

# bloody easy 4

## Blood Transfusions, Blood Alternatives and Transfusion Reactions

*A Guide to Transfusion Medicine*

**Fourth Edition**

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## Preface to the Fourth Edition

Since 2001 the Ontario Ministry of Health and Long-Term Care (MOHLTC) has provided funding and oversight for a variety of initiatives directed at promoting rational, evidence-based use of blood components, derivatives and alternatives, and reduction of transfusion errors. These included the publication of the First Edition of *Bloody Easy* in 2003. As the field of Transfusion Medicine is rapidly changing with new evidence to define acceptable practice, subsequent editions produced under the aegis of the Ontario Regional Blood Coordinating Network (ORBCoN) in 2006 and 2011, reflected this evolution.

The current Fourth Edition appears as two significant concepts are emerging in the guidance of Transfusion Medicine practice. The first is the approach covered under the rubric of “Patient Blood Management”, which is a discipline designed to optimize patient care for patients who may require transfusion, based on the application of evidence-based, multidisciplinary medical and surgical practices to integrate the best use of transfusion and its alternatives and adjuncts<sup>1,2</sup>. The second is the initiative known as “Choosing Wisely<sup>®</sup>” promoted in the U.S. by the American Board of Internal Medicine Foundation (ABIM) ([www.abimfoundation.org](http://www.abimfoundation.org)), and in Canada by the Canadian Medical Association (CMA) ([www.choosingwiselycanada.org](http://www.choosingwiselycanada.org)). “Choosing Wisely” seeks to promote avoidance of wasteful or unnecessary tests, treatments and procedures. An increasing weight of evidence from clinical trials is accumulating to support the clinical benefits of restrictive rather than liberal transfusion policies.

There are several significant changes from the Third Edition. The critical hemoglobin levels to prompt consideration of red blood cell transfusion have been reduced in light of increasing confidence that these recommended levels for restricting transfusion are not resulting in adverse consequences, and, indeed, may in some circumstances result in improved patient outcomes<sup>3</sup>. A lack of evidence of clinical benefit from frozen plasma transfusion for mild-marginal coagulopathy as defined by the INR<sup>4,5,6</sup> supports adoption of the “Choosing Wisely” recommendation that an INR of 1.8 or more should replace the convention hitherto of 1.5 or more. In “Adverse Events”, there has been a decline in transfusion transmitted infection and acute lung injury, offset by increasing recognition of circulatory overload, particularly in patients with compromised cardiac function<sup>7</sup>. Reference to obsolete practices such as acute normovolemic hemodilution and autologous pre-surgical blood deposit have been removed. The introduction in Ontario of a mandatory request process for IVIG for infusion<sup>8</sup> is intended to reduce inappropriate use of IVIG (about 25-30% of Canadian Blood Services annual budget is for IVIG). A pre-transfusion checklist for physicians (for RBC transfusion orders) has been placed on the back cover (for easy access) to help promote safe ordering practices to reduce the risk of transfusion complications. Finally, a section on the use of Rh immunoglobulin has been added. This and previous editions of *Bloody Easy* would have been impossible without the dedication, attention to detail and patience of Stephanie Cope, ORBCoN Central Office.

## Ten Things Physicians and Patients Should Question<sup>9,10</sup>



**1 Don't transfuse blood if other non-transfusion therapies or observation would be just as effective.**  
Blood transfusion should not be given if other safer non-transfusion alternatives are available. For example, patients with iron deficiency without hemodynamic instability should be given iron therapy.

**2 Don't transfuse more than one red cell unit at a time when transfusion is required in stable, non-bleeding patients.**  
Indications for red blood cell transfusion depend on clinical assessment and the cause of the anemia. In a stable, non-bleeding patient, often a single unit of blood is adequate to relieve patient symptoms or to raise the hemoglobin to an acceptable level. Transfusions are associated with increased morbidity and mortality in high-risk hospitalized inpatients. Transfusion decisions should be influenced by symptoms and hemoglobin concentration. Single unit red cell transfusions should be the standard for non-bleeding, hospitalized patients. Additional units should only be prescribed after re-assessment of the patient and their hemoglobin value.

**3 Don't transfuse plasma to correct a mildly elevated (<1.8) international normalized ratio (INR) or activated partial thromboplastin time (aPTT) before a procedure.**  
A mildly elevated INR is not predictive of an increased risk of bleeding. Furthermore, transfusion of plasma has not been demonstrated to significantly change the INR value when the INR was only minimally elevated (<1.8).

**4 Don't routinely transfuse platelets for patients with chemotherapy-induced thrombocytopenia if the platelet count is greater than  $10 \times 10^9/L$  in the absence of bleeding.**

A platelet count of  $10 \times 10^9/L$  or greater usually provides adequate hemostasis. Platelet transfusions are associated with adverse events and risks. Considerations in the decision to transfuse platelets include the cause of the thrombocytopenia, comorbid conditions, symptoms of bleeding, risk factors for bleeding, and the need to perform an invasive procedure.

**5 Don't routinely use plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists.**

Patients requiring non-emergent reversal of warfarin can often be treated with vitamin K or by discontinuing the warfarin therapy. Prothrombin complex concentrates should only be used for patients with serious bleeding or for those who need urgent surgery. Plasma should only be used in this setting if prothrombin complex concentrates are not available or are contraindicated.

**6 Don't use immunoglobulin therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated.**

Immunoglobulin (gammaglobulin) replacement does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccine immunizations or natural infections. Isolated decreases in immunoglobulins (isotypes or subclasses), alone, do not indicate a need for immunoglobulin replacement therapy. Exceptions include genetically defined/suspected disorders. Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy. Selective IgA deficiency is not an indication for administration of immunoglobulin.

**7 Don't order unnecessary pre-transfusion testing (type and screen) for all pre-operative patients.**

Pre-operative transfusion testing is not necessary for the vast majority of surgical patients (e.g., appendectomy, cholecystectomy, hysterectomy and hernia repair) as those patients usually do not require transfusion. Ordering pre-transfusion testing for patients who will likely not require transfusion will lead to unnecessary blood drawn from a patient and unnecessary testing performed. It may also lead to unnecessary delay in the surgical procedure waiting for the results. To guide you whether pre-transfusion testing is required for a certain surgical procedure, your hospital may have a maximum surgical blood ordering schedule or specific testing guidelines based on current surgical practices.

**8 Don't routinely order perioperative autologous and directed blood collection.**

There is no role for routine perioperative autologous donation or directed donation except for selected patients (for example, patients with rare red blood cell antigen types). Medical evidence does not support the concept that autologous (blood donated by one's self) or directed blood (blood donated by a friend/family member) is safer than allogeneic blood. In fact, there is concern that the risks of directed donation may be greater (higher rates of positive test results for infectious diseases). Autologous transfusion has risks of bacterial contamination and clerical errors (wrong unit/patient transfused). As well, autologous blood donation before surgery can contribute to perioperative anemia and a greater need for transfusion.

**9 Don't transfuse O negative blood except to O negative patients and in emergencies for female patients of child-bearing potential of unknown blood group.**

Males and females without childbearing potential can receive O Rh-positive red cells. O-negative red cell units are in chronic short supply, in some part due to over utilization for patients who are not O-negative. To ensure O-negative red cells are available for patients who truly need them, their use should be restricted to: (1) patients who are O-Rh-negative; (2) patients with unknown blood group requiring emergent transfusion who are female and of child-bearing age. Type specific red cells should be administered as soon as possible in all emergency situations.

**10 Don't transfuse group AB plasma to non-group AB patients unless in emergency situations where the ABO group is unknown.**

The demand for AB plasma has increased. Group AB individuals comprise only 3% of Canadian blood donors. Those donors who are group AB are universal donors for plasma, thus are the most in-demand type for plasma transfusion. Type-specific plasma should be issued as soon as possible in emergency situations to preserve the AB plasma inventory for those patients where the blood group is unknown.

**Important Notes**

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

**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.

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**A Overview**

**Who regulates**

- Health Canada regulates blood collection, testing, processing, and distribution.
- Health Canada Blood Regulations require hospitals to follow the national standard (see below) (<http://laws-lois.justice.gc.ca/eng/regulations/SOR-2013-178/>).
- Health Canada provides guidance to assist hospitals in complying with the blood regulations (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/blood-reg-sang/blood-guid-sang-ligne-2014-10-23-eng.php>).



**National Standard**

- Canadian Standards Association (CSA Group) publishes the national standard for all aspects of blood management (current version, CAN/CSA -Z902-15, available at <http://shop.csa.ca/>).
- Canadian Society for Transfusion Medicine (CSTM) publishes standards for Hospital Transfusion Services. These standards are consistent with the CSA national standard ([www.transfusion.ca](http://www.transfusion.ca)).



**Who collects**

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



**Donor screening**

- Donors are screened using:
  - ◆ donor questionnaire
  - ◆ donor vital signs (temperature, heart rate, blood pressure)
  - ◆ donor hemoglobin

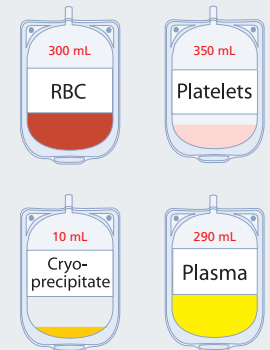
- Donor units tested for:

DONOR UNITS TESTED FOR:	SPECIFIC AGENTS	TESTS USED
<b>Blood groups</b>	ABO and Rhesus (Rh) D Red cell alloantibodies	Blood group serology
<b>Viruses</b>	HIV 1 and 2 Hepatitis B  Hepatitis C HTLV I and II West Nile Virus	Antibody and nucleic acid testing Surface antigen, core antibody and nucleic acid testing Antibody and nucleic acid testing Antibody testing Nucleic acid testing (seasonal)
<b>Bacteria</b>	Syphilis Bacterial contamination	Serology Bacterial culture (Platelets only)
<b>Parasites</b>	Chagas Disease (at risk donors only)	Antibody testing

- All whole blood and apheresis donors at CBS and HQ are unpaid volunteers.
- Plasma for fractionation is screened for parvovirus B19 by nucleic acid testing.

**Whole blood processing**

- Collect 500 mL whole blood.
- Divert the first 40 mL to reduce risk of bacterial contamination from donor skin; the 40 mL are used for donor unit testing.
- Blood is centrifuged and separated into three parts:
  - ◆ Red Blood Cells
  - ◆ Plasma
  - ◆ Buffy coat
- The Buffy coat units from four donors are combined with one plasma unit and further processed to separate the platelets.
- The red blood cell and platelet components are leukoreduced.



**Whole blood processing (cont'd)**

- Certain groups of patients need irradiated blood components to prevent transfusion-associated graft vs host disease (TA-GvHD).
- CBS and HQ provide irradiated products on demand.
  - ◆ Refer to TA-GvHD (see page 71) for list of patient groups that need irradiated blood

**B Red Blood Cells and Components: Storage Conditions and Volumes<sup>11</sup>**

COMPONENT	APPROX. VOLUME	STORAGE LIMIT	STORAGE TEMP.	PRE-TRANSFUSION PREPARATION TIME*
Red blood cells	300 mL	42 days	1-6 °C	10-45 minutes
Buffy coat derived platelets (from 4 units)	350 mL	5 days	20-24 °C	5 minutes
Apheresis platelets	330 mL	5 days	20-24 °C	5 minutes
Frozen plasma	290 mL	1 year	-18 °C or colder	30 minutes
Apheresis plasma	500 mL	1 year	-18 °C or colder	30 minutes
Cryoprecipitate	10 mL	1 year	-18 °C or colder	30 minutes

\*In addition to the 45 minutes required for pre-transfusion specimen testing

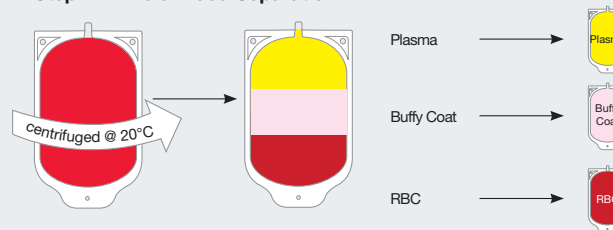


HQ provides buffy coat platelets from 5 units of buffy coat. HQ storage limit for platelets is 7 days.

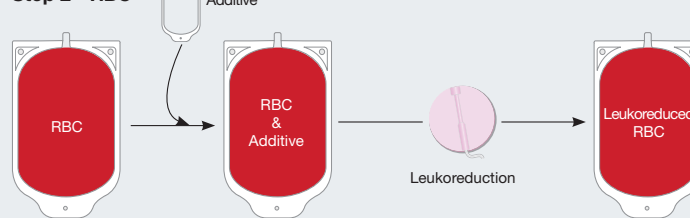
Please see Circular of Information, Canadian Blood Services ([www.blood.ca/en/hospitals/circular-information](http://www.blood.ca/en/hospitals/circular-information)) or Circular of Information, Hema-Quebec ([http://www.hema-quebec.qc.ca/userfiles/file/media/anglais/publications/SPE-00176%5B3%5D\\_C16075\\_LIVRET\\_HEMA\\_ANG\\_web.pdf](http://www.hema-quebec.qc.ca/userfiles/file/media/anglais/publications/SPE-00176%5B3%5D_C16075_LIVRET_HEMA_ANG_web.pdf)) for most up-to-date information.

**Process for Preparing Blood Components from Donated Units**

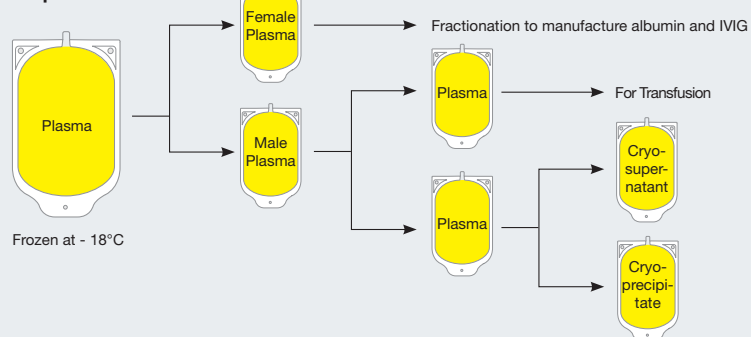
**Step 1 - Whole Blood Separation**



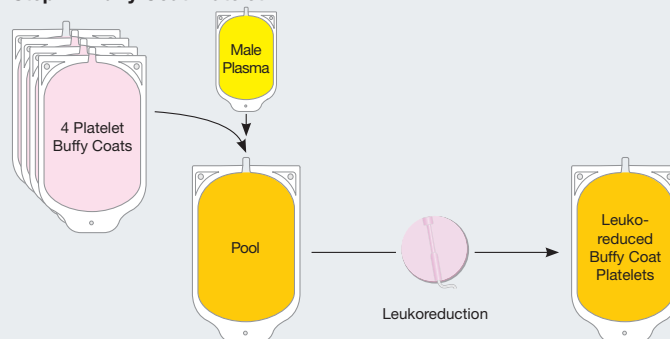
**Step 2 - RBC**



**Step 3 - Plasma**



**Step 4 - Buffy Coat Platelet**



**Ⓒ Informed Consent**

A requirement for transfusion consent is identified as an important priority element to be incorporated into Patient Blood Management Programs.<sup>12</sup>

**When**

- Discuss the option of a transfusion early enough to allow for a blood alternative(s) to be considered according to the principles of patient blood management.<sup>12</sup>


**A T T E N T I O N**  
Refer to pages 42-44 for risk charts, to assist discussion of risks with patients.

**What**<sup>13</sup>

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

**Of note**

- Confirm that you discussed consent with the patient, by noting it in the patient’s chart.
- Complete the informed consent documentation as required at your hospital.
- If transfusion is required, clearly document the reason in the patient’s chart.
- In the special case of Jehovah’s Witnesses, helpful advice may be obtained from their Hospital Information Services 24 hours a day at 1-800-265-0327 (see Appendix B, page 143).

 **Pediatrics**

- For children without decision-making capability, the parent or legal guardian must give informed consent.
- Teenagers with decision-making capability should give informed consent themselves. The age at which teenagers can give informed consent varies from province to province. Refer to provincial legislation.

**Ⓓ Directed Blood Donations**

**What**

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

**Who**

- Currently in Canada, directed blood donations are only recommended for patients with rare blood cell types.

**Where**

- Directed blood donations are collected by CBS and HQ.

**Of note**

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

**CHOOSE WISELY**

Directed blood donations are only indicated in RARE circumstances and should not be collected for routine surgical procedures or for routine top-up transfusions in premature neonates.



## Ⓔ Clinical Practice Guidelines

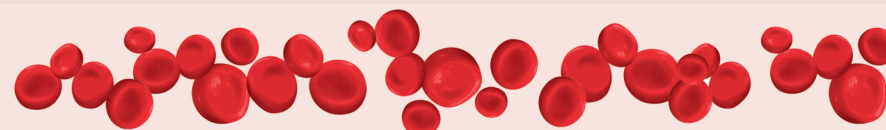
### Red Blood Cells<sup>14</sup>

- The American Association of Blood Banks (AABB) recommends adhering to a restrictive transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 70 g/L in hospitalized adult patients who are hemodynamically stable, including critically ill patients.
- The AABB recommends a restrictive RBC transfusion threshold of 80 g/L for patients undergoing orthopedic surgery, cardiac surgery and those with pre-existing cardiovascular disease.
- They also state: “The restrictive transfusion threshold of 70 g/L is likely comparable with 80 g/L, but RAC evidence is not available for all categories of patients.”

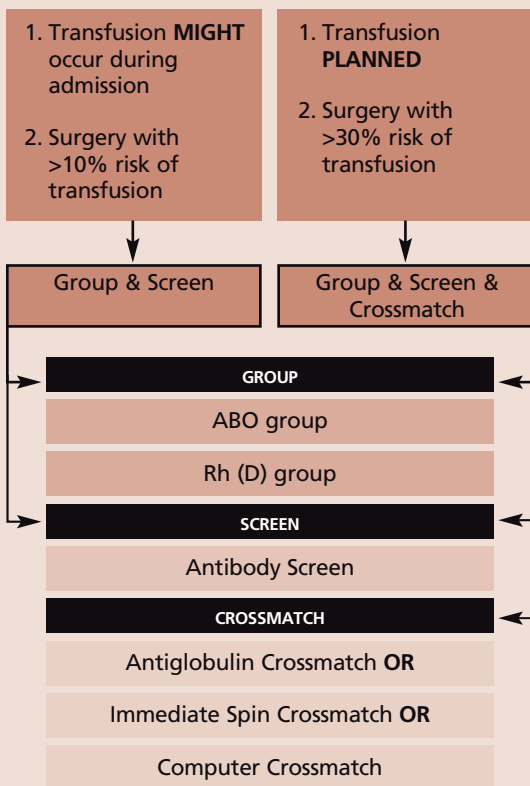
### Platelets<sup>15,16</sup>

- Prophylactic platelet transfusion should be given to patients with hypoproliferative thrombocytopenia when the platelet count is  $10 \times 10^9/L$  or less.
- For elective central venous catheter placement, a threshold of less than  $20 \times 10^9/L$  is recommended for prophylactic transfusion.
- For elective diagnostic lumbar puncture, a threshold of less than  $50 \times 10^9/L$  is recommended for prophylactic transfusion.
- For major elective non-neuraxial surgery, a threshold of less than  $50 \times 10^9/L$  is recommended for prophylactic transfusion.

- Female children and females of child-bearing age/potential who are Rh(D) negative should probably receive Rh immunoglobulin before, after or within 72 hours of receiving an Rh(D) positive platelet component.
- Males and females who are not of child-bearing potential who are Rh(D) negative and are transfused with Rh(D) positive platelet components probably do not require Rh immunoglobulin.



**A When and How to Order Tests**



**A T T E N T I O N**

Uncrossmatched blood is required if the clinical state precludes waiting for antibody screen and crossmatch (45 minutes).

**C H O O S E W I S E L Y**

The following surgeries should have a transfusion rate of <10% and do not require a group and screen: appendectomy, radical prostatectomy, transurethral resection of the prostate (TURP), hernia repair, single knee replacement, primary total hip replacement, laparoscopic cholecystectomy, isolated laminectomy, upper limb surgery and vaginal hysterectomy.

**B Routine Transfusion Medicine Tests**

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

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

\* For patients with a negative antibody screen and no history of RBC alloantibodies.



**Pediatrics**

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

Ⓒ Checking Identity of Patient

You must accurately identify the patient at the following times...

- When collecting a blood specimen:
  - Accurately label each specimen **BEFORE** leaving the patient's bedside
- BEFORE** beginning the transfusion, two clinical team members must:
  - Verify the patient's identity, by checking the name, date of birth and unique identifier (e.g., hospital file number) on their wristband against the identification on the blood component label before transfusing, and, where possible, also by verbal confirmation. For example, ask: "What is your name?" or "What is your date of birth?"
  - It is also important to ensure the correct component type is being transfused by checking the physician order



**A T T E N T I O N**

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.

Recommended IV access

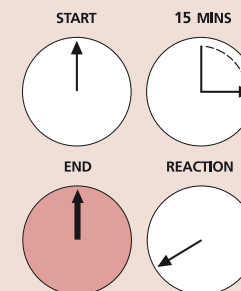
BLOOD COMPONENT/PRODUCT	IV ACCESS
Red blood cells – rapid transfusions in adults	16-18G (Gauge)
Red blood cells – routine transfusions in adults	20-22G
Other blood components/products	Any size is adequate
Pediatrics	22-25G
All components and products – adults and pediatrics	Central venous access devices (CVAD)

**Storage**

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

**Monitor patient**

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



**A T T E N T I O N**

Monitor patient closely for first 15 minutes.



**Pediatrics**<sup>11,13</sup>

For pediatric patients, transfuse slowly (1 mL/kg/h, up to 50 mL/h) for the first 15 minutes. Usual administration rate is 5 mL/kg/h, up to 150 mL/h.

**D Monitoring & Infusion Practices (cont'd)**

**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.
- Expect a 10 g/L increase in hemoglobin in the non-bleeding adult patient.
- Each unit is usually infused over 2 hours, but always **within 4 hours** of issue from blood bank.
- Consider a slower rate for patients at risk of circulatory overload and refer to prevention on page 61.
- In massive transfusion, blood should only be warmed using an approved blood warming device.

**A T T E N T I O N**

Transfuse one unit at a time.

**A T T E N T I O N**

Infuse each unit over 2 hours, maximum 4 hours.

