blood from the corpora cavernosa and irrigation with dilute epinephrine solution under local anesthesia)
Perioperative Management

Perioperative transfusion and anesthetic management should include all of the following:

1. Ensure that the patient is not actively in a sickle cell crisis.
2. Consider simple transfusion to increase the hemoglobin to, but not greater than, 100 g/L for all patients undergoing a general anesthetic, major surgery, or eye surgery.
   - This results in a reduction in the perioperative complication rate
3. Consider starting hydroxyurea 3 or more months preoperative for patients who require this therapy for other reasons (e.g. more than 3 sickle cell crises per year requiring admission to hospital, severe symptomatic anemia, or severe vaso-occlusive complications).
4. Test preoperative pulmonary function and treat any reversible airway disease.
5. Hydrate for 12 to 24 hours preoperative to avoid preoperative dehydration.
6. Administer incentive spirometry pre-op and until discharge.
7. Avoid hypoxia.
8. Avoid hypothermia – consider using warming blankets and blood warmers.
9. Avoid use of tourniquets.
10. Consider laparoscopic surgery where appropriate.
11. Aggressively remobilize post-op to prevent thromboembolic complications and atelectasis.
13. Consider post-operative monitoring in the critical care unit.

Chronic Transfusion

- Program of chronic transfusions for the following indications:
  - Hemorrhagic or ischemic stroke
  - Children at risk for stroke
  - Non-healing leg ulcers
  - Chronic symptomatic anemia – consider concurrent treatment with hydroxyurea
  - Debilitating vaso-occlusive disease that is unresponsive to hydroxyurea
  - Complicated pregnancy – severe sickle-related complications, history of recurrent fetal loss, multiple gestation, or chronic fetal distress (Intrauterine growth retardation/IUGR)
  - Consult high-risk obstetrical center

Perioperative Transfusion

- Patients with sickle cell disease have a very high rate of perioperative complications.
  - Approximately 33% of sickle cell patients experience a complication in the immediate perioperative period (infection, painful crisis, or acute chest syndrome)264
    - Acute chest syndrome is the most common post-operative complication (10% of patients265)
  - Patients who undergo major surgery without preoperative transfusions are at a substantially increased risk of major complications, particularly pulmonary complications, which affect 35-51% of un-transfused patients264,266
  - 7% of all deaths from sickle cell disease are directly related to surgery; therefore, optimal management is critical267

**ATTENTION**

Failure to carefully manage a patient with SCD at the time of surgery can result in serious morbidity!
Transfusion Risks

Patients with sickle cell disease are at higher risk of the following transfusion complications:

- Alloimmunization
- Delayed hemolytic transfusion reactions
- Iron overload
- Hyperhemolysis syndrome
- Lack of blood availability in medical emergencies
- Hyperviscosity

Alloimmunization

47% of adult sickle cell patients have at least one RBC alloantibody\(^{269}\)

- Risk per RBC unit transfused is 3.1%
- Anti-K, E, C, Jk account for 80% of the antibodies\(^{270}\)
- 17% of patients have 4 or more antibodies
- 10% of adult patients have positive DAT (‘autoantibodies’)\(^{269}\)

Alloimmunization is attributable to genetic differences in the antigens expressed on red blood cells in the donor population (primarily Caucasians) and the recipients, for example:\(^{255}\)

<table>
<thead>
<tr>
<th>Red Cell Antigen</th>
<th>Gene Frequency in Caucasians</th>
<th>Gene Frequency in African-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>R^a(Dce)</td>
<td>0.04</td>
<td>0.44</td>
</tr>
<tr>
<td>K1</td>
<td>0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Jka</td>
<td>0.77</td>
<td>0.92</td>
</tr>
<tr>
<td>Fy(a-b-)</td>
<td>&lt; 0.01</td>
<td>0.68</td>
</tr>
</tbody>
</table>

- Prophylactic matching for E, C, K1 reduces the alloimmunization rate from 3% per unit to 0.5% in children\(^{256}\)

Hyperhemolysis Syndrome\(^{271,272}\)

- A syndrome of unclear etiology with the following characteristics:
  - Destruction of donor and recipient RBCs
    - Hemoglobin is lower after transfusion
  - Markers for hemolysis (bilirubin and LDH) increase
  - Relative reticulocytopenia (patients with SCD have elevated reticulocyte counts at baseline & the level will drop below their usual range)
  - Direct antiglobulin test is usually negative
  - Platelet count may fall

Management:

- Consult hematology
- Consider administering corticosteroids, IVIG, and hemoglobin-based oxygen carriers
- Stop transfusion; continuation of blood transfusions can be lethal!