**A T T E N T I O N**

Consider a slower rate for patients at risk of circulatory overload.



**Pediatrics**

*Dosage:*

- A transfusion of 10 mL/kg of RBC stored in an additive solution is expected to raise the hemoglobin level by approximately 10 g/L.<sup>17</sup>

**E Ordering RBCs**

- If the patient is not adequately volume resuscitated, the hemoglobin value may be spuriously high OR, in the setting of over hydration, spuriously low.
- A falsely low hemoglobin value may result if test specimen are taken near a site of IV infusion.
- Certain patients require irradiated products. Refer to page 71.

**A T T E N T I O N**

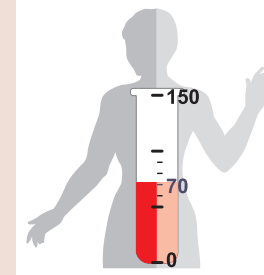
Record the order in the correct patient's chart.

**F Indications for RBCs**

**Acute blood loss**

- Maintain **hemoglobin >70 g/L during active bleeding**.<sup>18</sup>
  - ◆ 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 (>80 g/L) for patients with:**
  - ◆ Unstable or acute coronary syndromes<sup>19</sup>
  - ◆ Coronary artery disease<sup>20</sup>
  - ◆ Uncontrolled/unpredictable bleeding
- Liberal transfusion practices (**hemoglobin >90 g/L**) in the setting of gastrointestinal hemorrhage results in a higher rate of re-bleeding and mortality.<sup>21</sup>

**ACUTE BLOOD LOSS & ANEMIA IN CRITICAL CARE**



**Anemia in critical care and coronary care**

- Consider a transfusion when the patient's hemoglobin is less than 70 g/L.<sup>22</sup>
- Post-cardiac surgery, there is no benefit to a liberal transfusion strategy (when 75 g/L was compared to 90 g/L there was no difference in 30-day mortality).<sup>23</sup>
- In a patient with an acute coronary syndrome, there is controversy over where to maintain the hemoglobin level.<sup>14</sup>
  - ◆ 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

**CHOOSE WISELY**

Don't transfuse RBCs to an asymptomatic, non-bleeding, inpatient with a hemoglobin level above 70 g/L!

**F Indications for RBCs (cont'd)**

- Unnecessary phlebotomy for laboratory testing is a major contributor to anemia in a critically ill patient.
- Except for patients with unstable coronary artery syndromes, a restrictive transfusion policy (trigger hemoglobin 70 g/L) has proved at least as effective as a liberal transfusion policy for critically ill patients.<sup>22,24</sup>
- Recombinant erythropoietin reduces the risk of transfusion in critically ill patients but does not improve mortality, and its use is associated with an increased rate of thrombotic events.<sup>25</sup>

**A T T E N T I O N**

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



**Pediatrics**

*Anemia in pediatric critical care*

- In children whose condition is stable in the ICU, a transfusion is not usually required unless the patient's hemoglobin is less than 70 g/L.
- A restrictive transfusion strategy (trigger hemoglobin 70 g/L) was proven to be as safe as a liberal transfusion strategy (95 g/L).<sup>24</sup>
  - ◆ This recommendation may not be applicable to neonates under 28 days old, children with severe hypoxemia, hemodynamic instability, active blood loss or cyanotic heart disease as these groups were excluded from this clinical trial



**Pediatrics**

*Anemia in neonatal critical care*

- Several guidelines for small-volume RBC transfusions for newborns have been published in the last decade.<sup>26,27,28,29</sup>
- Two recent randomized controlled trials came to differing conclusions regarding whether a restrictive strategy was as safe as a liberal strategy.<sup>30,31</sup>
- Attention must be drawn to phlebotomy for laboratory testing since it is a significant cause of anemia in neonates.<sup>32</sup>
- Expert recommendations for transfusion thresholds have been published and are shown in the table below.<sup>33</sup>

RESPIRATORY STATUS	AGE OF NEONATE	HEMOGLOBIN THRESHOLD
Ventilated	Age <1 week	Hgb <120 g/L
	Age >1 week	Hgb <110 g/L
On O <sub>2</sub> /CPAP	Age <1 week	Hgb <100 g/L
	Age >1 week	Hgb <90 g/L
Stable and off O <sub>2</sub>	Age >1 week	Hgb ≤75 g/L

- Delayed cord clamping in premature neonates reduces morbidity including risk of transfusion.<sup>34</sup>

**F** Indications for RBCs (cont'd)

**Perioperative patients**

- Manage patients undergoing elective surgery preoperatively, intraoperatively, and postoperatively with strategies to minimize the need for RBCs<sup>18</sup> (see pages 86-96).
- Administer RBCs one unit at a time in non-urgent settings.<sup>35,36</sup>
- Assess patient prior to transfusing additional units (clinical exam and hemoglobin level).<sup>35</sup>
- For orthopedic patients with cardiovascular disease, post-operative transfusion for symptomatic anemia or hemoglobin of less than 80 g/L does not increase adverse outcomes or delay recovery compared to a transfusion trigger of 100 g/L.<sup>37</sup>
- Follow guidelines for perioperative patient:

**CHOOSE WISELY**

Before recommending red blood cell transfusion for the management of anemia, the possibilities for reversal of anemia by non-transfusion treatment should be thoroughly examined.

**A T T E N T I O N**

RBCs:  
One unit at a time.

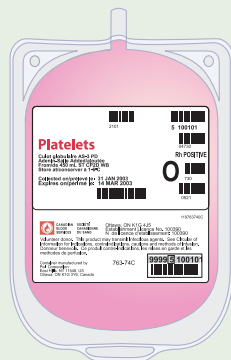
HEMOGLOBIN	RECOMMENDATION
>90 g/L	Likely inappropriate except in exceptional circumstances.
70-90 g/L	Likely to be appropriate if there are signs or symptoms of impaired oxygen delivery (e.g., tachycardia, hypotension, cardiac ischemia, syncope, pre-syncope).
<70 g/L	Likely to be appropriate.
<60 g/L	Transfusion recommended <sup>38</sup> <ul style="list-style-type: none"> <li>◆ Young patients with low risk of ischemic cardiovascular disease can sometimes tolerate greater degrees of anemia.</li> <li>◆ Patients with chronic iron deficiency may often be better managed with IV or PO iron alone. (PO iron works very well in children with iron deficiency anemia and Hgb level as low as 30 g/L in the absence of concerning symptoms of anemia and assurance of reliable follow-up.)</li> </ul>

**Chronic anemia**<sup>39,40</sup>

- Administer transfusions only when alternatives do not exist or have failed.<sup>18</sup>
- Administer RBCs at intervals to maintain the hemoglobin just above the lowest concentration that is not associated with symptoms of anemia.<sup>18</sup>
- Assess patients that are expected to have long-term transfusion dependent survival for iron overload.
- Chelation therapy should be considered in patients who are iron-overloaded, transfusion dependent, and who have a life expectancy of more than one year.
- Iron overload is typically present after 20 units of RBCs (patients with a significant component of ineffective erythropoiesis and upregulation of iron absorption may become iron overloaded more quickly).
- Monitor serum ferritin and transferrin saturation: tissue iron overload is likely if ferritin >1,000 ug/L and transferrin saturation >75%.<sup>39</sup>
- Desferrioxamine, deferasirox, and deferiprone are available agents for iron chelation, with target ferritin between 500 and 1,000 ug/L, and appropriate monitoring for drug toxicity (refer to package insert).

**A Basics**

- Platelets come in 3 forms:
  - ◆ Pool of 4 units of buffy coat derived platelets (pools of 5 in Québec)
  - ◆ Single donor (collected by apheresis)
  - ◆ HLA-matched single donor (for patients with HLA-alloimmunization and refractory to random donor platelets)
- In non-bleeding patients, the risk of spontaneous hemorrhage is low when platelet count is greater than  $10 \times 10^9/L$ .
- In Canada, all platelet products are tested for bacterial contamination which lowers but does not eliminate the risk of sepsis.
- Platelet transfusions may be associated with higher odds of arterial thrombosis and mortality among TTP and HIT patients.<sup>41</sup>



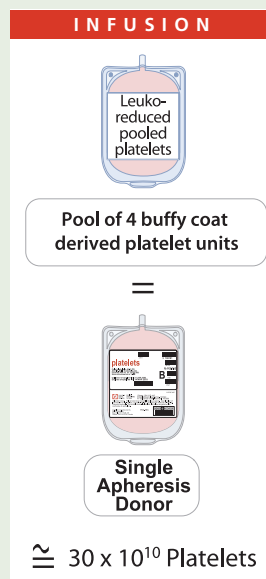
**CHOOSE WISELY**

Platelet transfusions are rarely required for patients with ITP except for the management of life-threatening hemorrhage!

**B Monitoring & Infusion Practices**

**How**

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



**What**

- ABO/Rh-identical platelets are preferred, but ABO/Rh non-identical platelets may be transfused when ABO/Rh-identical platelets are not available.
- Rh negative females of childbearing potential require Rh immunoglobulin (RhIG) when Rh positive platelets are transfused to avoid formation of anti-D antibody.
  - ◆ Each platelet pool contains up to 0.5 mL of RBCs<sup>42</sup>
  - ◆ Each 120 ug of RhIG covers 12 mL whole blood (6 mL RBC) and lasts approximately 21 days
- RhIG is not recommended for males, and females of non-childbearing potential, because risk of immunization from platelets is low (about 1%) and passive anti-D complicates compatibility testing and may delay transfusion.<sup>43</sup>

**Storage**

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



**Pediatrics**

Dose:<sup>26,27</sup>

- Children and neonates: 10 mL/kg up to a maximum of 1 pool of platelets.

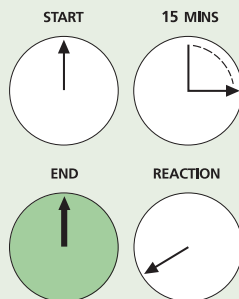
**ATTENTION**

Do NOT put platelets in red cell coolers or in the refrigerator.

**B Monitoring & Infusion Practices (cont'd)**

**Monitor patient**

- Check patient's vital signs:
  - prior to starting
  - 15 minutes after starting
  - at end of transfusion
  - during any transfusion reactions
- Transfuse slowly (50 mL/hr) for the first 15 minutes, where possible.
- Monitor the patient closely for the first 15 minutes especially for signs of bacterial sepsis.
- Each dose of platelets should increase the patient's platelet count at 1 hour by at least  $15-25 \times 10^9/L$ .<sup>44</sup>



**A T T E N T I O N**  
Monitor patient closely for first 15 minutes.

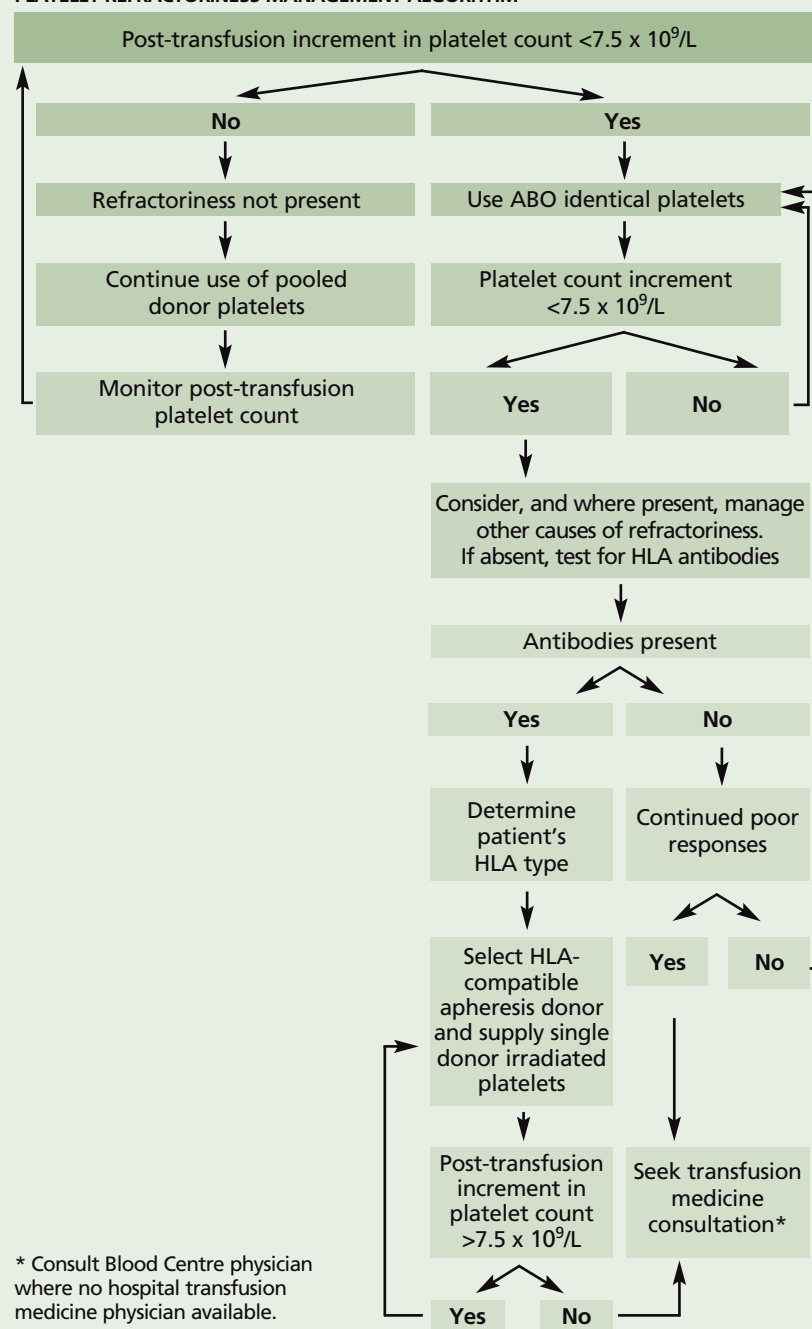
**Transfuse**

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

**Follow-up**

- Outpatients with hypoproliferative thrombocytopenia should have a post-transfusion platelet count every 3-5 platelet transfusions to ensure early detection of HLA-alloimmunization.
- Obtain post-transfusion platelet counts (10-60 minutes) after infusion if patient suspected to be refractory (poor increments at 24 hours) to ensure adequate replacement and recognition of platelet refractoriness.<sup>45</sup>
  - A platelet increment of  $<7.5 \times 10^9/L$  suggests refractoriness and requires investigation<sup>44</sup>
- If increments in platelet count are NOT adequate, special measures are required. Refer to the algorithm on page 31.

PLATELET REFRACTORINESS MANAGEMENT ALGORITHM<sup>44,46</sup>



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

Indications & Infusion Recommendations

PLT ( $\times 10^9/L$ )	CLINICAL SETTING	SUGGEST
<10	Non-immune thrombocytopenia	Transfuse 1 pool of platelets <sup>45</sup>
<10	Non-immune thrombocytopenia & HLA-alloimmunized	Transfuse 1 unit of HLA-matched apheresis platelets <sup>45</sup>
<20	Procedures not associated with significant blood loss (e.g., central line placement)	Transfuse 1 pool of platelets <sup>15</sup>
20-50	Procedures not associated with significant blood loss	1 pool of platelets on hold, transfuse only if significant bleeding <sup>38</sup>
<30	Patient on anticoagulants that should not be stopped	Transfuse 1 pool of platelets
<50	Epidural anesthesia and lumbar puncture	Transfuse 1 pool immediately before procedure <sup>15,47</sup>
<50	Procedures associated with blood loss or major surgery (>500 mL expected blood loss)	Transfuse 1 pool immediately before procedure <sup>38,48</sup>
<50	Immune thrombocytopenia	Transfuse platelets only with life-threatening bleeding <sup>49</sup>
<100	Pre-neurosurgery or head trauma	Transfuse 1 pool of platelets <sup>50,51</sup>
Any	Platelet dysfunction and marked bleeding (e.g., post cardiopulmonary bypass). <b>Exception: Transfusing platelets for intracranial hemorrhage not requiring surgical management in patients on antiplatelet agents leads to increased morbidity</b>	Transfuse 1 pool of platelets <sup>38,52</sup>

ATTENTION

The transfusion of platelets to non-operative patients with ICH on ASA/clopidogrel increases the risk of disability at 3 months.



Pediatrics – Platelet Transfusion Guidelines for Neonates

PLATELET COUNT ( $\times 10^9/L$ )	CLINICAL INDICATION	DOSE COLUMN
<20	Term infants <sup>53</sup>	10 mL/kg
<30	Pre-term >7 days old <sup>53</sup> Neonatal Alloimmune Thrombocytopenia <sup>53,54</sup>	10 mL/kg
<50	Pre-term and $\leq 7$ days old <sup>53,55</sup> Pre non-neuraxial surgery <sup>55</sup> Concurrent coagulopathy <sup>53,55</sup> Previous significant hemorrhage (i.e., grade 3-4 intraventricular or pulmonary hemorrhage) <sup>55</sup> Active Bleeding <sup>55</sup>	10 mL/kg
<100	Pre neuraxial surgery <sup>55</sup>	10 mL/kg

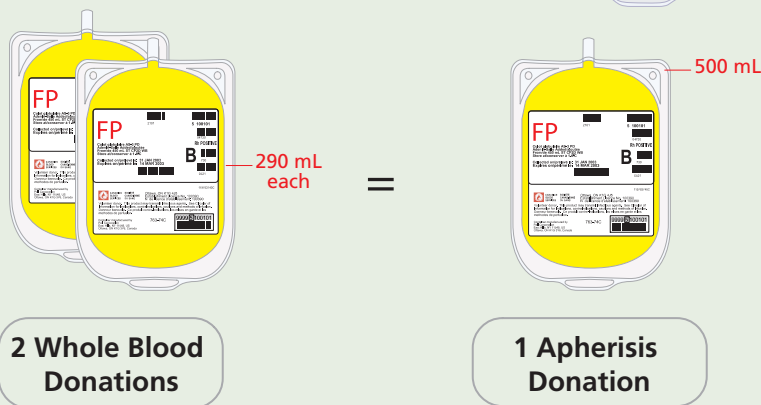
CHOOSE WISELY

Don't transfuse platelets in the following situations:

- ◆ Platelet count above  $10 \times 10^9/L$  with no bleeding in anticipation of a drop to less than  $10 \times 10^9/L$
- ◆ For patients with ITP without major hemorrhage, even when platelet count  $<10 \times 10^9/L$
- ◆ For patients undergoing procedures more than 6 hours later (give as close to procedure as feasible)
- ◆ For minor procedures with platelet counts  $>20 \times 10^9/L$  (e.g., paracentesis or thoracentesis)

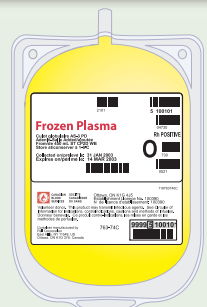
**A Basics**<sup>56,57</sup>

- Frozen plasma (FP) can be derived from two sources:
  - ◆ Whole blood donor plasma (290 mL)
  - ◆ Apheresis donors (290 or 500 mL)
    - large apheresis units (500 mL) are equivalent to 2 units of random donor plasma



**Notes:**

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



**B Monitoring & Infusion Practices**

**How**

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

**Dose**<sup>58</sup>

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

**When**

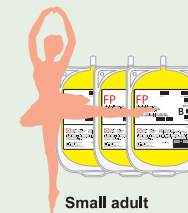
- The recommended infusion time is 30-120 minutes per unit (maximum time 4 hours).

**Storage**

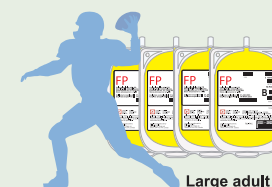
- Frozen plasma is kept *frozen* for up to one year.
  - ◆ Once thawed, plasma can be stored at 1-6 °C for 5 days
- After issue, FP and FFPA should be administered within 4 hours.
  - ◆ The biological half-life of plasma coagulation proteins is different for each protein:<sup>59</sup>
    - 3-6 hours for factor VII
    - 8-12 hours for factor VIII
    - 2-3 days for factors II and XI

**Monitor patient**

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



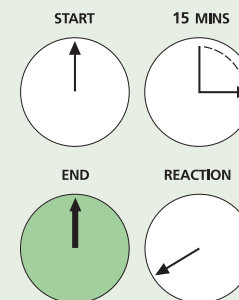
Small adult



Large adult

**ATTENTION**

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



**ATTENTION**

Patients receiving plasma are at high risk for Transfusion-Associated Circulatory Overload (TACO)!

Indications for Frozen Plasma

To determine if FP is indicated for abnormal coagulation test results, the cause of the elevation must be determined (i.e., liver disease vs. warfarin effect vs. single factor deficiency). See Section 4 of Bloody Easy Coagulation Simplified<sup>60</sup> for details. The reasons for this are as follows:

- There are numerous replacement options and the correct one must be selected for the patient (i.e., FP vs. Prothrombin Complex Concentrates (PCC) vs. single factor concentrate).
- Warfarin effect and vitamin K deficiency can often be managed with intravenous/oral vitamin K alone.
- Patients with liver disease have preserved thrombin generation despite elevated INR levels and often do not need correction of the abnormality before procedures.
- Patients with isolated high PTT (and normal INR) are managed with strategies other than FP.
- Patients on anticoagulants are never appropriately managed with FP.<sup>60</sup>

**1. Bleeding or prior to a significant operative procedure in patients with INR, PT or PTT 1.8 times normal or greater due to multiple factor deficiency when no coagulation factor concentrates or other alternative therapies are available.<sup>13</sup>**

- ◆ Repeating INR/PT/PTT after infusion of FP may be beneficial to ensure that replacement is adequate<sup>9</sup>

**ATTENTION**

FP is NOT indicated or required when INR <1.8 as coagulation factor levels are adequate for hemostasis.

**ATTENTION**

IV Vitamin K works faster than oral.

**ATTENTION**

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

**CHOOSE WISELY**

Don't transfuse plasma in the following situations:

- ◆ Bleeding and INR <1.8
- ◆ Procedure and INR <1.8
- ◆ INR elevated but patient is not actively bleeding
- ◆ Warfarin reversal
- ◆ Heparin/LMWH reversal
- ◆ Xa or IIa inhibitor anticoagulant reversal
- ◆ High aPTT with normal INR

**Note:** 61,62,63,64

- If available, prothrombin complex concentrates (PCCs) should be used for urgent reversal of warfarin therapy or treatment of vitamin K deficiency in a bleeding patient OR a patient requiring an emergency invasive procedure. Vitamin K (2-10 mg i.v.) should also be given. See page 124 in this guide.
- For non-emergent reversal of warfarin or vitamin K deficiency, vitamin K should be used rather than PCCs.
  - ◆ For patients without bleeding and INR >10 due to warfarin, 2 mg of oral Vitamin K will bring INR within the therapeutic range over 24-48 hours
  - ◆ After intravenous administration, Vitamin K effect can be detected after 2 hours and the INR should be normalized after 6-24 hours
  - ◆ SC and IM NOT recommended due to variable absorption: intravenous formulation can be used orally when required



**Pediatrics** <sup>65</sup>

Vitamin K dose:

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

● Indications for Frozen Plasma (cont'd)

- 2. Microvascular bleeding or massive transfusion AND patient's clinical status precludes waiting 30-45 minutes for INR/PT/PTT results.<sup>13</sup>
- 3. Thrombotic thrombocytopenic purpura.

**A T T E N T I O N**

Ratio based replacement (i.e., 2:1 RBC:FP) with FP not required when patient is expected to need less than 10 RBC units over 24 hours or time allows replacement based on laboratory testing.

INR/PT/PTT	INDICATION (PEDIATRIC AND ADULT PATIENTS)
1.8 or greater	Active bleeding or prior to significant operative procedure in patient with multiple coagulation factor deficiency when no coagulation factor concentrates or other alternative are available  Note: Patients with liver disease have preserved thrombin generation despite elevated INR levels and often do not need correction of the abnormality before procedures
Results not immediately available	Microvascular bleeding or massive transfusion AND patient's clinical status precludes waiting 30-45 minutes for INR/PT/PTT results
Any	Thrombotic thrombocytopenic purpura (TTP)

**A Basics** 38,66

**What**

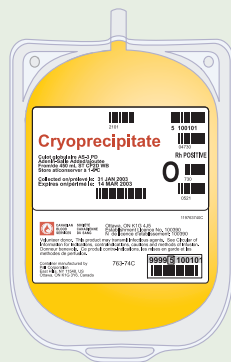
- It is acceptable to use non ABO compatible cryoprecipitate, where required.
- Cryoprecipitate contains factor VIII, factor XIII, fibrinogen, and von Willebrand factor.
  - ◆ Each unit of cryoprecipitate contains a minimum of 150 mg of fibrinogen
- 10 units of cryoprecipitate on average contains 4 grams of fibrinogen

**How**

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

**Dose**

- Adults: 10 units. Pediatrics: 1 unit/10 kg body weight to maximum of 10 units.
- Each dose will increase the fibrinogen by 0.5 g/L in the bleeding patient.<sup>67</sup>
- Recommended infusion time is 10-30 minutes per dose (maximum infusion time 4 hours).
- Half-life of fibrinogen is about 7 days.



**B Indications**

- For bleeding with fibrinogen <1 g/L.<sup>38</sup>
- For massive hemorrhage with fibrinogen <1.5-2.0 g/L.<sup>68</sup>
- For acute phase of acute promyelocytic leukemia with fibrinogen <1.5 g/L.<sup>69</sup>
- Intracranial hemorrhage secondary to treatment with Tissue Plasminogen Activator with fibrinogen <2.0 g/L.
- Treatment of bleeding in patients with von Willebrand disease or Hemophilia A **only**:
  - ◆ when factor concentrates are unavailable (remote geographic region); and
  - ◆ DDAVP is unavailable or ineffective

**CHOOSE WISELY**

**Don't transfuse** cryoprecipitate in the following situations:

- ◆ DIC with low fibrinogen level in the absence of bleeding or a planned procedure (other than the acute phase of acute promyelocytic leukemia)
- ◆ Any congenital bleeding disorder

**C Alternatives to Cryoprecipitate**

- Fibrinogen concentrates are licensed for congenital hypofibrinogenemia in Canada.
- There is one fibrinogen concentrate available in Canada: RiaSTAP™ (CSL Behring).
- The vials are 1 gram of lyophilized product that is reconstituted in 50 mL of sterile diluent.
- In hospitals where cryoprecipitate can not be provided, it is reasonable to utilize fibrinogen concentrates (adult dose 4 grams equivalent to 10 units of cryoprecipitate).

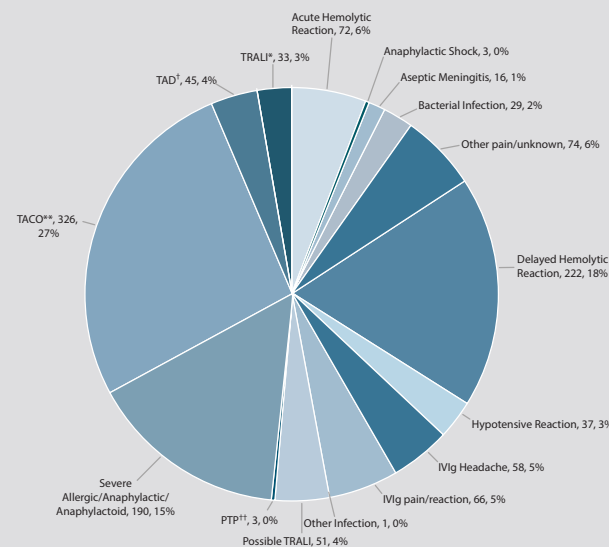
RISK OF EVENT	EVENT
1 in 13	Red cell sensitization, increasing risk of hemolytic transfusion reaction and hemolytic disease of the fetus and newborn <sup>70</sup>
1 in 20	Febrile non-hemolytic transfusion reaction per pool of platelets <sup>71</sup>
1 in 100	Transfusion-associated circulatory overload per transfusion episode <sup>72</sup>
1 in 100	Minor allergic reactions (urticaria)
1 in 300	Febrile non-hemolytic transfusion reaction per unit of RBC (1 'donor exposure')
1 in 7,000	Delayed hemolytic transfusion reaction
1 in 10,000	Transfusion-related acute lung injury (TRALI)
1 in 10,000	Symptomatic bacterial sepsis per pool of platelets
1 in 40,000	ABO-incompatible transfusion per RBC transfusion episode
1 in 40,000	Serious allergic reaction per unit of component
1 in 100,000	Post-transfusion purpura
1 in 200,000	Death from bacterial sepsis per pool of platelets
1 in 250,000	Symptomatic bacterial sepsis per unit of RBC
1 in 500,000	Death from bacterial sepsis per unit of RBC
<1 in 1,000,000	Transmission of West Nile Virus
1 in 4,000,000	Transmission of Chagas disease per unit of component
1 in 7,500,000	Transmission of hepatitis B virus per unit of component
1 in 7,600,000	Transmission of HTLV per unit of component
1 in 13,000,000	Transmission of hepatitis C virus per unit of component
1 in 21,000,000	Transmission of human immunodeficiency virus (HIV) per unit of component

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

**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) 2014.
  - ♦ 1 in 177,000 components issued possibly, probably or definitely related to patient death<sup>73</sup>
- United States (Food and Drug Administration) 2011.
  - ♦ 1 in 360,000 components transfused resulted in a death from transfusion<sup>74,75</sup>
- The Hemovigilance Network in France 2003.
  - ♦ 1 in 208,000 components transfused resulted in a death from transfusion<sup>76</sup>

**TRANSFUSION TRANSMITTED INJURIES SURVEILLANCE SYSTEM (TTISS), ONTARIO. MAJOR ADVERSE EVENTS REPORTED 2008-2014<sup>77</sup>**



\* Transfusion-related acute lung injury (TRALI)  
 \*\* Transfusion-Associated Circulatory Overload (TACO)  
 † Transfusion-associated dyspnea (TAD)  
 †† Post-transfusion purpura (PTP)

RISK OF EVENT	EVENT
1 in 13	Red blood cell antibodies that can complicate future pregnancies or transfusion
1 in 100	Hives (itchy skin rash)
1 in 100	Heart failure
1 in 300	Fever from red cell transfusion
1 in 7,000	Delayed hemolysis. Hemolysis is when your red blood cells are destroyed
1 in 10,000	Lung injury
1 in 10,000	Symptomatic bacterial sepsis, per pool of platelets. Sepsis is when you get an infection in your bloodstream or tissue
1 in 40,000	Wrong ABO (blood) group, per unit of red blood cells
1 in 40,000	Anaphylaxis, which is an extreme sensitivity to a drug or substance that can result in death
1 in 200,000	Death from bacterial sepsis, per pool of platelets
1 in 250,000	Symptomatic bacterial sepsis, per unit of red blood cells
1 in 500,000	Death from bacterial sepsis, per unit of red blood cells
<1 in 1,000,000	Transmission of West Nile Virus
1 in 4,000,000	Transmission of Chagas Disease. Chagas Disease is a parasite that can be transmitted through transfusion
1 in 7,500,000	Hepatitis B Virus (HBV) transmission per unit of component
1 in 7,600,000	Human T-cell lymphotropic virus (HTLV) transmission, per unit of component. HTLV is a virus that can be transmitted by exposure to blood or sexual contact, and can cause a form of cancer of the blood
1 in 13,000,000	Hepatitis C Virus (HCV) transmission, per unit of component
1 in 21,000,000	Human Immunodeficiency Virus (HIV) transmission, per unit of component

FREQUENCY OF NON-TRANSFUSION ASSOCIATED RISKS FOR COMPARISON WITH RISKS OF COMPLICATIONS OF BLOOD TRANSFUSION	
HAZARD	PROBABILITY
1 in 10 <sup>78</sup>	Dying from lung cancer after smoking 1 pack a day for 30 years
1 in 60 <sup>79</sup>	Stroke within 30 days of cardiac surgery
1 in 100 <sup>80</sup>	Death associated with hip replacement surgery
1 in 10,000 <sup>81</sup>	Annual risk of death in a motor vehicle crash
1 in 60,000 <sup>81</sup>	Annual risk of being murdered in Canada
1 in 200,000 <sup>82</sup>	Death from anesthesia in fit patients
1 in 300,000 <sup>83</sup>	Death from oral contraceptives age <20 years
1 in 1,000,000 <sup>81</sup>	Annual risk of death from accidental electrocution in Canada
1 in 5,000,000 <sup>81</sup>	Annual risk of death from being struck by lightning in Canada

**A Reporting**

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

**A T T E N T I O N**

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

**What**

- The Transfusion Medicine Laboratory (TML) will investigate, assess and report the event to Transfusion-transmitted injuries surveillance system (TTISS) which will then report to Public Health Agency of Canada (PHAC)\*. In Québec, the hospital's transfusion service reports all transfusion reactions to Québec Hemovigilance System, which then reports to PHAC.
- Component reactions relating to the quality of the product must also be reported to CBS/HQ.
- Plasma derivative reactions related to quality must also be reported to the particular manufacturer.

**How**

- CBS/HQ and PHAC\* reporting forms are available from all hospital transfusion services.
  - ◆ Contact your transfusion service for more information
  - ◆ It is the transfusion service's responsibility to submit them to CBS/HQ and PHAC

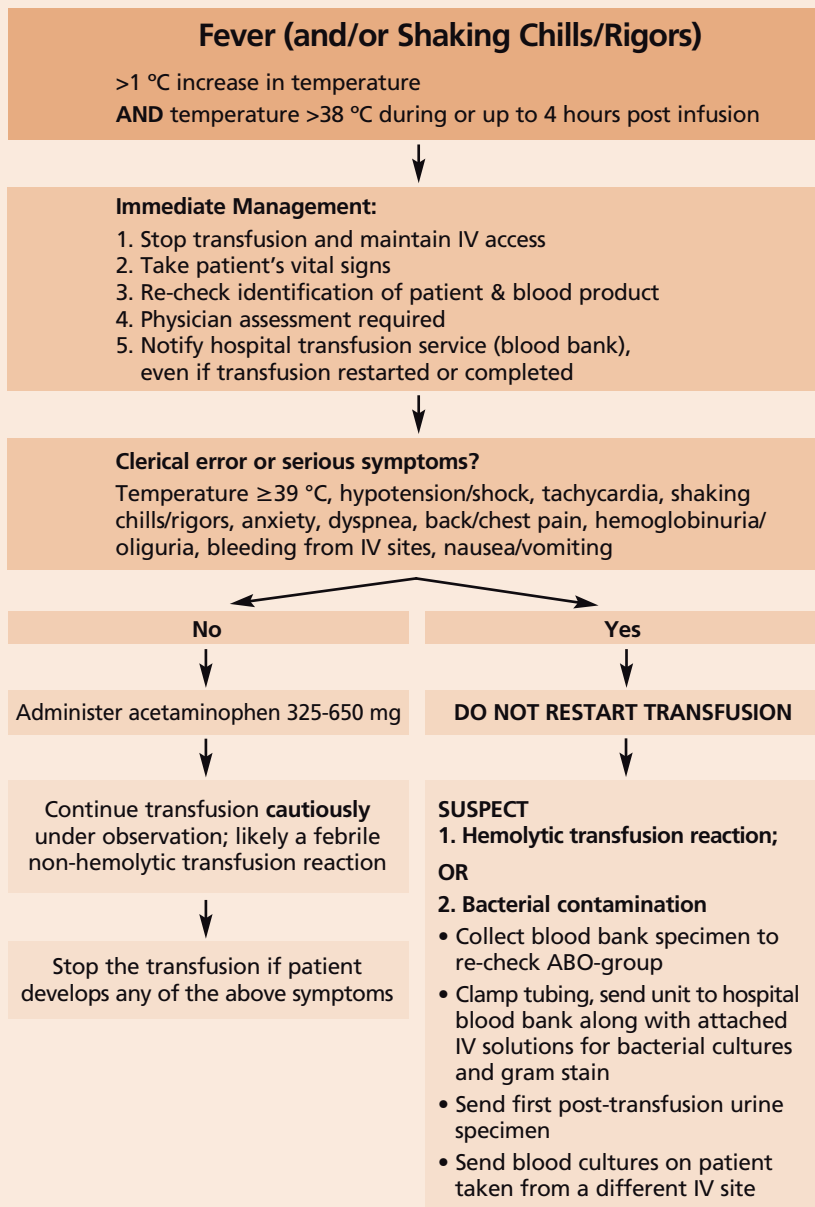
\* www.phac-aspc.gc.ca (click on Infectious Diseases; Blood Safety)

**B Reaction by Symptom**

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Fever

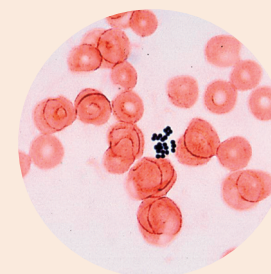
MANAGEMENT ALGORITHM



BACTERIAL SEPSIS OR CONTAMINATION

ETIOLOGY<sup>84</sup>

- Blood components may be contaminated by:
  1. Skin commensals from the donor (each venipuncture may result in a small skin plug that may be retained in the donation bag)
  2. Unrecognized bacteremia in the donor
  3. Contamination from the environment or from handling of the product
- Organisms:
  - ♦ Serious morbidity and mortality occur most frequently with Gram-negative bacteria,<sup>85</sup> but are also reported with Gram-positive skin bacteria
  - ♦ A number of bacteria have been implicated, including:<sup>84,86</sup>



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

**Gram-negative**

- Escherichia coli
- Serratia marcescens
- Klebsiella pneumonia
- Pseudomonas species
- Yersinia enterocolitica

**Gram-positive**

- Staphylococcus aureus
- Staphylococcus epidermidis
- Bacillus cereus

INCIDENCE<sup>84,85,87,88,89,90</sup>

	BACTERIAL CONTAMINATION	SYMPTOMATIC SEPTIC REACTIONS	FATAL BACTERIAL SEPSIS
Buffy coat platelet pool	1 in 1,000	1 in 10,000	1 in 200,000
1 unit of RBC	1 in 50,000	1 in 250,000	1 in 500,000

- Bacterial sepsis accounts for at least 10% of transfusion-associated fatalities.<sup>74</sup>
- Bacterial sepsis occurs most frequently with platelets due to their storage at 20-24 °C for preservation of function.
- About two thirds are Gram-positive and one third Gram-negative.<sup>74</sup>

**CLINICAL PRESENTATION**

- Clinical features of transfusion-associated sepsis may include:<sup>88,91</sup>
  - ◆ 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.
  - ◆ Delayed presentation of symptoms up to 24 hours post-transfusion reported<sup>90</sup>

**MANAGEMENT<sup>89,91</sup>**

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

**A T T E N T I O N**  
 Stop transfusion immediately if bacterial infection is suspected.

**A T T E N T I O N**  
 Arrange for Gram stain on unit(s) suspected of being contaminated.

**A T T E N T I O N**  
 Start antibiotic therapy immediately, do not wait for results of blood cultures.

**PREVENTION**

- The skin is disinfected at the donation site to reduce bacterial contamination by skin flora.
- The first 40 mL of blood collected is diverted and sequestered in a pouch to reduce risk of transmitting organisms from skin (can be used for infectious agent testing).
- Apheresis and buffy coat platelets are cultured by CBS/HQ prior to issue to hospitals.
- RBCs are stored at 1-6 °C in a monitored blood bank refrigerator.

**A T T E N T I O N**  
 Keep RBCs in an approved fridge or cooler until immediately prior to transfusion!

**ACUTE HEMOLYTIC TRANSFUSION REACTION**

**ETIOLOGY**

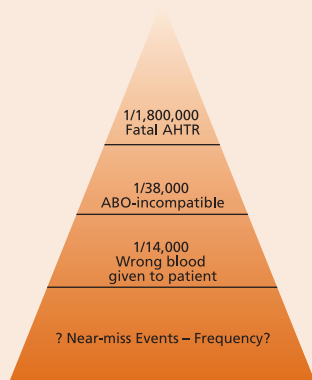
- Acute hemolytic transfusion reactions may be associated with:
  - ◆ ABO-incompatibility
  - ◆ Other blood group incompatibilities
    - There are 29 blood group systems and 346 known blood group antigens that may cause incompatibility (in addition to ABO)<sup>92</sup>
  - ◆ Rare cases when group O platelets with high titers of anti-A and/or anti-B are transfused to a non-group O recipient<sup>93</sup>
- **ABO-incompatibility:**
  - ◆ Is due to a clerical error or other error in patient identification
  - ◆ HALF of all errors are due to administering properly labelled blood to the wrong patient<sup>94</sup>
  - ◆ Other errors are the result of improper labelling of specimens or testing errors

**RBC alloantibodies (non-ABO):**

- ◆ Result from patient immunization from a prior pregnancy or transfusion
- ◆ Causes of reactions include:
  - Red cell alloantibodies in the patient’s plasma below the level detected by the antibody screen
  - Clerical error during patient antibody screening
  - Failure to detect RBC antibody due to limitations of the laboratory assay
  - Uncrossmatched blood transfused to a patient who is alloimmunized

**INCIDENCE**

- 1 in 38,000 red cell transfusions are ABO-incompatible due to transfusing the wrong blood to a patient.<sup>94</sup>
- Less than 10% of ABO-incompatible transfusions result in a fatal outcome.<sup>94</sup>
- Over 50% of patients have no morbidity from an ABO-incompatible transfusion.
- Risk of death correlates with the amount of incompatible blood transfused.<sup>95</sup>



**CLINICAL PRESENTATION<sup>96</sup>**

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

**MANAGEMENT**

- **Stop the transfusion!**
- Check if there is a clerical error. Check identity of patient vs. patient identity on blood product label.
- Notify hospital transfusion service (blood bank).
- Send specimens to hospital transfusion service to re-check ABO-group.
- Return residual of blood product(s) and tubing (clamped) to the hospital transfusion service.
- Send first post-transfusion urine specimen for urinalysis.
- Provide supportive care.
  - ◆ Maintain good urine output
  - ◆ Manage DIC and hemorrhage as clinically indicated

**PREVENTION**

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

**A T T E N T I O N**

Stop transfusion immediately if acute hemolytic reaction suspected.

**A T T E N T I O N**

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

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

**ETIOLOGY**

- Attributable to:<sup>97</sup>
  - ◆ 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**<sup>98</sup>

	INCIDENCE
RBC	1 in 300
Platelet pool	1 in 20

**CLINICAL PRESENTATION**

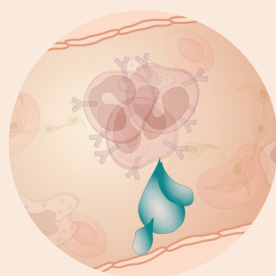
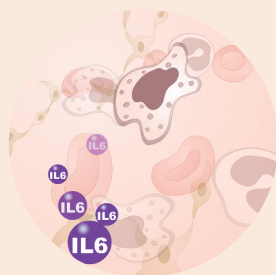
- Fever usually occurs during or up to 4 hours post transfusion.
  - ◆ May be associated with chills, rigors, nausea, vomiting and hypotension
- Fever is not always present (i.e., chills, nausea, etc., alone).

**MANAGEMENT**

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

**PREVENTION**

- Pre-medication with acetaminophen and diphenhydramine has not been shown to be effective in preventing FNHTR.<sup>99,100</sup>
- In patients with significant and recurrent FNHTR, the following measures have been used but efficacy is unproven:
  - ◆ Acetaminophen, corticosteroids, fresh components, plasma-depleted components, washed red blood cells (washing platelets results in 50% loss of platelets)
- Antihistamines are not effective.



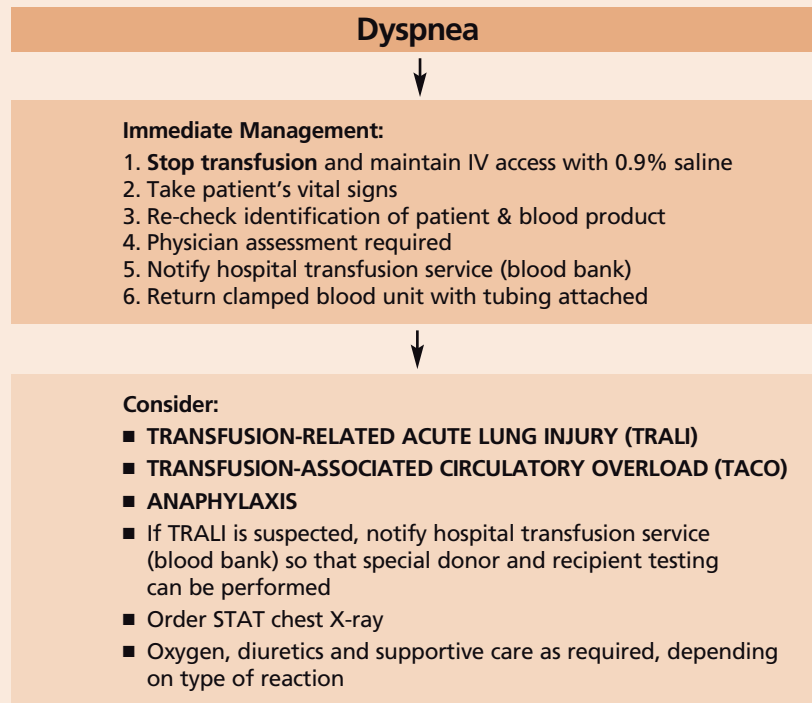
**A T T E N T I O N**  
 Fever is **not** a contraindication to commencing a blood transfusion!