Hyperviscosity

- Blood viscosity of a patient with SCD is higher than in normal patients, even when corrected for hematocrit
- With transfusion, the viscosity can increase dramatically and impair organ perfusion
- It is recommended not to transfuse above a hemoglobin of 100 g/L or hematocrit of 0.30\(^{255}\)
- Excessively rapid correction of anemia in patients with SCD can result in acute hypertension, intracerebral hemorrhage, and seizures\(^{273}\)
- Patients with SCD may have asymptomatic anemia and despite a low hemoglobin (sometimes less than 50 g/L) do not require transfusions unless other reasons exist
- Consult hematology before transfusing a patient with SCD

Attention

Correcting anemia excessively rapidly in SCD patients can result in severe adverse reactions.
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
- Autologous blood obtained for acute normovolemic hemodilution or by cell salvage
- Recombinant factor VIIa

A valuable and detailed discussion of the position of Jehovah’s Witnesses on blood transfusion and related interventions is available.274

Appendix B

Information for Physicians Treating Patients Who Are Jehovah’s Witnesses

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 (e.g. perfluorochemicals when available), and non-blood volume expanders.

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.

Consider consulting the Hospital Information Services for Jehovah’s Witnesses. This service is available 24 hours a day at 1-800-265-0327.

Appendix A

Price List

<table>
<thead>
<tr>
<th>ITEM</th>
<th>PRICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>$400</td>
</tr>
<tr>
<td>Autologous (whole) blood</td>
<td>$400</td>
</tr>
<tr>
<td>Erythropoietin 40,000 IU/week for 2 to 4 weeks</td>
<td>$1,140 $2,280†</td>
</tr>
<tr>
<td>Erythropoietin 1,000 IU</td>
<td>$14.25†</td>
</tr>
<tr>
<td>5 units platelets</td>
<td>$500</td>
</tr>
<tr>
<td>4 units buffy coat derived platelets</td>
<td>$500</td>
</tr>
<tr>
<td>1 unit single donor (apheresis) platelets</td>
<td>$500</td>
</tr>
<tr>
<td>1 unit HLA-matched single donor (apheresis) platelets</td>
<td>$1,250</td>
</tr>
<tr>
<td>Apheresis fresh frozen plasma</td>
<td>$220</td>
</tr>
<tr>
<td>4 units frozen plasma</td>
<td>$700</td>
</tr>
<tr>
<td>8 units cryoprecipitate</td>
<td>$225</td>
</tr>
<tr>
<td>Aprotinin 3 million units</td>
<td>$500</td>
</tr>
<tr>
<td>Tranexamic acid 6 g</td>
<td>$150</td>
</tr>
<tr>
<td>IVIG per gram</td>
<td>$75</td>
</tr>
<tr>
<td>Albumin 5% 500 mL</td>
<td>$100</td>
</tr>
<tr>
<td>Pentaspan® per 500 mL</td>
<td>$70</td>
</tr>
<tr>
<td>Hextend® 500 mL</td>
<td>$60</td>
</tr>
<tr>
<td>CMV antigen-negative, additional cost per unit</td>
<td>$20</td>
</tr>
<tr>
<td>Irradiation per unit</td>
<td>$25</td>
</tr>
<tr>
<td>Blood group (ABO, Rh D)</td>
<td>$10</td>
</tr>
<tr>
<td>Antibody screen</td>
<td>$25</td>
</tr>
<tr>
<td>Crossmatch (no antibody)</td>
<td>$15</td>
</tr>
<tr>
<td>Crossmatch (antibody positive patient)</td>
<td>$45</td>
</tr>
</tbody>
</table>

† All prices quoted represent an approximate guide except those supplied courtesy of Janssen-Ortho Inc.
References


239 Rosse WF, Telen MJ, Ware RE. Transfusion Support Management of Sickle Cell Disease. AABB Press.


260 Appenices


Special thanks to the following people and organizations that were not part of an Advisory Panel, but who contributed specific knowledge, expertise, or materials to this Bloody Easy Guide and the associated e-learning program:

Bayer Health Care Division
Biopure Corp., USA
Zenon Bodnaruk
Bristol Myers Squibb
Peter Chu, MD
Perry Cooper, MD
William Cornish
Lidia Cosentino, PhD
Jill Hopkins, MD
John Iazzetta
Peggy Kee

Huw Lloyd, MD
Nivaldo Medeiros, MD
Sam Rhadakrishnan, MD
Marciano Reis, MD
Rosane Reis, BSc, MLT
Sandro Rizoli, MD
Roche Diagnostics Canada
Joel Rubenstein, MD
Andrew Simor, MD
Graeme Woodfield, MD

Bloody Easy website: [www.sunnybrookandwomens.on.ca](http://www.sunnybrookandwomens.on.ca)

Bloody Easy E-learning Tool
Bloody Easy is also available as an electronic learning tool. It is accessible at the Sunnybrook & Women’s website, as follows:

[www.sunnybrookandwomens.on.ca](http://www.sunnybrookandwomens.on.ca)

From the Home page, go to “Research & Education”; go to “Transfusion Medicine Program”, and click on the last sentence of text, “To learn more about the handbook and the transfusion course, please click here”.

Ordering Information
Copies of this pocket guide, can be ordered on-line at
[http://www.swshopping.ca](http://www.swshopping.ca)

Sang Difficulté
The French language version of Bloody Easy can be ordered on-line at:
[http://www.swshopping.ca](http://www.swshopping.ca)

The publication of the first edition of Bloody Easy was partially funded by an unrestricted grant from Ortho Biotech Canada.