**A T T E N T I O N**  
 Meperidine has numerous serious drug interactions. Consult pharmacy if the patient is on SSRIs, MAOIs, antibiotics, antifungals, or medications for seizures.

**Dyspnea**

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

**MANAGEMENT ALGORITHM**



**TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)**<sup>101,102</sup>

**DEFINITION OF ACUTE LUNG INJURY (ALI)**

- Acute onset.
- Hypoxemia:
  - ◆ PaO<sub>2</sub>/FiO<sub>2</sub> <300 mmHg; OR
  - ◆ Oxygen saturation is <90% on room air; OR
  - ◆ Other clinical evidence
- Bilateral lung infiltrates on the chest radiograph.
- No evidence of circulatory overload.

**DEFINITION OF TRALI**

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

**DEFINITION OF POSSIBLE TRALI**

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

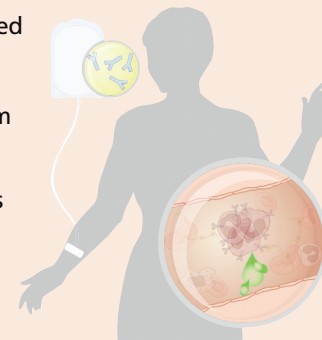
**RISK FACTORS FOR ACUTE LUNG INJURY**

Predisposing factors for ALI include:

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

**ETIOLOGY**

- Presently not fully defined. Two postulated mechanisms have been implicated:<sup>102,103</sup>
  1. Antibody-mediated: Passive transfer of HLA or granulocyte antibodies from donor to blood product recipient; or, less commonly, HLA or granulocyte antibodies in the recipient (antibodies detected in donor or recipient in 80% of cases).<sup>104,105</sup>
    - Antibodies are most common in multiparous female donors as a consequence of prior pregnancies
  2. Neutrophil priming hypothesis: Biologic response modifiers such as biologically active lipids in the transfused component may induce TRALI in a susceptible patient.<sup>106</sup>



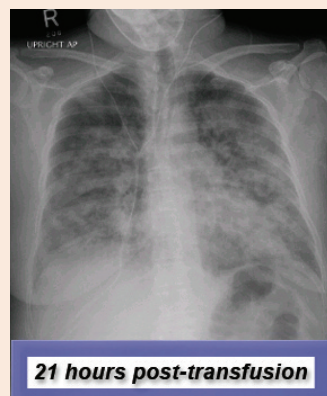
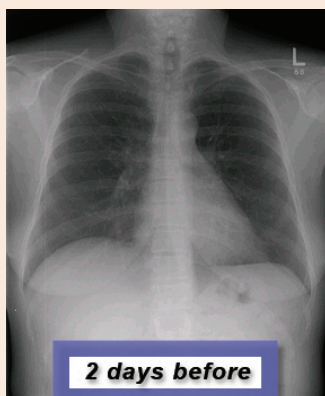
**INCIDENCE**

- 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.<sup>104,107</sup> (Both studies were performed before TRALI reduction measures.)
- The incidence of TRALI has decreased by approximately half with implementation of TRALI reduction measures with SHOT and American Red Cross reporting large reductions in cases (see Prevention).<sup>73,108</sup>
- TRALI is known to be under-diagnosed and under-reported.

**PRESENTATION**

- Dyspnea, hypoxemia, fever and hypotension.
- Chest X-ray reveals interstitial and alveolar infiltrates (pulmonary edema), without elevated pulmonary pressures.
- Usually occurs with transfusion of RBCs, platelets and plasma, but rarely with other blood products (including cryoprecipitate and IVIG).
- Almost always within the first 1-2 hours after the start of transfusion but can be delayed for up to 6 hours.<sup>104</sup>
- Usually resolves in 24-72 hours.
- 72% of reported cases required mechanical ventilation and death occurs in 5-10% of patients experiencing a TRALI reaction.<sup>104</sup>
- Milder forms of TRALI are thought to exist and may present as transient hypoxia.<sup>109</sup>
- Acute transient leukopenia may be observed after a TRALI reaction.<sup>110</sup>

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



**MANAGEMENT**

- Supportive care, including mechanical ventilation when clinically indicated.
- Diuretics and steroids are not believed to be useful in treating TRALI.<sup>111</sup>
- Accurate reporting to hospital transfusion service is critical to identify implicated donors and prevent TRALI in other recipients.
- Patient and donor testing should be arranged through the hospital transfusion service (testing performed through CBS/HQ).

**PREVENTION**

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

**TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)** <sup>112</sup>

**ETIOLOGY**

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

**INCIDENCE**

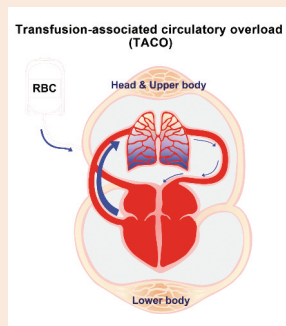
- Current estimate of the frequency of TACO range from 1 in 700 to 8% of transfusion recipients.<sup>7</sup>
- Patients over 70 years of age, infants, and patients with severe euvolemic anemia (hemoglobin <50 g/L), renal impairment, fluid overload, and cardiac dysfunction are particularly susceptible.

**CLINICAL PRESENTATION**

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

**MANAGEMENT**

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



**A T T E N T I O N**

TACO is the most common cause of death from transfusion!

**A T T E N T I O N**

Interrupt transfusion.  
Administer oxygen and diuretics if required.  
Consider restarting transfusion at reduced rate.

**PREVENTION**

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

**A T T E N T I O N**

The following are risk factors for TACO:

- ◆ Age over 70 years
- ◆ History of heart failure
- ◆ Left ventricular dysfunction
- ◆ History of myocardial infarction
- ◆ Renal dysfunction
- ◆ Positive fluid balance

**A T T E N T I O N**

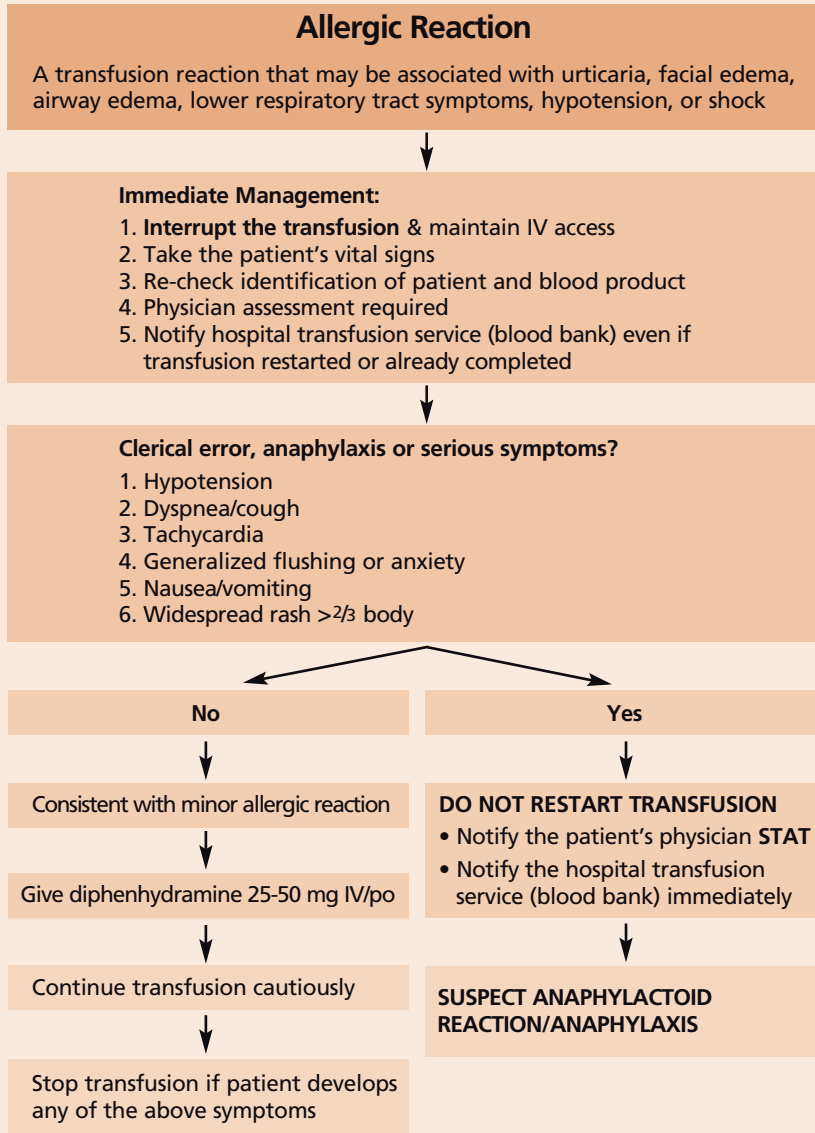
In patients at risk, avoid transfusing more than one unit at a time.

**C H O O S E W I S E L Y**

Avoid unnecessary transfusion of blood products and maximize the use of alternatives.

## Urticaria & Other Allergic Reactions/Anaphylaxis

### MANAGEMENT ALGORITHM



## ANAPHYLAXIS

### ETIOLOGY<sup>113</sup>

- Vast majority of anaphylactic reactions are unexplained.
- The following mechanisms have been implicated in anaphylaxis/anaphylactoid reactions:
  - ◆ Anti-IgA in an IgA deficient recipient
  - ◆ Antibodies to polymorphic forms of serum proteins (IgG, albumin, haptoglobin, α-1-antitrypsin, transferrin, C3, C4, etc.)
  - ◆ Transfusing an allergen to a sensitized patient (e.g., penicillin, ASA, etc., consumed by donor)
  - ◆ Passive transfer of IgE (to drugs, food)
- 1 in 500 blood donors are IgA deficient (IgA <0.05 mg/dL), and 1 in 1,500 blood donors have anti-IgA, but most are NOT at risk of an anaphylactic transfusion reaction (reasons are not clear at this time).<sup>114</sup>
  - ◆ Anti-IgA as a cause of anaphylaxis from transfusion has recently been called into question due to the lack of evidence implicating IgA deficiency in this entity<sup>115</sup>
- Haptoglobin deficiency is not uncommon in Asian patients (1 in 1,000) and has been associated with anaphylactic reactions.<sup>116</sup>

### INCIDENCE

- Transfusion-associated anaphylactic shock is rare.<sup>117</sup>
- Anaphylaxis accounts for approximately 5% of transfusion associated fatalities.<sup>86</sup>

CLINICAL PRESENTATION<sup>113</sup>

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

TREATMENT

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

PREVENTION OF RECURRENT ANAPHYLAXIS

- Pre-medication with intravenous steroids and diphenhydramine.
- If a patient is found to be IgA-deficient with anti-IgA, the following products are recommended:
  - ◆ IgA-deficient blood products from IgA deficient donors, available from CBS/HQ
  - ◆ Washed RBCs (2L normal saline in 6 wash cycles) or platelets<sup>113,118</sup>

A T T E N T I O N

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

A T T E N T I O N

Epinephrine should be readily available whenever transfusion is carried out.

MINOR ALLERGIC REACTION – URTICARIA

ETIOLOGY

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

INCIDENCE

- Urticarial reactions are commonly encountered: 0.42% of red blood cell, 3.04% of platelet and 3.15% of plasma transfusions.<sup>119</sup>

CLINICAL PRESENTATION

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

MANAGEMENT

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

PREVENTION

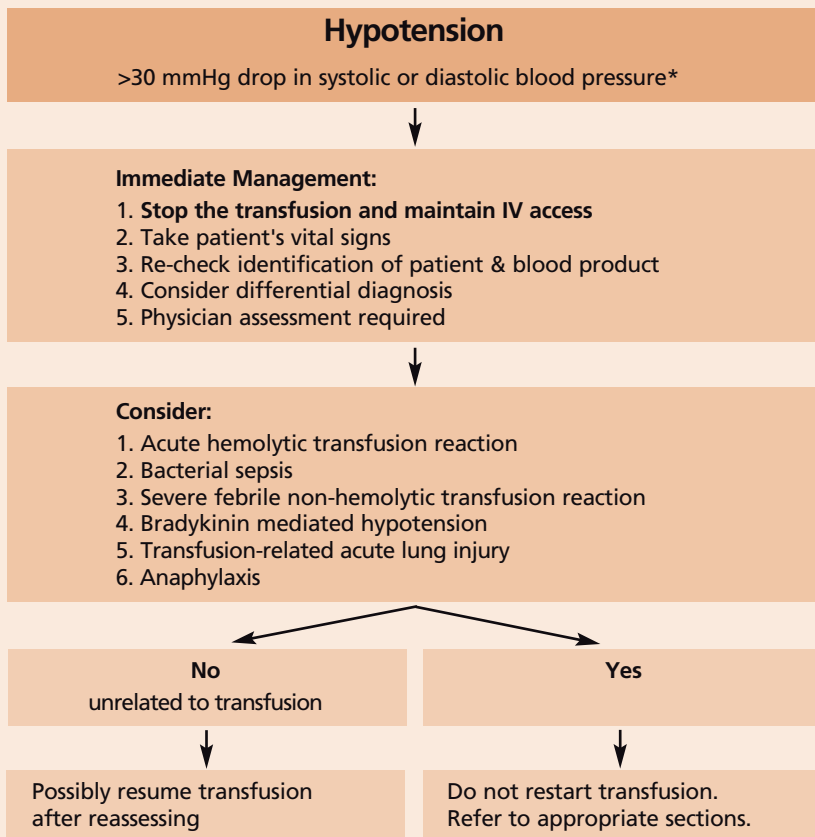
- If the urticarial reactions are recurrent, the following precautionary measures may be used although their efficacy is unknown:
  - ◆ Pre-medication with diphenhydramine and/or corticosteroids
  - ◆ Plasma depletion of RBCs or platelets
  - ◆ Washed RBCs or platelets

A T T E N T I O N

Interrupt transfusion. Give diphenhydramine. Restart transfusion slowly.

## Hypotension<sup>120</sup>

### MANAGEMENT ALGORITHM



\* Definition refers to adult patients only



### Pediatrics

Hypotension in children is defined as:

- Infants, children and adolescents (1 year to less than 18 years old):
  - ◆ Greater than 25% drop in systolic BP from baseline.
- Neonates and small infants (less than 1 year old OR any age and less than 12 kg body weight):
  - ◆ Greater than 25% drop in baseline value using whichever measurement is being recorded (e.g., mean BP).

## BRADYKININ MEDIATED HYPOTENSION

### ETIOLOGY

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

### INCIDENCE

- Unknown.

### CLINICAL PRESENTATION

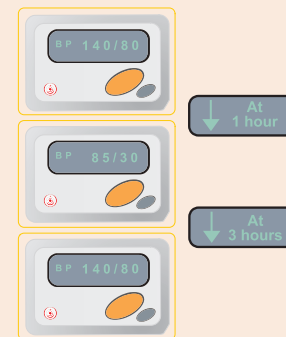
- Majority of hypotensive reactions occur with platelet transfusions.
- Of reported cases, over half of the patients were on ACE inhibitors.
- Other symptoms may be present, including dyspnea, urticaria, nausea, and vomiting.
- Rarely associated with significant morbidity or mortality.

### TREATMENT

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

### PREVENTION

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



### ATTENTION

Monitor patient for first 15 minutes and vital signs at 15 minutes.  
Stop transfusion if hypotension develops.

## Hemolysis After Transfusion

### HEMOLYSIS NOT RELATED TO RBC ALLOANTIBODIES

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

### DELAYED HEMOLYTIC TRANSFUSION REACTIONS

#### ETIOLOGY

- Results from the formation of antibodies in the recipient (to transfused red cell alloantigens or from RBC antigen exposure during a prior pregnancy) and below the level of detection on the initial antibody screen testing.
- Commonly implicated antigens are (in order of frequency): E, Jk<sup>a</sup>, c, Fy<sup>a</sup>, K.<sup>121</sup>
- Delayed hemolysis may occur with transfusion-transmitted malaria and babesiosis.

#### INCIDENCE

- 8% of recipients will have newly formed RBC alloantibodies detected in the first 6 months.<sup>70</sup>
- 1 in 6715 units of RBCs transfused are associated with a delayed hemolytic transfusion reaction.<sup>121</sup>

#### 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).<sup>122</sup>

#### COMPLICATIONS

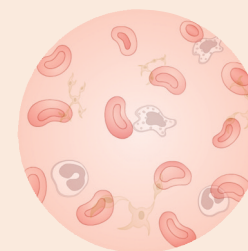
- Most are benign, but life-threatening hemolysis with severe anemia and renal failure may occur.

#### TREATMENT

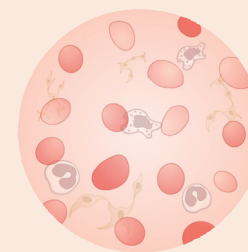
- Transfuse compatible blood ('antigen negative'; i.e., if the offending antibody is anti-Jk<sup>a</sup>, then the transfusion service will provide units that do not carry the Jk<sup>a</sup> antigen).

#### PREVENTION

- Avoid RBC transfusions.
- Use of antibody screening methods with maximal sensitivity.
- Notify patient and provide an antibody card for the patient to carry in their wallet.



Normal Blood Film



Spherocytes

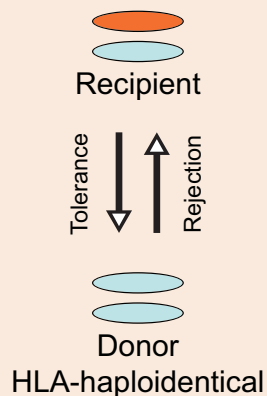
Antibody Card	
Blood Bank	Date: June 11, 2011
Name: Mary Bloodworthy	
Date of Birth: Oct 25, 1981 Hospital File # 1175380	
ABO/Rh: O NEG	
Special Requirements:	
<b>ANTIBODY (IES)</b> <b>ANTI-E</b>	

## Cytopenias After Transfusion

### TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GvHD)<sup>123,124</sup>

#### ETIOLOGY

- TA-GvHD has been reported in immunocompromised patients or in immunocompetent individuals transfused a fresh (<14 day old) haploidentical product. (The risk of an HLA-haploidentical donor in North America is estimated at 1 in 17,700 to 39,000.)<sup>125,126</sup>
  - ◆ A donor who is homozygous for an HLA type (haploidentical), whose blood product is transfused to a recipient who is heterozygous for the same HLA type and a different HLA type places the recipient at risk
    - The donor's lymphocytes mount a reaction against the non-matching HLA determinants on the recipient's cells



#### INCIDENCE

- Unknown; there were 13 cases reported in the UK SHOT program from 1996 to 2001; since 2001 there has been one case in 2012 attributed to failure to irradiate maternal blood for an intra-uterine fetal transfusion.<sup>73</sup>

#### CLINICAL PRESENTATION

- Fever, rash, liver dysfunction, and diarrhea commencing 1-2 weeks post-transfusion followed by pancytopenia later.
- Overwhelming infections are the most common cause of death.
- Mortality is >90%.<sup>126</sup>
- Diagnosis can be made by biopsy of skin, liver, or bone marrow.
- Confirmation requires documentation of the presence of donor lymphocytes (e.g., HLA typing, short tandem repeat analysis).

#### TREATMENT

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

#### PREVENTION

- For patients at risk (see below), it is critical to irradiate cellular blood components (RBC and platelets).
- To avoid unacceptable high hemolysis (>0.8%) and elevated potassium levels from irradiation, adherence to the Council of Europe's guidelines is advised. Red cells may be irradiated up to 28 days after collection and should be transfused as soon as possible, but no later than 14 days after irradiation, and no later than 28 days after collection.<sup>127,128</sup>

#### PATIENTS REQUIRING IRRADIATED BLOOD<sup>129</sup>

- ◆ Patients with severe T-cell congenital immunodeficiency states
  - ◆ Intrauterine transfusions (IUT)
  - ◆ Neonatal exchange transfusions for infants with prior IUT
  - ◆ Neonatal top-up transfusion if there has been a previous IUT
  - ◆ Patients with Hodgkin's lymphoma
  - ◆ Patients undergoing bone marrow or stem cell transplants
    - It is reasonable to continue providing irradiated products until immunosuppression discontinued
  - ◆ Recipients of directed transfusions from family members
  - ◆ Recipients of HLA-matched platelets
  - ◆ Patients treated with purine analogs (e.g., fludarabine), purine antagonists (e.g., bendamustine), alemtuzumab and anti-thymocyte globulin
- Notify patient in need of irradiated blood and provide a card for the patient to carry in their wallet.

#### ATTENTION

Some immunocompromised patients must receive irradiated blood. Refer to box to the left.

Special Needs Card	
Blood Bank	Date: June 11, 2011
Name: Mary Bloodworthy	Date of Birth: Oct 25, 1981 Hospital File # 1178380
ABO/Rh: O NEG	
Special Requirements:	REQUIRES IRRADIATED PRODUCTS

**POST-TRANSFUSION PURPURA (PTP)**<sup>130</sup>**ETIOLOGY**

- Transfusion of platelet antigen-positive RBCs, plasma, or platelets to a patient who lacks the same platelet antigen.
  - ◆ 75% of cases occur in an Human Platelet Antigen-1b (HPA-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**

- 1 in 100,000; post-transfusion purpura occurrence among the inpatient U.S. elderly, as recorded in large medicare databases during 2011 through 2012.<sup>131</sup>

**CLINICAL PRESENTATION**

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

**TREATMENT**

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

**PREVENTION**

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

**WARNING**

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

**A T T E N T I O N**

Family members of patients with PTP are at risk of NAIT.

**TRANSFUSION-RELATED ALLOIMMUNE THROMBOCYTOPENIA**

- Uncommon cause of thrombocytopenia.
- Due to platelet specific donor alloantibodies to patient platelet antigens.<sup>132</sup>

**TRANSFUSION-RELATED ALLOIMMUNE NEUTROPENIA**<sup>133</sup>

- Rare cause of neutropenia.

## Virus, Parasite and Prion Infections

(Bacterial contamination is described under **Fever**)

### VIRUSES

#### Risks

- Donating blood in the ‘window period’ – the interval between the time of infectivity and the appearance of detectable disease markers such as specific antibodies or viral nucleic acid sequences.
- Current ‘window period’ estimates are:<sup>134</sup>
  - ◆ 10 days for HIV
  - ◆ 8 days for HCV
  - ◆ 38 days for HBV
- Figures in chart below are risk per donor exposure: (i.e., 1 unit of RBC).<sup>135,136</sup>



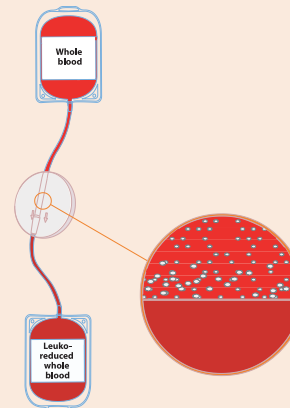
HIV Virus

West Nile Virus (WNV)	<1 in 1,000,000
Hepatitis B virus (HBV)	1 in 7,500,000
Human T-cell lymphotropic virus	1 in 7,600,000
Hepatitis C virus (HCV)	1 in 13,000,000
HIV	1 in 21,000,000

#### Cytomegalovirus (CMV):

- Leukoreduced cellular components have a very low residual risk of transfusion transmitted CMV.
- It is unknown if CMV seronegative units have any additional benefit to leukoreduction.
  - ◆ The estimated residual risk of CMV from leukoreduced red cell and platelet units is 1 in 13,575,000<sup>137</sup>

- An allogeneic stem cell transplant program recently reported on a decade of patients undergoing allogeneic transplant with leukoreduction as the sole strategy without a single patient developing transfusion transmitted CMV.<sup>138</sup>
- The current requirement for residual WBC after leukoreduction is  $<5.0 \times 10^6$  WBC/unit.
  - ◆ For fiscal year 2014/15 the mean monthly residual WBC far exceeded these requirements (data from CBS):
    - Pooled platelet –  $0.006 \times 10^6$  WBC/unit (fail rate 0.00%)
    - RBCs –  $0.063 \times 10^6$  WBC/unit (fail rate 0.15%)
- CMV serology must be drawn before allogeneic transfusions commence, otherwise false positive results may be found due to passive antibody detection.



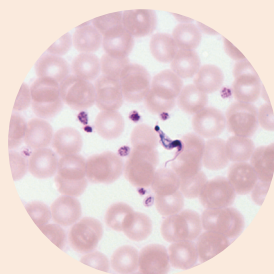
#### West Nile Virus (WNV)

- No reported cases of transfusion transmitted WNV in Canada since nucleic acid testing of donations began in 2003.<sup>139</sup>
- Facts about transfusion-transmitted WNV:
  - ◆ The virus can be transmitted through RBCs, platelets, plasma, and cryoprecipitate, but not through manufactured blood products (e.g., albumin, IVIG, clotting factor concentrates)
  - ◆ The onset of symptoms post-transfusion has ranged from 3 to 13 days (median 7 days)
  - ◆ Symptomatic recipients were primarily immunocompromised patients; however, post-partum and post-operative patients have been affected

PARASITES

Chagas Disease

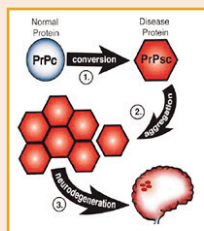
- Chagas Disease is caused by the protozoan *Trypanosoma cruzi* found predominantly in Central and South America.
- There have been 7 reported cases of transfusion transmitted Chagas in US and Canada, mostly with platelet products.<sup>140</sup>
- Since May 2010, at risk donors in Canada are tested for Chagas Disease.
- The current risk of transfusion-transmission is estimated to be 1 in 4 million, based on U.S. data.<sup>141</sup>



PRIONS

Variant Creutzfeldt-Jakob Disease (vCJD)

- 4 suspected cases of transfusion-associated transmission have been reported in the U.K.<sup>142</sup>
- 1 suspected case of transmission from U.K.-derived Factor VIII concentrate.<sup>143</sup>
- At present, high-risk blood donors (resident in the U.K. or France for more than 3 months, or Saudi Arabia for more than 6 months between 1980-1996, or in Europe for more than 5 years between 1980 and 2007) are deferred in Canada.



Public Health Agency of Canada

OTHER TRANSFUSION-TRANSMISSIBLE AGENTS<sup>140,144,145</sup>

- Other rare infectious agents confirmed to be transmitted by blood components that may cause symptomatic infection include:
  - ♦ **Viral** – Parvovirus B19, Hepatitis A and E, Dengue, Chikungunya, Tick-borne encephalitis, Colorado Tick Fever, Human Herpes virus 8, SEN virus, Simian foamy virus and Zika virus
  - ♦ **Protozoal** – Malaria, Babesiosis, Leishmaniasis, Toxoplasmosis
  - ♦ **Helminthic** – Filariasis
  - ♦ **Spirochetal** – *Treponema pallidum* (Syphilis)
  - ♦ **Rickettsial** – *R. rickettsii* (Rocky Mountain Spotted Fever), *R. burnetii* (Q fever), Ehrlichia (Ehrlichiosis)
- It is extremely important to report cases of the above infections in transfusion recipients and recent blood donors.

## 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.<sup>146</sup>

### Complications<sup>147</sup>

- 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<sup>9</sup>/L.<sup>148</sup>
- Number of RBCs transfused does not accurately predict the need for platelet and FP transfusion; frequent laboratory measurements are required to guide transfusion decisions.
- In one large randomized controlled trial, resuscitation of trauma patients with 1:1:1 was not found to be superior to resuscitation with a ratio of 2:1:1 (RBC:FP:PLT).<sup>149</sup>
  - ◆ Only patients with extremely rapid hemorrhage were enrolled in this trial and formula-driven resuscitation should not be applied to less extreme hemorrhage situations.<sup>149</sup>

#### 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.**



### Pediatric definitions

150,151

- Transfusion support to replace ongoing blood loss of >10% TBV per min
- Transfusion >100% TBV in 24 hours
- Transfusion >50% TBV in 3 hours

### ATTENTION

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

### ATTENTION

RBCs currently contain 20 mL of plasma or less. Trauma patients can safely be transfused their native blood group if they have received 20 or less units of group O uncrossmatched RBCs (approximately 400 mL of group O plasma or less).

- Mortality after massive transfusion is inversely related to core temperature (data from 1987):<sup>152</sup>
  - ◆ <34 °C – 40%
  - ◆ <33 °C – 69%
  - ◆ <32 °C – 100%
- Every 1 °C drop in temperature increases blood loss by 16% and the risk of transfusion by 22%.<sup>153</sup>
- Risk of clinically important hypothermia is significantly increased by infusion of 5 or more units of blood.<sup>152</sup>
- Consequences of hypothermia:
  - ◆ Platelet dysfunction
  - ◆ Decreased coagulation factor activity
  - ◆ Reduced clearance of citrate
  - ◆ Decreased cardiac output
  - ◆ Hypotension
  - ◆ Arrhythmias (especially if cold blood is transfused rapidly through a central line)

### ATTENTION

Every 1 °C drop in temperature increases blood loss by 16% and the risk of transfusion by 22%.<sup>153</sup>

#### 3. Hypocalcemia/Hypomagnesemia/ Citrate toxicity

- Citrate is the anticoagulant used in blood components.
- It is usually rapidly metabolized by the liver.
  - ◆ A normothermic adult not in shock can tolerate upwards of 20 units per hour without calcium supplementation
- With massive transfusion, the capacity of the liver to degrade citrate may be overwhelmed.
- Citrate binds ionic calcium and magnesium, causing functional hypocalcemia, hypomagnesemia, and also metabolic alkalosis (from bicarbonate, a metabolite of citrate).

- Clinical symptoms include: hypotension, narrow pulse pressure, elevated pulmonary artery pressure, tetany, paresthesia and arrhythmias.
- If hypocalcemia develops OR patient develops signs or symptoms of hypocalcemia then administer:
  - ◆ 1 gram (1 ampoule) of calcium chloride IV at maximum rate of 100 mg/minute

#### 4. Metabolic acidosis

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

#### 5. Hyperkalemia<sup>154</sup>

- Release of potassium from stored RBCs increases with storage time and after irradiation.
- Potassium concentration in a non-irradiated SAGM-RBC unit is approximated by the number of days of storage (110 mL of supernatant/unit).
  - ◆ For example, a 42 day old RBC has a potassium concentration of approximately 45 mmol/L<sup>155</sup>
- Order bloodwork q1h (e.g., CBC, INR, PTT, fibrinogen, calcium, arterial blood gas, potassium).

### KEY COMPONENTS OF A HOSPITAL MASSIVE HEMORRHAGE PROTOCOL

Every hospital must have a Massive Hemorrhage Protocol to ensure standardized care is delivered.<sup>156</sup>

- Prompt use of measures to prevent hypothermia, including use of a blood warmer for all IV fluids and blood components.
- Monitor core temperature and maintain above 36 °C.
- Watch for dilutional coagulopathy with q1h blood work.
  - ◆ While patient is actively bleeding, transfuse to keep:
    - Platelet count  $>50 \times 10^9/L$  (with head injury  $>100 \times 10^9/L$ )
    - INR  $<1.8$
    - Fibrinogen  $>2.0 \text{ g/L}$
  - ◆ Institute ratio-based resuscitation if the required rate of transfusion exceeds 4 units of RBC per hour
  - ◆ Administer tranexamic acid 1 gram IV bolus and then 1 gram IV over 8 hours<sup>157</sup>
- Watch for hypocalcemia, acidosis and hyperkalemia.
- Blood tubing must be changed every 2-4 units and within the number of hours specified by your hospital policy. In massive transfusion this may be impractical so an add-on filter can be used to minimize the frequency of tubing changes. Rapid infusers with large blood filters may allow for less frequent tubing changes.

## Postpartum Hemorrhage (PPH)

- The above Massive Hemorrhage Protocol also applies to the patient with a massive postpartum hemorrhage.
- All postpartum females should be closely monitored for early signs of hemorrhage
- Protocols for rapid administration of uterotonics must be in place at all hospitals with obstetrical patients.
- Use of intrauterine balloons should be a key part of the early management while a decision is being made regarding definitive therapy (i.e., hysterectomy vs. uterine artery embolization).
- RBC transfusion, when indicated clinically, should NOT be delayed while waiting for pre-transfusion testing and uncrossmatched blood should be administered.
  - ◆ uncrossmatched blood must be available within 10 minutes of the onset of a postpartum hemorrhage at all hospitals with obstetrics
- Maintain fibrinogen level above 2.0 g/L with early and aggressive use of cryoprecipitate.<sup>158</sup>



## Blood Conservation in the Perioperative Setting

Patient Blood Management Programs are the vehicle for delivery of blood conservation measures, and may be defined as integration of multi-modal, multi-disciplinary measures to reduce the risk of unnecessary transfusion and optimize patient outcomes.<sup>159,160</sup>

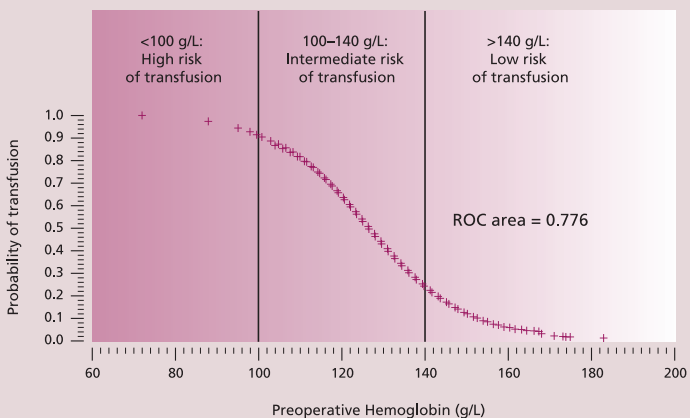
- There are currently several perioperative blood conservation strategies available to patients.
- Patients that are at high risk of perioperative transfusions (>10% chance of allogeneic RBC transfusion) must be identified as early as possible, preferably at least 28 days before surgery, and must be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

### Likelihood of Transfusion

- The risk of transfusion is increased by the following factors: lower hemoglobin, older age, lower weight, female gender, type of surgery, urgency of surgery, and renal dysfunction.
- Shown here is the probability of transfusion for patients undergoing cardiac surgery based on pre-operative hemoglobin.<sup>161</sup>

A T T E N T I O N

Through Patient Blood Management Programs, appropriate blood conservation measures must be offered to all patients with a >10% chance of blood exposure.



## Blood Conservation Strategies

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

TIME UNTIL SURGERY	BLOOD CONSERVATION STRATEGIES AVAILABLE	PAGE
<b>&gt;35 days</b>	◆ Investigate and treat anemia	–
	◆ Delay surgery until anemia corrected	–
	◆ Iron	88
<b>10-35 days</b>	◆ Delay surgery until anemia corrected	–
	◆ Erythropoietin	92
	◆ Iron	88
<b>&lt;10 days before surgery</b>	◆ Delay surgery (if possible) until anemia corrected	–
<b>Intraoperative</b>	◆ Attention to surgical hemostasis	86
	◆ Antifibrinolytics	94
	◆ DDAVP	96
	◆ Intraoperative cell salvage	90
	◆ Regional anesthesia	96
	◆ Topical hemostatic agents (e.g., fibrin sealants)	96
	◆ Adherence to strict transfusion guidelines	16

**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 clinical practices** are highly recommended:
  - ◆ Assess and treat nutritional status preoperatively
  - ◆ Maintain normothermia intraoperatively
  - ◆ Careful ligation of blood vessels
  - ◆ Avoid tissue trauma
  - ◆ Optimal use of electrocautery
  - ◆ Meticulous attention to surgical hemostasis
  - ◆ Utilize avascular tissue planes
  - ◆ Appropriate use of topical hemostatic agents

**Consider stopping anti-platelet and anticoagulants before major surgery**

- **Acetylsalicylic acid (Aspirin®), clopidogrel (Plavix®) and prasugrel (Effient®):**<sup>162,163</sup>
  - ◆ In most clinical situations, withholding ASA before non-cardiac surgery is not associated with an increase in adverse cardiac events<sup>164</sup>
  - ◆ Primary prevention: 48 hours minimum, 7 days preferable
  - ◆ Secondary prevention (after remote MI, stroke, peripheral artery disease)
    - low risk of bleeding procedure (e.g., cataract surgery, plastic surgery): no need to stop antiplatelet agents
    - high risk of bleeding procedure (e.g., neurosurgical procedure): 48 hours minimum, 7 days preferable
  - ◆ Secondary prevention (high risk for arterial thrombosis – recent percutaneous coronary intervention, MI, stroke OR coronary stent <12 months)
    - consult patient’s cardiologist or neurologist for expert advice
    - only stop antiplatelet agents if risk of bleeding exceeds risk of cardiovascular complications

**A T T E N T I O N**

Do not stop antiplatelet agents without consultation with the patient’s cardiologist or neurologist, if:

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



- **Dabigatran (Pradaxa®):**

- ◆ Consider stopping therapy 2-4 days before major surgery in patients with normal renal function
- ◆ In patients with renal dysfunction (creatinine clearance <50 mL/min) consider stopping 4-5 days before major surgery

- **Rivaroxaban (Xarelto®) and Apixiban (Eliquis®):**

- ◆ Consider stopping therapy 2-3 days before major surgery in patients with normal renal function
- ◆ In patients with renal dysfunction (creatinine clearance <50 mL/min) consider stopping 3-4 days before major surgery

- **NSAIDs:**

- ◆ Consider stopping therapy 4-7 days before major surgery
- ◆ Celecoxib does not inhibit platelet aggregation at usual doses

**Minimize blood sampling and loss**<sup>165</sup>

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

**Preoperative patients on Warfarin:**<sup>166</sup>

- If low risk of thromboembolic events (e.g., primary prophylaxis of atrial fibrillation):
  - ◆ Stop warfarin 4-5 days preoperatively; repeat INR 1 day preoperatively
  - ◆ If INR >1.5 then give 2 mg oral vitamin K
  - ◆ Then repeat INR preoperatively
- If high risk of thromboembolic events (e.g., recent deep vein thrombosis):
  - ◆ Consider switch to unfractionated or low molecular weight heparin 4 days preoperatively; consult with hematology on timing and preferred regimen or consult recommendations at <http://thrombosiscanada.ca/>

**Emergency reversal of anticoagulants**

- See page 126.

**IRON**

- All patients undergoing procedures with significant blood loss should be evaluated for iron deficiency and where present corrected preoperatively.<sup>160</sup>
- There are several randomized trials of iron therapy administered perioperatively, finding that:
  - ◆ **Preoperative iron** may be helpful for patients with low preoperative hemoglobin levels, but not confirmed beneficial in all studies<sup>167,168,169,170</sup>
  - ◆ **Randomized trials failed to confirm a benefit of post-operative iron therapy in patients that were not anemic preoperatively**<sup>171,172,173,174,175,176</sup>

**A T T E N T I O N**  
 Routine post-operative iron therapy in preoperatively non-anemic patients is NOT useful.

**Dosage**

- 60 mg of elemental iron/day is sufficient for the majority of patients. (Higher doses do not appear to improve the response, higher doses decreases compliance, and higher doses causes decreased absorption by increasing the hormone hepcidin.)<sup>177</sup>

**A T T E N T I O N**  
 Ensure anemic patient is prescribed 60 mg of elemental iron (e.g., ferrous sulphate 300 mg once daily).

COMMONLY USED IRON REPLACEMENT THERAPIES	DOSE MG	ELEMENTAL MG
Ferrous gluconate	300	35
Ferrous sulfate	300	60
Ferrous fumarate (Palafer®)	300	100
Polysaccharide-iron complex (FeraMax®)	150	150
Polysaccharide-iron complex (Triferex®)	150	150
Proferrin	398	11



**Pediatric Dose 6 mg elemental iron/kg body weight**

PREPARATION (ORAL LIQUID)	CONCENTRATION	ELEMENTAL IRON
Ferrous fumarate (Palafer®)	60 mg/mL	20 mg/mL
Ferrous sulphate (Fer-in-sol)	75 mg/mL	15 mg/mL

**Common Adverse Events\***

- **GI upset** (diarrhea, nausea, constipation) was twice as frequent with oral iron as with placebo.<sup>178</sup>
- **Dark stools.**
- Patient compliance with oral treatment is about 50%.<sup>179</sup>

\* See product monograph for details

**INTRAVENOUS IRON**

- There is currently insufficient evidence to support the routine use of intravenous iron in **elective surgery patients**.<sup>180</sup>
- 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.<sup>181</sup> IV iron tends to restore iron stores and hemoglobin levels more rapidly than oral iron.<sup>179,182,183</sup>

**Dosage**

- ◆ Check your hospital's formulary to determine the recommended type of parenteral iron

**Adverse reaction**

- ◆ 24/100,000 risk of anaphylactic reaction to iron dextran<sup>184</sup>
- ◆ 16/100,000 risk of anaphylactic reaction to iron sucrose Venofer®<sup>184</sup>
- ◆ **Give sufficient iron to correct the anemia (e.g., 300–1,000 mg of elemental iron, Venofer® 300 mg in 250 mL of normal saline over 2 hours for 1-3 infusions.)**



**Pediatric**

FeraMAX (15 mg elemental iron per ¼ teaspoon)<sup>185</sup>

- May be dissolved in water or mixed into soft foods or powdered cereals:
  - ◆ Age based dosing:
    - Less than 2 months: ¼ teaspoon daily
    - More than 2 months to 13 yrs: ¼ to ½ teaspoon daily
    - More than 13 yrs to 18 yrs: ¼ to ¾ teaspoon daily

## INTRAOPERATIVE CELL SALVAGE

## Principles

- A patient's own blood shed at the time of an operation is collected and processed in such a way that it can be re-infused into the patient (auto-transfusion).
- Up to 80% of red cells can be recovered.<sup>186</sup>

## Indication

- Meta-analysis of 75 studies:<sup>187</sup>
  - ◆ Cell salvage in orthopedic surgery (all types of salvage devices, washed and unwashed)
    - Relative risk of transfusion 0.46 (95% CI 0.37-0.57)
  - ◆ Cell salvage in cardiac surgery (unwashed only)
    - Relative risk of transfusion 0.77 (95% CI 0.69-0.86)
  - ◆ No increase in adverse events in the treatment group
- Meta-analysis of 31 randomized controlled trials, including 2282 patients, in the setting of cardiac surgery found that cell salvage decreased the risk of allogeneic blood exposure (OR 0.63, 95% CI 0.43-0.94, P=0.02).<sup>188</sup>
- Consider in the setting of: trauma, hepatic resection, major orthopedic and spine surgery, or ruptured aneurysm with appropriate quality assurance.
- May be an acceptable alternative for some Jehovah's Witnesses (see Appendix B, page 145).

## 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
  - ◆ Hemolysis – ensure correct wash fluids are used
  - ◆ A formal maintenance program is required for equipment

## Contraindications

- Malignant cells in operative field (risk may be mitigated by leukoreduction filter).
- Bacterially-contaminated operative fluid, ascitic fluid, or amniotic fluid in operative field.
- Use of hypotonic solutions in the operative field.
- Use of topical thrombogenic agents in the operative field.

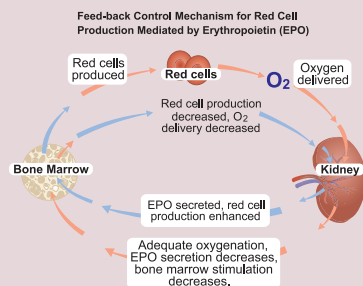
## A T T E N T I O N

Air embolism is a risk of intraoperative cell salvage.

**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.<sup>189</sup>
  - ◆ Expected rise in hemoglobin is 10-20 g/L



**Eligibility and Dosage**

- Patients with a hemoglobin <130 g/L and a probability of requiring a blood transfusion of 10% or greater.<sup>189,190,191</sup>
- Preferred dose: 600 U/kg sc qwk for up to 4 doses commencing 28 days before surgery.<sup>192,193,194</sup>
  - ◆ 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.<sup>195</sup>
  - ◆ e.g., 20,000 U sc qd x 15 days, start day 10 pre-op
- Supplemental iron advised.<sup>196</sup>

**Contraindications (in elective surgery patients)**

- Uncontrolled hypertension.
  - Hypersensitivity to mammalian-derived cell products, albumin, or other components of the product.
  - Contraindicated in patients scheduled for elective surgery with severe arteriosclerotic disease.
- For more details, refer to product monograph.

**Adverse Effects**

- Safety of short-term use before surgery has not been thoroughly studied.
  - A recent study found an increased risk of thrombosis in patients undergoing elective spine surgery.<sup>197</sup>
- For more details, refer to product monograph.

## ANTIFIBRINOLYTICS

**General Principles**<sup>198,199</sup>

- Inhibitors of plasminogen activation are administered to prevent/treat increased fibrinolysis during surgery, particularly cardiac surgery.

**Indications****1. Antifibrinolytics in Cardiac Surgery**<sup>198,200</sup>

- Prophylactic administration is preferred rather than at time of marked hemorrhage.
- Tranexamic acid reduces bleeding and transfusion rates.

**2. Tranexamic Acid in Non-Cardiac Surgery**<sup>157,201,202,203</sup>

- Used in orthopedic surgery, trauma, and hepatic surgery.
- Evidence suggests a high degree of safety:
  - ◆ A major meta-analysis included 252 RCTs including over 25,000 participants
  - ◆ In the **tranexamic acid trials**, there was a significant reduction in allogeneic transfusion (RR 0.61, 95% CI 0.53-0.70)

- The CRASH-2 study, which included over 20,000 patients (most from developing countries), provides strong evidence of benefit for tranexamic acid in patients with traumatic hemorrhage (dose used: 1 g loading over 10 minutes, then infusion of 1 g over 8 hours).<sup>157</sup>
- The use of topical tranexamic acid in knee and hip joint replacement is equally effective as intravenous use.<sup>204</sup>

**Adverse Effects**

- Tranexamic acid: GI upset, seizures.
  - ◆ Data from meta-analyses do not suggest an increased risk of thrombosis<sup>199</sup>

**Contraindications**<sup>205</sup>

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

Refer to product monograph for more details.

**A T T E N T I O N**

Tranexamic acid saves 1 in 68 traumatically injured patients from death if administered within 3 hours of injury!

**DDAVP**

- There is no convincing evidence that DDAVP minimizes perioperative allogeneic RBC transfusion in patients who do not have congenital bleeding disorders and its routine use is not recommended.<sup>206,207,208</sup>
- DDAVP is of no benefit in the management of bleeding post cardiac surgery.<sup>209</sup>

**A T T E N T I O N**

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

**REGIONAL ANESTHESIA**

- One systematic review of literature found that the use of **neuroaxial blockage with epidural or spinal anesthesia** reduced the risk of:<sup>210</sup>
  - ◆ transfusion
    - risk of transfusion was reduced by 50%
  - ◆ venous thromboembolism
  - ◆ pneumonia and respiratory depression

**TOPICAL AGENTS**<sup>200,211</sup>

- Fibrin sealants:
  - ◆ Mixture of fibrinogen, thrombin, calcium chloride and anti-fibrinolytic agent
  - ◆ Meta-analysis of 18 trials indicates effectiveness in reducing peri-operative allogeneic blood transfusion (RR 0.63 95% CI 0.45-0.88)<sup>212</sup>
- Topical thrombin:
  - ◆ Bovine thrombin products are not recommended for clinical use<sup>200</sup>
  - ◆ Recombinant human thrombin available (e.g., Recothrom®)<sup>213</sup>
  - ◆ No data on effectiveness in reducing peri-operative allogeneic blood transfusion

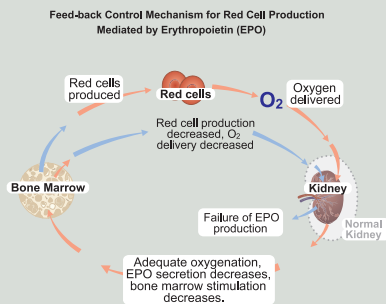
**OTHER BLOOD CONSERVATION STRATEGIES UNDER CLINICAL INVESTIGATION**

The following blood conservation strategies are obsolete, under investigation or highly limited in application:

- Pre-operative autologous blood donation.
- Hemoglobin-based oxygen carriers.<sup>214</sup>
- Recombinant factor VIIa.<sup>215</sup>
- Hypervolemic hemodilution.
- Acute normovolemic hemodilution.

**General Principles**<sup>216,217</sup>

- Erythropoietin (EPO) is synthesized by DNA technology:
  - ◆ Currently available formulations in Canada do not contain albumin
- Requires readily available iron for full efficacy.
- Takes time to increase hemoglobin (weeks).
- EPO response to anemia may be blunted in the presence of malignancy, chemotherapy and chronic inflammatory diseases.

**Indications**

- Chronic renal failure.
- Anemia associated with malignancy.

**Contraindications**<sup>218</sup>

- 1) Uncontrolled hypertension.
- 2) Known sensitivity to mammalian cell derived products.
- 3) Hypersensitivity to the active substance or to any of the excipients.
- 4) Patients scheduled for elective surgery, who are not participating in an autologous blood pre-deposit program and who have severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.
- 5) Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis or treatment.
- 6) Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive EPREX or any other erythropoietin (see PRCA paragraph in Precautions in monograph).

Refer to product monograph for more details.

**CHRONIC RENAL FAILURE (CRF)**<sup>219,220</sup>**Rationale**

- Patients with end-stage renal disease are unable to produce erythropoietin; it is administered as a replacement therapy.
- Erythropoietin decreases the likelihood of transfusion (RR 0.32, 95% CI 0.12-0.83).<sup>221</sup>

**Eligibility**

- Patients with clinically and biochemically established CRF with a hemoglobin <90-110 g/L should be considered.<sup>222,223</sup>
- Usually erythropoietin is considered when the creatinine clearance is <60 mL/min/1.73 m<sup>2</sup>.<sup>224</sup>
- Other causes of anemia must be excluded or successfully treated:
  - ◆ Initial laboratory work up should include a CBC, reticulocyte count, serum ferritin, and transferrin saturation

**Target therapeutic outcome**

- To maintain the hemoglobin in the range of 100 to 120 g/L.<sup>218,225,226</sup>

**Iron**<sup>227</sup>

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

Refer to intravenous iron product monographs for more details.

**Dosage****Correction Phase:**

- ◆ Initial dose of Epoetin Alfa (EPREX) -50 IU/kg of body weight three times a week intravenously or subcutaneously or darbopoietin (Aranesp™) 0.45 ug/kg sc per week

- ◆ If the hemoglobin does not increase by 10 g/L after one month of treatment, the dosage may be raised to 75 IU/kg three times per week (EPREX) or by 25% (Aranesp™)
- ◆ If further increments are needed they should be at 25 IU/kg, three times per week, at monthly intervals, to achieve a hemoglobin NOT to exceed 120 g/L
- ◆ The maximum dosage should not exceed 200 IU/kg three times per week
- **Maintenance Phase:**
  - ◆ The intravenous/subcutaneous dose adjusted individually to maintain a hemoglobin not to exceed 120 g/L
  - ◆ The maintenance dose should be individualized for each patient with chronic renal failure
  - ◆ The recommended weekly dose is between 75 and 300 IU/kg
  - ◆ In patients who are converting from the subcutaneous to intravenous route, the same dose should be used
  - ◆ Follow hemoglobin closely (e.g., weekly) so that appropriate changes in the dose can be made to keep the hemoglobin in the target range
- **Dose Adjustment:**
  - ◆ If the hemoglobin is increasing and approaching 120 g/L, the dose should be reduced by approximately 25%
  - ◆ If the hemoglobin continues to increase, withhold treatment until the hemoglobin begins to decrease, then resume therapy at a dose approximately 25% below the previous dose
  - ◆ If the hemoglobin increases by more than 10 g/L in any two week period, decrease the dose by by approximately 25%
  - ◆ Dose reduction may be achieved either by reducing the amount per dose or the number of doses per week, or both
- Where inadequate responses occur, re-examine for other causes of anemia.

## ANEMIA ASSOCIATED WITH MALIGNANCY

*Eligibility*<sup>228,229</sup>

- **Patients with chemotherapy-induced anemia; AND**
- **Hemoglobin <100 g/L and/or requiring red cell transfusions.**
  - ◆ Other contributing causes of anemia must be excluded or successfully treated
  - ◆ Carefully weigh the risks of thromboembolism in patients prescribed erythropoietin
    - The relative risk of thromboembolic complications is increased (RR 1.52, 95% CI 1.34-1.74).<sup>230</sup>
  - ◆ Erythropoietin should not be used in treatment of anemia associated with malignancy in patients not receiving chemotherapy
    - A meta-analysis of 91 studies including 20,102 patients suggested erythropoietin therapy increases the risk of death compared to placebo (Hazards Ratio 1.05, 95% CI 1.00-1.11)<sup>230</sup>
    - Red blood cell transfusion should be considered the preferred strategy in patients undergoing potentially curative treatment

*Target outcome*

- To maintain the lowest hemoglobin level sufficient to avoid RBC transfusions.
- Erythropoietin increases the hemoglobin level and decreases the likelihood of transfusion (RR 0.65, 95% CI 0.62-0.68).<sup>230</sup>

*Dosage*

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

**A 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).<sup>231</sup>
- 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 2014-2015, 8 million grams of albumin were used in Canada, at a cost of about \$15 million dollars.

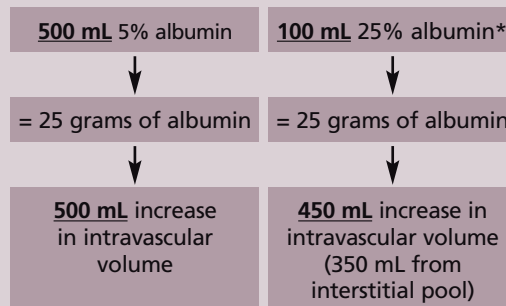
**A T T E N T I O N**  
 Albumin is a blood product.  
 Consent required.

**B 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:

**A T T E N T I O N**  
 Administering 25% albumin instead of 5% in error could result in circulatory overload!



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

**Administration**<sup>232,233</sup>

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

**Adverse reactions / Risks**

- Anaphylaxis – rare.
- Circulatory overload.
- Hypotension – rare case reports of transient hypotension in patients on angiotensin-converting enzyme inhibitors.<sup>234</sup>
- There are no reports of HIV, HCV, or other viruses transmitted through albumin.

Indications

ALBUMIN MAY BENEFIT THE FOLLOWING GROUPS OF PATIENTS:

1. Paracentesis

- Albumin has been shown to reduce morbidity and mortality in the management of tense ascites by paracentesis.<sup>235</sup>
- For paracentesis of <5 litres – albumin is unnecessary.<sup>236</sup>
- For large volume paracentesis, albumin should be considered as the replacement fluid of choice.

VOLUME OF ASCITES	# VIALS OF 100 mL 25% ALBUMIN*
<5 L	0
5-8 L	2
8-12 L	3
12-15 L	4-5

\* 8 grams albumin per L of fluid removed for paracentesis >5 L.<sup>237</sup>

- There is preliminary evidence that midodrine<sup>238</sup> and terlipressin<sup>239</sup> may be alternative therapies to intravenous albumin in this setting, but have not been shown to be superior to albumin.<sup>240</sup>
- **Malignant ascites** – there is no evidence to support the use of albumin in patients with malignant ascites post-paracentesis.<sup>241</sup>

ATTENTION

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

2. Spontaneous bacterial peritonitis

- One RCT (n=126) found that patients resuscitated with antibiotics alone compared to antibiotics plus albumin had a higher mortality (OR 4.5, 95% CI 1.0 to 20.9).<sup>242</sup>
  - ◆ 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<sup>243,244,245</sup> or midodrine/octreotide<sup>246</sup> may be effective in salvaging some patients with type 1 hepatorenal syndrome who are candidates for liver transplantation. There is evidence that the combination of terlipressin and albumin has a greater beneficial effect on renal failure than the combination of either midodrine or octreotide with albumin.<sup>247</sup>
  - ◆ This therapy has not been shown to change mortality rates in hepato-renal syndrome
  - ◆ Albumin alone, without terlipressin or other agent is ineffective

DOSAGE

- 100-200 mL of 25% albumin daily with above agents, up to a maximum of 14 days.<sup>244,245,246</sup>

4. Plasma exchange

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

ATTENTION

Use of Intravenous albumin alone is ineffective for hepatorenal syndrome.

THE CURRENT MEDICAL LITERATURE CANNOT CONFIRM ANY BENEFIT OF INTRAVENOUS ALBUMIN IN THE FOLLOWING SUBGROUPS OF PATIENTS:<sup>248</sup>

**1. Resuscitation**

- Current evidence: **albumin is not superior to crystalloid for resuscitation in intensive care.**
- A large randomized controlled trial<sup>249</sup> showed no overall advantage of albumin over crystalloid for resuscitation in intensive care patients.
- A large randomized trial in critically ill patients with hypovolemic shock (half with septic shock) found no difference in 28 day mortality when albumin was compared to crystalloid.<sup>250</sup>

**2. Hypoalbuminemia**

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

	ODDS RATIO (OR)*	OR RANGE	% INCREASE IN MORTALITY
Cochrane Injuries Group <sup>248</sup>	1.69	1.07-2.67	69% (7 to 167%)
Wilkes et al <sup>251</sup>	1.59	0.91-2.78	59% (-9 to 178%)

**3. Severe burns**

- 4 small randomized controlled trials with important methodological limitations in patients with thermal injuries failed to show that 5% albumin was superior to crystalloids.<sup>248,252</sup>
- There is currently a wide variation in fluid resuscitation practice in burn patients.<sup>253</sup>

- Current expert opinion recommends resuscitation with lactated Ringer’s solution according to the Parkland formula, with addition of colloids if the fluid volume exceeds 4 mL/kg/% burn (known as ‘fluid creep’) and urine output is less than 0.5 mL/kg/hour, with hemostatic instability after the first 8-24 hours.<sup>254,255</sup>

**PARKLAND FORMULA**

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

**A T T E N T I O N**

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

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

**4. Hypotension during dialysis**

- There are currently no data to support the use of albumin in the treatment of hypotension during dialysis.
  - ♦ Small comparison trials of normal saline, albumin (20%), and starch did not suggest a superiority of albumin over the other agents<sup>256</sup>
  - ♦ A small RCT concluded that 5% albumin was no more effective than normal saline for the treatment of hypotension during dialysis<sup>257</sup>

**5. Cardiac surgery<sup>258</sup>**

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

**6. Acute Lung Injury**

- Two small, industry funded randomized control trials (n=40<sup>259</sup>, n=37<sup>260</sup>) in hemodynamically stable patients found the combination of furosemide and intravenous albumin to result in weight loss of 10 kg over 5 days, without improvement in the rate of extubation success or mortality.

**A Basics**

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



**Products Available** <sup>261</sup>

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

Refer to product's package insert for further details.

**ATTENTION**

IVIG is a blood product.  
Consent required.

**IVIG PRODUCTS LICENSED IN CANADA\***

PRODUCT	IGIVNEX	GAMUNEX	PRIVIGEN	GAMMAGARD LIQUID	GAMMAGARD S/D	HIZENTRA	OCTAGAM
Manufacturer	Grifols	Grifols	CSL Behring	Baxalta	Baxalta	CSL Behring	Octapharma
Plasma Source	Canada	United States	United States	United States	United States	United States	United States
IgG (g/L)	98 ± 20	100 ± 10	100	100	>90	200	100
IgA (mg/L)	46 mcg/mL (average)	46 mcg/mL (average)	2.5-12 mcg/mL (5.6 mcg/mL average) <sup>262</sup>	≤140 mcg/mL	≤2.2 mcg/mL (in 5% solution)	≤50 mcg/mL	<400 mcg/mL
Sugar content	Not specified	Not specified	Contains no carbohydrate stabilizers	Not specified	20 mg/mL (2%) glucose (in 5% solution) no sucrose	Contains no carbohydrate stabilizers	Maltose 90 mg/mL
Osmolality (mOsmol/kg)	258	258	320	240-300	Not indicated in product monograph	380	310-380
Form	Liquid	Liquid	Liquid	Liquid	Lyophilized	Liquid	Liquid
Route of administration	IV	IV/SC	IV	IV	IV	SC	IV

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

**Cost**

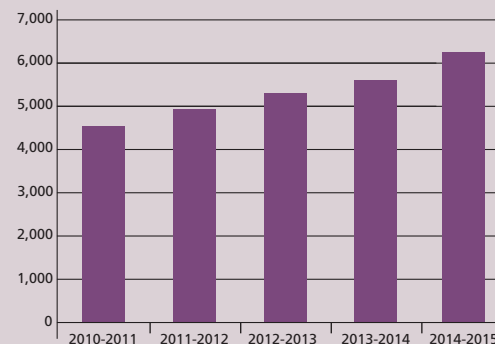
- IVIG costs \$54 per gram, depending on US\$ exchange rate.
- ◆ A single course of treatment for a 70 kg patient with the commonly prescribed dose of 1 g/kg each day for 2 days, costs \$7,500

**IN 2015-2016**  
Canada (minus Quebec) used 4,780 kg of IVIG at a cost of \$235 million dollars.<sup>263</sup>

**Availability & Consumption**

- Approximately 20% of the IVIG used in Canada is derived from Canadian plasma.<sup>263</sup>
- The rest is derived from paid U.S. donors.
- Canada has the highest *per capita* consumption of IVIG in the world.<sup>264</sup>

**IVIG USED IN CANADA, 2010-2011 TO 2014-2015  
IN THOUSANDS OF KILOGRAMS**



**IN ONTARIO**  
In Ontario, requests for IVIG for infusion are required to be made on a MOHLTC – mandated request form. The IVIG request form can be found at [www.transfusionontario.org](http://www.transfusionontario.org).

**Manufacturing**

- IVIG is manufactured from pooled plasma obtained from several thousand donors per pool.
- The constituent plasma units are tested for human immunodeficiency virus (1 and 2), hepatitis B, hepatitis C, human T-cell lymphotropic virus (I and II), and parvovirus B19.
- The process includes rigorous viral inactivation steps (e.g., caprylate, low pH, chromatography, solvent detergent treatment).
- There is no evidence of transmission of prion disease (e.g., variant CJD) through IVIG.
- Steps in manufacturing are believed to reduce the risk of transmission of prion disease.<sup>265</sup>

**B Administration & Infusion Recommendations**

**Administration**

- For detailed recommendations for infusion of IVIG, refer to “Intravenous Immune Globulin Toolkit for Ontario”.<sup>266</sup>
- Administered as 5% or 10% solution usually dispensed by the Transfusion Medicine Laboratory or Pharmacy.
- Safe for use in pregnancy.  
Refer to package insert for further details.

**General Principles**

- Refer to Institution specific policies
- Use Adjusted Body Weight Dosing Calculator<sup>267</sup>, check every 6 months or if significant weight change.
- Round dose to nearest vial size.

**DOSE CALCULATOR**

<http://ivig.transfusionontario.org/dose/>

**Pre-infusion**

- Verify documentation of order, clinical indication and consent.
- Identify patients at risk for complications, especially TACO (see page 60) and thromboembolic events.
- Check vital signs.

**Infusion**

- Slow initial rate for first 30 minutes.
- Check vital signs.
- Increase rate and monitor vital signs as per institutional policy.
- Monitor for signs of adverse reactions and report according to institutional policy.

**Post-infusion**

- Complete documentation including dose, brand and lot number.
- Report and return to the TML or Pharmacy any unused or defective vials, and any vials associated with an adverse event.

**IVIG INFUSION RATES\***

PRODUCT	INITIAL RATE	MAXIMUM RATE	COMMENT
IGIVnex	0.6-1.2 mL/kg/hour (0.01-0.02 mL/kg/min) for 30 minutes	Increase gradually to a maximum rate of 8.4 mL/kg/hour if initial dose is tolerated	Time to infuse 70 g is approximately 1¾ hours
GAMUNEX™	0.6-1.2 mL/kg/hour (0.01-0.02 mL/kg/min) for 30 minutes	Increase gradually to a maximum rate of 8.4 mL/kg/hour if initial dose is tolerated	Time to infuse 70 g is approximately 1¾ hours
GAMMAGARD® SD™	A 5% solution should be used for initial infusion at 0.5 mL/kg/hour. If well tolerated, use 10% solution subsequently at the same rate. Use filter supplied with product	Increase gradually to a maximum rate of 8.0 mL/kg/hour if initial dose is tolerated	Use of ante-cubital vein is recommended, especially for 10% solution
GAMMAGARD® Liquid	0.5 mL/kg/hour (0.01 mL/Kg/min) for 30 minutes	Increase gradually to a maximum rate of 8.0 mL/kg/hour if initial dose is tolerated	
Privigen	0.3 mL/kg/hour (0.005 mL/kg/min)	Increase gradually to maximum rate of 7.2 mL/kg/hour (4-8 mg/kg/min)	Product monograph recommends slower rate to be used for patients receiving >1 g/kg (4 mg/kg/min)
OCTAGAM	Initial 0.6 mL/kg/hr for 30 minutes	Escalate to a maximum of 4.2 mL/kg/hr if initial dose tolerated	

\* Refer to package insert for further information.

**B Administration & Infusion Recommendations (cont'd)**

**Adverse reactions**

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

**ADVERSE REACTIONS TO IVIG** <sup>266,268,269,270,271</sup>

REACTION	SEVERITY	FREQUENCY**	COMMENT/TREATMENT
Anxiety, chills/fever, rash, flushing, headache, chest, back or abdominal pain, nausea/vomiting, tachycardia, hypo- or hypertension	Mild-moderate	Common	Slow or pause IVIG treatment. Symptomatic treatment. Recurrent reactions – pre-medicate and/or change to another manufacturer’s IVIG product
Aseptic meningitis	Moderate	7 in 10,000 <sup>272</sup>	Stop infusion. Administer analgesics. Usually resolves spontaneously in 24-48 hours
Anaphylaxis	Severe	Rare	Stop infusion. <b>May require epinephrine promptly.</b> Consider testing for IgA and anti-IgA (see page 63)
Acute renal failure	Severe	Rare (120 cases reported to FDA in 13 years)	Usually with sucrose-containing product (none currently licensed in Canada). Predisposing factors: age >65, diabetes mellitus, pre-existing renal insufficiency
Hemolysis	Mild-Severe	10% <sup>273,274</sup>	More common in non-group O patients
Thrombo-embolic events	Severe	0.5-1% <sup>275</sup>	Causative relationship not clearly established. Possibly related to increases in viscosity
Infectious disease transmission	Severe	No reported case since HCV in 1995, <sup>276</sup> No known case of transmission of HIV or HBV	Modern viral reduction measures are robust. Prion (vCJD) transmission remains an entirely theoretical risk

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

**C 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 (see the “Choose Wisely” statement)
  - ◆ Clinical evidence consistent with defective humoral immunity (e.g., recurrent infection)
  - ◆ The full text describing a scoring system to aid clinical decision making regarding immunoglobulin therapy is available at [ncbi.nlm.nih.gov/pubmed/23518142](http://ncbi.nlm.nih.gov/pubmed/23518142)<sup>277</sup>
  - ◆ Treatable conditions to which antibody deficiency may be secondary must be excluded
- Subcutaneous immunoglobulin also available for home-based immunoglobulin replacement therapy. Consult a transfusion medicine specialist or immunologist for additional information.

**CHOOSE WISELY**

Immunoglobulin (gammaglobulin) replacement does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccine immunizations or natural infections. Isolated decreases in immunoglobulins (isotypes or subclasses), alone, do not indicate a need for immunoglobulin replacement therapy. Exceptions include genetically defined/suspected disorders. Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy. Selective IgA deficiency is not an indication for administration of immunoglobulin.

**IVIG IN IMMUNOGLOBULIN DEFICIENCY** <sup>278,279</sup>

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Primary Immune Deficiency <sup>280</sup>	IVIG is recommended in hypogammaglobulinemia (total IgG or IgG subclasses reduced) with recurrent bacterial infections	<b>Adult:</b> 0.4-0.6 g/kg/ every 4 weeks
Secondary Immune Deficiency (SID)		<b>Pediatric:</b> 0.3-0.6 g/kg/ every 4 weeks  Monitor IgG trough level to maintain low range
Hematopoietic Stem Cell Transplant in primary immunodeficiencies <sup>281</sup>	IVIG is recommended in PID patients undergoing stem cell transplant	0.4-0.6 g/kg/every 4 weeks; requirements may increase and should be based on clinical outcome

IVIG IN SOLID ORGAN TRANSPLANTATION<sup>281</sup>


DIAGNOSIS	EFFICACY/COMMENT	DOSE
Kidney transplant from living donor to whom the patient is sensitized <sup>281</sup>	IVIG is recommended to decrease donor-specific sensitization	2 g/kg/month for 4 months
Pre-Transplant (heart) <sup>281</sup>	For desensitization in selected heart transplant recipients who are highly sensitized, medically urgent and unlikely to receive a transplant otherwise – this should be preceded by discussion at the transplant program level	Suggested dose is up to 1 g/kg/month until transplant
Peri-Transplant (heart, lung, kidney, pancreas) <sup>282,283,284,285</sup>	Solid-organ transplant recipient with donor-specific antibodies identified at time of transplant surgery (heart, lung, kidney, pancreas) on virtual crossmatch – first-line agent	Suggested dose 1 g/kg, can give as divided doses if in association with a course of plasmapheresis
Post-Transplant <sup>281,282,283,284,285</sup>	Acute antibody-mediated rejection in a solid-organ transplant recipient – first-line agent	1 g/kg/dose, can give as divided doses if in association with a course of plasmapheresis
	Chronic antibody-mediated rejection in a solid-organ transplant recipient	1 g/kg/month

Hematology

IVIG IN HEMATOLOGICAL DISORDERS AND BONE MARROW/STEM CELL TRANSPLANTATION<sup>278,280,286,287</sup>

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Immune Thrombocytopenic (ITP) refractory to standard treatment, platelet count <20 x 10 <sup>9</sup> /L	Benefit established	1 g/kg for 1 day. Repeat if platelet count not >30 x 10 <sup>9</sup> /L
ITP with persistent or life-threatening bleeding and platelet count <50 x 10 <sup>9</sup> /L	Benefit established	1 g/kg for 1-2 days
Thrombocytopenia associated with HIV unresponsive to antiviral therapy, platelet count <20 x 10 <sup>9</sup> /L or <50 x 10 <sup>9</sup> /L with bleeding	Benefit established	1 g/kg for 2 days
ITP in pregnancy <ul style="list-style-type: none"> <li>◆ platelet count &lt;10 x 10<sup>9</sup>/L</li> <li>◆ platelet count 10-30 x 10<sup>9</sup>/L in 2<sup>nd</sup> or 3<sup>rd</sup> trimester</li> <li>◆ platelet count &lt;30 x 10<sup>9</sup>/L and bleeding at any stage in pregnancy</li> </ul>	Appropriate initial treatment	1 g/kg; longest inter-treatment interval consistent with maintaining adequate platelet count
Post-transfusion purpura	Recommended as first-line treatment	1-2 g/kg over 2-5 days
Fetal/neonatal allo-immune thrombocytopenia (F/NAIT) (treatment of mother or fetus)	Considered standard first-line antenatal treatment. Considered adjunctive therapy for newborn with F/NAIT. Appropriate consultation advisable with high-risk pregnancy and neonatal unit	<p><b>Maternal:</b> 1 g/kg weekly</p> <p><b>Infant:</b> Give IVIG if platelet transfusion not immediately available <b>or</b> there is no response to platelet transfusion <b>or</b> prolonged thrombocytopenia (&gt;7 days). Dose 1.0 g/kg and reassess</p>

Pediatrics

-  ■ Transfuse platelets to maintain platelets over 30 x 10<sup>9</sup>/L.
- Transfuse platelets in the setting of life-threatening hemorrhage (intracranial or GI bleeding) to maintain platelets over 100 x 10<sup>9</sup>/L.

Hematology

IVIg in Hematological Disorders and Bone Marrow/ Stem Cell Transplantation<sup>280</sup> (cont'd)

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Pure red cell aplasia (PRCA) (viral or immunologic) <sup>279,286</sup>	Considered first line therapy for PRCA associated with parvovirus B19 occurring in an immunocompromised patient. Reasonable option for immunologic PRCA in patients who have failed other therapies	Up to 2 g/kg divided over 2-5 consecutive days
Hemolytic transfusion reaction (HTR) <sup>286</sup>	IVIg may be considered as an option among supportive therapies for urgent situations in this disorder	Up to 2 g/kg divided over 2-5 days, short term up to 3 months
Hemolytic disease of the fetus and newborn (HDFN) <sup>278,286</sup>	Not recommended for use in management of HDFN without established hyperbilirubinemia. Recommended if total serum bilirubin is rising despite intensive phototherapy or if level is within 34-51 umol/L of the exchange level <sup>288</sup>	0.5 g/kg  (Unlikely to be of benefit with ABO-hemolytic disease of the newborn as IVIg contains anti-A and anti-B)
Virus associated hemophagocytic syndrome (VAHS) <sup>286</sup>	Not recommended for routine use. Option in severe life threatening VAHS	Determine in consultation

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Rare cases of auto-immune hemolytic anemia or neutropenia, auto-antibodies to factor VIII or von Willebrand factor <sup>278,279,286</sup>	Anecdotal evidence only; consider use only after failure of other treatments or in urgent situations	1 g/kg for 2 days. Determine in consultation
Allogeneic bone marrow/ stem cell transplant <sup>278,289</sup>	IVIg is not recommended for routine use after HSCT. IVIg may be considered in exceptional cases:  1) Active CMV-induced pneumonitis following transplantation  2) High-risk allogeneic stem cell transplantation (e.g., if hypogammaglobulinemia) for prevention of GVHD	Not indicated. Determine in consultation  1) No recommended dose or duration listed; use in conjunction with appropriate antiviral medication  2) 0.4 g/kg weekly, starting one day before transplantation and continuing to day 100 post-transplant

Neurology

IVIG IN NEUROLOGICAL DISORDERS\*278,290

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Guillain-Barre Syndrome (including Miller-Fisher syndrome and other variants) <sup>291</sup>	Benefit established. Recommended as treatment option within 2 weeks of symptom onset for patients with severe and/or progressing symptoms. May be considered as a treatment option for relapsed patients who initially responded to IVIG	Total dose of 2 g/kg divided over 2-5 days (adults) or 2 days (children). Evaluate response at 4 weeks
Chronic inflammatory demyelinating polyradiculopathy <sup>292,293</sup>	Benefit established; option for short-term management of new-onset CIDP or relapse. Option for long-term therapy in combination with other immunosuppressive therapy	Total dose of 2 g/kg divided over 2-5 days: 1g/kg q3weeks as maintenance and then adjust accordingly
Multifocal motor neuropathy <sup>294</sup>	Benefit established. Recommended as first-line therapy. Diagnosis should be made by neuromuscular specialist	Total dose of 2 g/kg divided over 2-5 days; maintenance therapy should be individualized and tailored to the lowest dose that maintains clinical efficacy (usually 1 g/kg or less)
Myasthenia gravis <sup>295,296,297,298</sup>	First line treatment for moderate to severe exacerbations or crises. Should not be used as maintenance therapy. Appropriate consultation advisable	2 g/kg over 2-5 days: maintenance therapy should be individualized

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

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Acute disseminated encephalomyelitis (ADEM) <sup>279,290</sup>	IVIG is an option for monophasic ADEM when first-line therapy with high-dose corticosteroids fails or when there are contraindications to steroid use, and for treatment of relapsing ADEM to eliminate steroid dependency or for those patients who fail to respond, or have contraindications to steroids	<b>Adults:</b> Total dose of 2 g/kg divided over 2-5 days  <b>Pediatric:</b> Total dose of 2 g/kg divided over 2 days
Lambert-Eaton Myasthenic Syndrome (LEMS) <sup>279,290</sup>	IVIG is an option for treatment of LEMS. Objective evidence of clinical improvement is needed for sustained use of IVIG.	<i>Initial treatment:</i> Total dose of 2 g/kg divided over 2-5 days  <i>Maintenance therapy:</i> A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. The maximum dose of IVIG per treatment course should be 2 g/kg
Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS) <sup>279,290</sup>	IVIG is an option for treatment of patients with PANDAS. Diagnosis of PANDAS requires expert consultation	Total dose of 2 g/kg divided over 2 days is recommended as a reasonable option
Rasmussen's encephalitis <sup>279,290</sup>	IVIG is an option as a short-term, temporizing measure for patients with Rasmussen's encephalitis. Not recommended for long-term therapy	<b>Adults:</b> Total dose of 2 g/kg divided over 2-5 days  <b>Pediatric:</b> Total dose of 2 g/kg divided over 2 days

Neurology

IVIG IN NEUROLOGICAL DISORDERS\* (cont'd)

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Stiff Person's syndrome <sup>279,290</sup>	IVIG is an option for treatment of Stiff Person syndrome if GABAergic medications fail or for patients who have contraindications to GABAergic medications	<i>Initial treatment:</i> <b>Adults:</b> Total dose of 2 g/kg divided over 2-5 days  <b>Pediatric:</b> Total dose of 2 g/kg divided over 2 days  <i>Maintenance therapy:</i> A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose of IVIG per treatment course should be 2 g/kg
NMDA Encephalitis <sup>299</sup>	IVIG is an option for treatment of patients with NMDA. Diagnosis of NMDA requires expert consultation. IVIG is used in conjunction with immunosuppressive medications and/or plasmapheresis	<i>Initial treatment:</i> Total dose of 2 g/kg divided over 2-5 days in adults and children  <i>Maintenance therapy:</i> May be considered depending on response to treatment
Opsoclonus-myooclonus syndrome	Possible treatment option. Objective evidence of clinical improvement required for sustained use	Total dose of 2 g/kg given over 2-5 days (adults) or 2 days (children)

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

Rheumatology

IVIG IN RHEUMATOLOGY

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Idiopathic Inflammatory myopathy Includes: Dermatomyositis and Polymyositis references <sup>300</sup>	IVIG is indicated in patients with Idiopathic Inflammatory myopathy as adjunctive therapy to corticosteroids and/or a steroid sparing agent in patients with Idiopathic Inflammatory myopathy who have failed first-line therapy or as clinically indicated in the management of severe disease	Total dose of 2 g/kg divided over 2-5 days (adults) or 2 days (children); maintenance therapy should be individualized
Systemic lupus erythematosus** <sup>301,302,303</sup>	Current evidence does not support use	
Kawasaki disease <sup>304,305,306,307,308</sup>	Benefit established	2 g/kg x 1 day

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

Dermatology

IVIG IN DERMATOLOGY

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Toxic epidermal necrolysis <sup>309</sup>	IVIG is an option when other treatments are contraindicated, or when the condition is life-threatening	1 g/kg daily for 3 days
Pemphigus vulgaris and variants <sup>278,279</sup>	Consider IVIG when there is no response or a contraindication to corticosteroids and immunosuppressive agents	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized
Epidermolysis bullosa acquisita	Anecdotal evidence <sup>310</sup> supports use of IVIG as adjunctive or second-line treatment if conventional treatment is ineffective	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized
Bullous pemphigoid	Anecdotal evidence <sup>311</sup> supports use of IVIG as second-line treatment if conventional treatment is ineffective	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized

Obstetrics and Gynecology

IVIG IN OBSTETRICS AND GYNECOLOGY <sup>312</sup>

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Anti-phospholipid syndrome	Uncertain benefit <sup>313</sup> may improve fetal outcomes when Aspirin <sup>®</sup> and heparin have been ineffective; appropriate consultation advisable	Determine in consultation with high-risk pregnancy unit and attending specialist
Recurrent spontaneous abortion	Ineffective <sup>314</sup>	Not indicated
<i>In Vitro</i> fertilization/implantation procedures	Ineffective <sup>315</sup>	Not indicated

Infectious Diseases

IVIG IN BACTERIAL INFECTION <sup>278,279</sup>

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Septic/Toxic Shock Syndrome (Group A streptococcal sepsis with hypotension and multi-organ failure) <sup>316,317,318,319</sup>	Recommended as an adjunctive therapy when evidence of systemic inflammation and end organ hypoperfusion with fever, tachycardia, tachypnea and hypotension	1 g/kg on day one and 0.5 g/kg on days 2 and 3 or 0.15 g/kg per day over 5 days
Necrotizing fasciitis <sup>320,321</sup>	Possibly recommended for severe invasive group A streptococcal disease if other approaches have failed	Adjunctive treatment in rapidly progressing disease 1-2 g/kg over 6 hours
Sepsis in patients in critical care <sup>316,317,322,323</sup>	No large randomized controlled trials to confirm benefit	Not recommended for use

- Bone marrow transplant and red cell aplasia due to parvovirus B19: see **Hematology**.
- Specific hyper-immune globulins are available from Canadian Blood services for the listed conditions:
  - ◆ Varicella-Zoster Immune Globulin (VZIG)
  - ◆ Hepatitis B Immune Globulin (HBIG; BayHepB)
  - ◆ Anti-RSV Immune Globulin (Respigam<sup>®</sup>)
  - ◆ Cytomegalovirus Immune Globulin (CMVIG, Cytogam<sup>®</sup>) <sup>324</sup>

Dosing of IVIG for Obese Patients <sup>325</sup>

The dose of IVIG varies depending on the clinical condition. In general, the dose is based on the patient's weight. In the case of obese patients, the appropriate dosing regimen is unclear. It is suggested that patients weighing more than 100 kg and with a body mass index greater than 30 kg/m<sup>2</sup> should have their IVIG dose calculated using an adjusted body weight. The adjusted weight takes into account the increased volume of distribution in these patients (because of increased body fluids) without accounting for the increase in weight from body fat.

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

Requests for IVIG for infusion in Ontario

Requests for IVIG for infusion are required to be submitted on the Request Form prescribed by the MOHLTC. The form and the protocol for its use are posted at [www.transfusionontario.org](http://www.transfusionontario.org).

**Dose Calculator**  
<http://ivig.transfusionontario.org/bmi/>

**A T T E N T I O N**  
 IVIG in Ontario can only be requested using the prescribed request form.

FACTORS IN CHOOSING IVIG OR SCIG

INTRAVENOUS IMMUNOGLOBULIN (IVIG)	SUBCUTANEOUS IMMUNOGLOBULIN (SCIG)
<ul style="list-style-type: none"> <li>◆ Good maintenance of clinical benefit</li> <li>◆ Local reactions to SCIG</li> <li>◆ Patient uncomfortable with home or self-medication</li> </ul>	<ul style="list-style-type: none"> <li>◆ Clinical response not well maintained</li> <li>◆ Adverse effects of IVIG</li> <li>◆ Poor venous access</li> <li>◆ Able to manage home or self-medication</li> <li>◆ Patient prefers convenience of home self-injection</li> </ul>

**A Basics** 326,327

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

**Manufacturing**

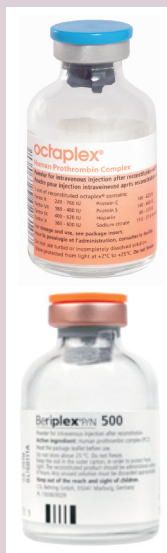
- The factor concentrate is made from pools of 1,000-2,000 plasma donations.
- Plasma units are tested for HIV (1 and 2), hepatitis B, hepatitis C.
- Manufacturing processes include viral inactivation steps.

**Products available**

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

**COAGULATION FACTOR LEVELS (IU/ML) IN PCCS**<sup>327</sup>

PRODUCT	MANUFACTURER	FACTOR II	FACTOR VII	FACTOR IX	FACTOR X	PROTEIN C	PROTEIN S	AT III	HEPARIN
Octaplex®	Octapharma	31.4	16.1	22.3	24.4	12.0	22.2	0.1	6.0
Beriplex®	CSL Behring	31.0	16.2	28.9	41.3	17.9	21.6	0.6	0.5



**B Monitoring & Infusion Practices for Octaplex® and Beriplex®** 326

**How**

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

**Dose**<sup>326</sup>

- The National Advisory Committee on Blood and Blood Products (NAC) Recommendations on dosing are based on the INR as detailed in the table to the right.
- If the INR is unknown and major bleeding is present, 2,000 IU (80mL) should be administered.
- The published NAC Recommendations include a table of detailed dosages based on a combination of INR and body weight, as an alternative dosing strategy.
- The maximum dose should not exceed 3,000 IU.

**When**

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

**Storage**

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

**ATTENTION**

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

INR	PCC DOSE
<3	1,000 IU
3-5	2,000 IU
>5	3,000 IU

<http://www.nacblood.ca/resources/guidelines/PCC-Recommendations-Final-2014-05-16.pdf>

**B Monitoring & Infusion Practices for Octaplex® and Beriplex® (cont'd)**

**Monitor patient**


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

**A T T E N T I O N**

Giving plasma for warfarin reversal is associated with a 3-fold higher risk of TACO.<sup>328</sup>

**INDICATIONS FOR PCCs**

- Emergency reversal of warfarin effect.
  - ◆ For patients with INR  $\geq 1.5$  AND
  - ◆ “Life or limb” threatening bleeding
  - ◆ Emergency surgery within 6 hours
 Give:
  - ◆ Vitamin K 10mg IV
  - ◆ PCC
 For dosages, see table on page 125.
- PCCs should NOT be administered if:
  - ◆ INR  $\leq 1.5$  as individual coagulation factors are not below the level needed to maintain hemostasis
  - ◆ Patients with coagulopathies not related to warfarin or Vitamin K deficiency as they are deficient in coagulation factors not contained in PCCs (with the exception of the off-label uses described)
  - ◆ Patients with known HIT (Beriplex® and Octaplex® both contain heparin)
  - ◆ Patient has received or will receive recombinant Factor VIIa
- Clinical situations where vitamin K alone will suffice are shown in the “Choosing Wisely” box to the right.<sup>10</sup>
- Its use should be limited to life-threatening hemorrhage and patients requiring emergency surgery.



**PCCs should not be given to correct coagulopathies other than warfarin.**  
**If PCCs is not effective in reversing warfarin, then other etiologies should be considered.**

**C H O O S E W I S E L Y**

PCCs should not be administered in clinical situations where vitamin K alone will suffice.

Situation	Vitamin K dose/route
INR >8-10, no bleeding	2 mg po
Surgery >6 hours later	10 mg iv
Non-critical bleeding	1 mg iv

**OFF-LABEL USES OF PCCs**

- Reversal of anti-Xa inhibitors (Rivaroxaban and Apixiban).
  - ◆ Currently specific reversal agents are in clinical trials and are not available outside of clinical trials
  - ◆ PCCs at a dose of 2,000 IU (repeated in 1 hour if hemostasis is not achieved) is being used across Canada
  - ◆ Data to support its use is limited to studies in animals and human volunteers
- Reversal of anti-IIa inhibitors (Dabigatran).<sup>329</sup>
  - ◆ A licensed antidote (Idarucizumab, Praxbind®) is available in Canada
  - ◆ The dose of Idarucizumab is 5 g, administered in two 2.5 g bolus infusions each over 5 minutes, not more than 15 minutes apart

**Rh(D) Immune Globulin (WinRho®)** <sup>324,330</sup>

**Purpose**

- Prevention of immunization in Rh(D) negative patients exposed to Rh(D) positive red cells.

**Dosages Available**

- 120 ug (600 IU), 300 ug (1,500 IU), 600 ug (3,000 IU), 1,000 ug (5,000 IU), IV or IM.

**Prevention of Rh(D) immunization by Rh(D) positive fetal red cells in pregnancy in non-sensitized Rh(D) negative females:**

- Recommended doses:
  - ◆ Prophylactic dose at 28 weeks 300 ug IV or IM
  - ◆ Post-partum, newborn Rh(D) positive (including weak D), 300 ug IV or IM, within 72 hours of delivery (give as soon as possible if 72 hour deadline is missed)
    - Quantify fetomaternal hemorrhage; additional doses of RhIG required if fetomaternal hemorrhage present (dose should be calculated by using the College of American Pathologist's on line calculator at [www.cap.org](http://www.cap.org))
  - ◆ Complications of pregnancy:
    - Pregnancy before 12 weeks, 120 ug IV/IM
    - Pregnancy 12-20 weeks, 300 ug IV/IM
    - Pregnancy after 20 weeks, 300 ug IV/IM – Plus Fetal Maternal Hemorrhage (FMH) testing to determine if additional doses required

**A T T E N T I O N**

Rh immunoglobulin is a blood product: informed consent is required.

- Complications of pregnancy requiring Rh(D) immune globulin:
  - ◆ Antepartum hemorrhage
  - ◆ Amniocentesis, chorionic villus biopsy or cordocentesis
  - ◆ External version, abdominal trauma
  - ◆ In-utero therapeutic interventions
  - ◆ Ectopic pregnancy, intrauterine death and stillbirth
  - ◆ Abortion, threatened, actual or therapeutic
- Immunization with other red cell antigens:
  - ◆ Severe hemolytic disease of the fetus and newborn may involve many antigens other than Rh(D), including, but not restricted to, Rh C, c, E, K and k, Fya, Jka, Jkb and S
  - ◆ Specific immune globulin prophylaxis is not available for specificities other than Rh(D)

**Other indications for treatment/prophylaxis with Rh(D) immune globulin:**

- After transfusion of platelet components from Rh(D) positive donors.
  - ◆ **ONLY** to Rh(D) negative patients of childbearing potential
  - ◆ The presence of “passive” anti-D complicates red cell compatibility testing and may delay transfusion without significant benefit
  - ◆ The risk of Rh(D) immunization by platelet components is about 1%<sup>331,332</sup>

Note: RhIG contains IgA at a concentration of 40 ug/mL or less.

**A Principles of Transfusion in Sickle Cell Disease**<sup>333</sup>

Transfusion in patients with sickle cell disease presents particular challenges, both in the practicalities of providing optimally matched red cells and in determining when transfusion is likely to provide superior outcomes to other available therapeutic measures. It is therefore important that expert consulting assistance be sought for the individual case.

**A T T E N T I O N**

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

Patients with sickle cell disease:

- Have elevated blood viscosity which may be exacerbated by increases in hematocrit.
- Are more likely to experience complications from transfusion.

The indications for transfusion in patients with sickle cell disease differ significantly from other patients:

- ◆ **Treatment of severe anemia:** in the absence of heart failure, dyspnea, hypotension or marked fatigue, transfusion should be avoided unless the hemoglobin (Hgb) has decreased to  $<50 \text{ g/L}$ <sup>334</sup>
  - A rapid decrease in Hgb can be anticipated if the reticulocyte count falls below  $250 \times 10^9/\text{L}$
- ◆ Aim to decrease the sickle cell hemoglobin (HgbS) concentration while keeping the total Hgb below  $100 \text{ g/L}$  in patients with sickle cell complications<sup>335</sup>
  - Augmentation of oxygen delivery in patients with sickle cell disease is achieved more efficiently through decreasing the HgbS% than by increasing the total Hgb level<sup>336</sup>

**A T T E N T I O N**

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

**A T T E N T I O N**

Never transfuse a sickle cell patient to a hemoglobin  $>100 \text{ g/L}$ .

**B Special Transfusion Requirements**

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

**Phenotypically-matched RBCs**

- Determine extended phenotype (Rh, Kell, Duffy, Kidd and MNS blood groups) at first visit. Due to the high prevalence of partial antigens in this population, genotyping should also be performed if possible.
- In patients with no previous clinically significant alloantibodies, select RBCs matched for the patient's Rh (D,C,c,E,e) and Kell (K1) antigens.
- If known alloantibodies, select RBCs that are matched for the patient's Rh (D, C, c, E, e), Kell (K1), Kidd (Jk<sup>a</sup>, Jk<sup>b</sup>), Duffy (Fy<sup>a</sup>) and S (S,s) antigens, as well as any antigens to which the patient is immunized.
  - ◆ Matching for Fyb in sickle cell patients with the Fy(a-b-) phenotype is rarely necessary
- If there is not sufficient time or resources to determine the patient's phenotype, contact other hospitals that may have transfused the patient previously. (In some regions of Canada, CBS maintains a phenotype registry of patients with sickle cell disease.) In Quebec, phenotype can be obtained from the Transfusion Laboratory by accessing the transfusion summary in the IT system.

**A T T E N T I O N**

Notify blood bank immediately about sickle cell disease patients.

**A T T E N T I O N**

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

**A T T E N T I O N**

Patients with sickle cell disease must be issued a card with their extended phenotype and specificities of any alloantibodies present. The reason for and importance of the card must be clearly explained to the patient

Antibody Card	
Blood Bank	Date: June 11, 2011
Name: Mary Bloodworthy	
Date of Birth: Oct 25, 1981 Hospital File # 1178380	
ABO/Rh: O NEG	
Special Requirements:	
<b>ANTIBODY (RES)</b> <b>ANTI-E</b>	

## B Special Transfusion Requirements (cont'd)

### Sicklelex<sup>®</sup>-negative blood

- RBC units which test positive by Sicklelex<sup>®</sup> test are from donors with sickle cell trait (HgbAS). This blood is therefore safe to administer to patients with sickle cell disease, but it will confound post-transfusion measurements of the patient's HgbS% and should be avoided, if possible.<sup>337</sup>

## C Exchange Transfusion

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

### Manual/partial exchange:

- A typical protocol (for children, smaller comparable volumes, e.g., 10 mL/kg):<sup>335</sup>
  1. Phlebotomize 1st 500 mL of whole blood (for patients who are very anemic at baseline [e.g., Hgb <70 g/L], a top-up transfusion may be required before first phlebotomy)
  2. Bolus 500 mL of 0.9% normal saline
  3. Phlebotomize 2nd 500 mL of whole blood
  4. Transfuse 2 units of RBCs
  5. Repeat as necessary to achieve target HgbS% (typically a 1.5 blood volume exchange is necessary for first treatment; single volume cycle may be adequate for maintenance therapy). Note that for patients starting with Hgb near 100 g/L, step 4 should alternate between transfusion of 1 and 2 units in order to keep total Hgb from exceeding 110 g/L

## D Primary indications for Transfusion

### THERAPEUTIC TRANSFUSION

#### Aplastic Crisis

- Most commonly due to parvovirus B19 infection, with profound reticulocytopenia.
- Transfusion support may be required if symptomatic anemia, or if Hgb <50 g/L.
- Due to a compensatory increase in plasma volume, transfuse slowly to avoid volume overload and consider pre-transfusion diuretic.

#### Sequestration crisis

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

### ATTENTION

Due to decreased lifespan of sickle RBCs (16-20 days), significant fall in Hgb will occur before the reticulocyte count recovers.<sup>338</sup>



#### Pediatrics

In children, consider administering RBCs in smaller than normal aliquots (e.g., 3-5 mL/kg). Often a single transfusion is sufficient to reverse a sequestration crisis.<sup>339</sup>

- Less commonly, patients may present with hepatic sequestration crises, characterized by a rapidly enlarging liver accompanied by a decrease in hemoglobin, a rise in reticulocyte count, and a conjugated hyperbilirubinemia.
  - ◆ Transfusions should also be administered cautiously due to the risk of autotransfusion and hyperviscosity. Recurrences are common<sup>334</sup>

#### Acute chest syndrome<sup>340</sup>

- A new infiltrate on CXR in a patient with sickle cell disease, associated with one or more symptoms of fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia.
- RBC transfusion in setting of acute chest syndrome results in improved oxygenation.<sup>341</sup>
- “Top-up” transfusion to 100 g/L may be sufficient to achieve improved oxygenation.
- In some cases progression to exchange transfusion to reduce HgbS to <30% may be necessary.
- Some studies have observed equivalent outcomes whether patients treated with exchange transfusion (HgbS% goal of 30%) or top-up transfusion (Hgb goal of 100 g/L).<sup>341,342</sup>
- However, other studies suggest that patients receiving top-up transfusions may progress to requiring exchange.<sup>343</sup>
- In absence of evidence from randomized controlled trials, most patients with acute chest syndrome should be transfused, with exchange transfusions reserved for patients with more severe or rapidly progressing disease with concerning symptoms (see yellow box to the right).<sup>344</sup>

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

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

#### Progressive cholestasis

- Syndrome marked by right upper quadrant pain, extreme elevation of bilirubin and alkaline phosphatase, and variable elevation in transaminases.
  - ◆ May be accompanied by renal failure, thrombocytopenia, and prolonged coagulation times
  - ◆ Without prompt institution of exchange transfusion, patient may develop progressive fulminant liver failure

#### Acute ischemic stroke or retinal artery occlusion

- Transfusion recommended for adult patients without other obvious stroke etiology (e.g., cardioembolism).<sup>339</sup>
- In patients with hemorrhagic stroke secondary to underlying vasculopathy, implementation of regular transfusion support may be beneficial in secondary prevention once the patient has stabilized.



#### Pediatrics

Transfusion recommended for all pediatric patients with acute ischemic stroke. Within 3 hours of the first unit of transfused RBCs, MCA flow velocity decreases by 20%.<sup>345</sup> Exchange transfusion associated with lower recurrence rate than top-up transfusion.<sup>346</sup>

## PROPHYLACTIC

## Perioperative

- Due to high rates of perioperative complications (e.g., 10% rate of acute chest syndrome), aggressive supportive care and close observation is indicated.<sup>347,348</sup>
  - ◆ Avoid surgery during vaso-occlusive episodes
  - ◆ IV fluids if NPO  $\geq$  2 hours pre-op and continue post-op until oral fluids tolerated
  - ◆ Maintain SpO<sub>2</sub> >96% and encourage incentive spirometry
  - ◆ Avoid hypothermia
  - ◆ Favour laparoscopic approaches
  - ◆ Post-operative prophylaxis for deep venous thrombosis if immobile >24 hours
  - ◆ Aggressive control of pain
  - ◆ Early mobilization
- Low-risk procedures: transfusion likely not required.
- Moderate risk procedures: A recent RCT of patients undergoing predominantly moderate-risk surgery established the necessity of pre-operative transfusion: without transfusion, the risk of serious adverse events (predominantly acute chest syndrome) increased from 3% to 33%, with median time to onset 2-3 days post-operatively.<sup>349</sup>
  - ◆ The transfusion protocol in this study aimed to achieve a HgbS of ~60% within 10 days of surgery: in patients with a Hgb of <90 g/L this was achieved by a top-up transfusion to a Hgb of ~100 g/L, whereas those with a Hgb  $\geq$  90 g/L underwent a partial exchange transfusion. A previous RCT in a similar patient population had established that a pre-operative HgbS of ~60% was no less effective at preventing sickle cell complications than a target HgbS of 30%.<sup>347</sup>
- High-risk procedures or serious patient comorbidities (e.g., end-stage renal disease or baseline SpO<sub>2</sub><90%): a more aggressive pre-operative target HgbS of <30% is advisable.
- Pre-operative transfusions (whether top-up or exchange) should be performed within 10 days of the surgical procedure.

SURGICAL PROCEDURE	TRANSFUSION MANAGEMENT
<b>Low risk:</b> Skin, dental, perineal, inguinal or distal extremity surgery	Transfusion likely not necessary
<b>Moderate risk:</b> Abdominal, ENT or orthopedic surgery	Hgb <90 g/L top up to 100 g/L; Hgb >90 g/L exchange to HgbS<60%
<b>High risk of serious co-morbidities:</b> Intracranial, cardiovascular, or intrathoracic procedures; pars plana vitrectomy or scleral buckling	Exchange transfusion likely necessary (target HgbS<30%)

## High Stroke Risk

- In children, transfusion is indicated for secondary prevention of ischemic stroke and for primary prevention in patients with high-risk features (e.g., high middle cerebral artery or internal carotid blood flow by pediatric transcranial ultrasound).
  - ◆ In the latter group, maintaining HgbS <30% while keeping total Hgb <120 g/L results in a 92% reduction in stroke incidence<sup>350</sup>
- Children (ages 4-16) without significant cerebral vasculopathy can be safely transitioned to hydroxyurea after 12 months of transfusion if they have no prior history of stroke or TIA [i.e., isolated high Transcranial Doppler (TCD)]. TCD should be performed every 3 months once the switch to hydroxyurea has been done and an immediate restart of transfusion in the case of reversion.<sup>351</sup>
  - ◆ Transfusion and hydroxyurea need to be overlapped by 4-9 months<sup>352</sup>
  - ◆ However, a safe alternative to transfusion has not yet been established in children who have already experienced a stroke, whether it was clinically apparent<sup>352,353</sup> or silent<sup>354</sup>
- Little evidence to guide initiation of transfusions for stroke prophylaxis in adults, or following primary hemorrhagic strokes.
  - ◆ The underlying pathophysiology for both thrombotic and hemorrhagic strokes in sickle cell disease is likely the same<sup>355</sup>

## E Supplemental indications for transfusion

The following conditions should be managed with exchange transfusion for patients who have failed non-transfusion based therapies. The initial therapeutic goal should be HgbS <30%.

### 1. Recurrent pain episodes/acute chest syndrome

- In patients who have failed an adequate trial of hydroxyurea, chronic transfusion support may be considered as means of decreasing recurrence of vaso-occlusive pain episodes or acute chest syndrome.<sup>356,357</sup>
- Transfusion not indicated as treatment of uncomplicated acute vaso-occlusive pain episodes, or for treatment of chronic pain syndromes (e.g., avascular necrosis, osteomyelitis, neuropathic pain).<sup>339,358</sup>

#### ATTENTION

Transfusion not indicated as treatment of uncomplicated acute vaso-occlusive pain episodes.

### 2. Priapism

- Transfusion may be of benefit for episodes lasting >4 hours, unresponsive to aspiration of blood from the corpora cavernosa and irrigation with dilute epinephrine.<sup>359,360</sup>

### 3. Malleolar ulcers

- Transfusion may speed healing if no response to bed rest, wound care, antibiotics, hyperbaric oxygen.<sup>361</sup>

### 4. Pregnancy<sup>362</sup>

- Although hydroxyurea is contraindicated in pregnancy, the role of transfusion is unclear.
- A single RCT of transfusion support to maintain the maternal HgbS <35% did not result in improved fetal outcomes compared to a strategy of transfusing only if Hgb <60 g/L accompanied by a reticulocyte response of <3%.<sup>357</sup> However, maternal sickle cell complications were nonetheless decreased.<sup>362</sup>

- Transfusion support should be considered for pregnant patients with:<sup>339</sup>

- ◆ A history of frequent vaso-occlusive pain crises
- ◆ Chronic renal, pulmonary or hepatic disease
- ◆ History of recurrent fetal loss
- ◆ Multigestational pregnancy or evidence of chronic fetal distress/intrauterine growth retardation

### 5. Pulmonary hypertension<sup>363</sup>

- Defined as a resting mean pulmonary pressure (mPAP) on right heart catheterization of  $\geq 25$ mmHg. Increased tricuspid regurgitant jet velocity (TRV)  $\geq 2.5$ m/sec is associated with increased morbidity and mortality but does not necessarily reflect pulmonary arterial hypertension (PAH).
- In patients with TRV of >2.5 m/s, NT-pro-BNP >160 pg/ml, or PAH confirmed by right heart catheterization, chronic transfusion therapy should be considered if lack of response (or contraindication) to treatment with hydroxyurea.<sup>363</sup>

#### ATTENTION

Priapism, pulmonary hypertension and malleolar ulcers may represent complications of chronic intravascular hemolysis (e.g., nitric oxide depletion) rather than acute vaso-occlusion.<sup>364</sup>

## F Transfusion Complications

### Delayed hemolytic transfusion reactions

- Without prophylactic phenotypic matching, 30% of transfused patients with sickle cell disease will develop alloantibodies, two thirds of them directed towards C, E and K1 antigens.<sup>365</sup>
  - ◆ Alloimmunization due in part to genetic differences in the antigens expressed on red blood cells in the donor population (primarily Caucasians) and recipients
- 30-50% of antibodies will be undetectable on retesting within the year; patients may be inadvertently challenged with subsequent transfusions, resulting in delayed hemolytic transfusion reactions.<sup>337</sup>
- Prophylactic matching for antigens therefore advised when selecting RBCs for sickle cell patients; advance notification of blood bank required.
  - ◆ Prophylactic matching decreases the rate of alloimmunization (from 3.0% to 0.5%/unit) but it remains an issue<sup>366</sup>
- Due to the high frequency of partial RBC antigens in individuals of African ethnicity, genotyping of patients with sickle cell disease is highly recommended.

**ATTENTION**

Alloimmunized sickle cell patients require antibody card.

Antibody Card	
Blood Bank	Date: June 11, 2011
Name: Mary Bloodworthy	Date of Birth: Oct 25, 1981 Hospital File # 1175380
ABO/Rh: O NEG	
Special Requirements:	<b>ANTIBODY (IES)</b> <b>ANTI-E</b>

### Hyperhemolysis<sup>367</sup>

- Defined as post-transfusion RBC destruction accompanied by fall in Hgb to below pre-transfusion levels.
  - ◆ Hemolytic indices increased from baseline, occasionally accompanied by relative reticulocytopenia<sup>368</sup>
  - ◆ Acute: occurs less than 7 days after transfusion, often with no new antibodies detectable
  - ◆ Delayed: occurs between 1 and 4 weeks following transfusion and often accompanied by new RBC antibodies

**ATTENTION**

Continuing to transfuse a patient with hyperhemolysis may cause worsening of anemia!

- Enhanced hemolysis appears to involve both transfused and autologous RBCs, and may be exacerbated by further transfusion of even crossmatch compatible/antigen-negative RBCs.
- **Avoid further transfusions, if at all possible:**
  - ◆ Treat with IVIG 2 g/kg over 2-5 days
  - ◆ Accompany by high dose steroids (e.g., prednisolone 1 mg/kg/d x 7 days)
  - ◆ Consider brief course of erythropoietin if relative reticulocytopenia<sup>369</sup>

### Hyperviscosity

- Sudden onset hypertension during or shortly after transfusion, accompanied by signs of congestive heart failure and profound alterations in mental status, including stupor, coma, seizures, or features of intra-cerebral infarct or hemorrhage.<sup>370</sup>
- Risk increases if Hgb transfused above 100-110 g/L in patients with SCD and HgbS% >25%, particularly if patient dehydrated and hypoxemic.<sup>335</sup>
  - ◆ May also occur secondary to auto-transfusion following transfusion support of sequestration crises
- Manage with emergency phlebotomy.

### Transfusional iron overload

- Each transfused unit of RBCs delivers 180 mg of iron.<sup>11</sup>
- Significant iron overload therefore likely after repeated top-up transfusions: may eventually result in hepatic, cardiac or endocrine dysfunction.
- Selecting fresh RBCs (<7 days old) may slow iron loading in chronically transfused patients to a small degree.
- Exchange transfusions can more effectively mitigate or even reverse iron loading.<sup>371</sup>



**ATTENTION**

Never give a top-up transfusion to a sickle cell patient with a hemoglobin >100 g/L

- Iron chelation therapy indicated once hepatic iron concentration >7 mg/g dry weight, as assessed by either biopsy or calibrated MRI scan.<sup>372</sup>
  - ◆ This degree of iron loading can be anticipated after the transfusion of more than 70 mg/kg of iron (in adult patients, approximately 20-30 RBC units)
  - ◆ Small volume phlebotomy while receiving hydroxyurea may be useful<sup>351</sup>
  - ◆ Iron overload correlates poorly with serum ferritin in sickle cell patients but is likely present if serum ferritin persistently >3,000 ng/mL<sup>373</sup>
- Iron chelators licensed for use in Canada include deferoxamine, deferasirox and deferiprone.
  - ◆ Referral to a centre with expertise in iron chelation therapy advised prior to initiation of treatment

## Appendix A

### Price List

ITEM	PRICE
Red blood cells*	\$423
4 units buffy coat derived platelets	\$185
1 unit single donor (apheresis) platelets	\$484
Apheresis fresh frozen plasma	\$375
4 units frozen plasma**	\$380
10 units cryoprecipitate	\$880
Tranexamic acid 2 g	\$14
IVIG per gram	\$54
Albumin 5% 500 mL	\$47
Blood group (ABO, Rh D)	\$10
Antibody screen	\$10
Crossmatch (no antibody)	\$25
Crossmatch (antibody positive patient)	\$30
Prothrombin Complex Concentrates 1,000 IU	\$610
Recominant Factor VIIa/mg	\$1,180
Anti-D 120 mcg	\$34
Anti-D 300 mcg	\$84

\* This cost refers only to the acquisition cost of a unit of RBC. The cost of delivery of a unit of blood to a patient ranges from \$522 to \$1,183 (US).<sup>374</sup>

\*\* This cost refers only to the acquisition cost of plasma. The total cost of plasma is \$409.62 per unit or \$1,608.37 per patient transfused.<sup>375</sup>

## Appendix B

### Information for Physicians Treating Patients Who Are Jehovah's Witnesses

- Jehovah's Witnesses refuse transfusion of allogeneic blood based on their understanding of several Biblical passages, which they view as **prohibiting** the use of:
  - ♦ Whole blood, including predonated autologous blood (predeposit)
  - ♦ Red blood cells
  - ♦ White blood cells
  - ♦ Platelets
  - ♦ Plasma
- Their religious understanding **may permit** the use of products containing fractions of plasma or cellular components, such as:
  - ♦ Cryoprecipitate
  - ♦ Clotting factor concentrates
  - ♦ Albumin
  - ♦ Intravenous immunoglobulin
  - ♦ Fibrin glue
  - ♦ Autologous blood obtained by cell salvage
- Witness patients will accept most:
  - ♦ Surgical and anesthetic procedures promoting conservation
  - ♦ Diagnostic and therapeutic procedures (e.g., phlebotomy, angiography)
  - ♦ Pharmacological enhancement of hemostasis
  - ♦ Pharmacologic stimulation of erythropoiesis (e.g., erythropoietin) that do not contain blood derivatives
- A useful discussion of the position of Jehovah's Witnesses on blood transfusion and related issues is available.<sup>376</sup>
- Physicians should discuss the various options with individual patients, as each person must make a personal choice according to their conscience.
- Jehovah's Witnesses have established a network of **Hospital Liaison Committees (HLC)** across Canada. On call local HLC members can be contacted through the hospital switchboard or by contacting the **Hospital Information Services for Jehovah's Witnesses**. This service is available 24 hours a day at **1-800-265-0327**.

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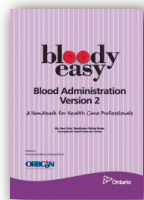
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## Bloody Easy Blood Administration



Bloody Easy Blood Administration handbook is ideal for nurses or healthcare professionals administering blood. It provides an overview of blood and blood products, the risks associated with them, and how they should be administered. In addition, it describes the types of transfusion reactions that may occur.

## Bloody Easy Coagulation



Bloody Easy Coagulation handbook provides practical information on Coagulation. It is designed to enhance the knowledge of physicians, nurses and medical laboratory technologists about the basics of coagulation from laboratory testing to anticoagulant drugs and management of common bleeding disorders.

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## Red Blood Cell Pre-Transfusion Checklist

Alternatives failed or have been ordered?	<input type="checkbox"/> Anemia investigations completed (e.g., CBC, blood film, ferritin, iron saturation, vitamin B12, reticulocyte count) <input type="checkbox"/> Iron (oral and IV), vitamin B12, erythropoietin ordered or not indicated
Consent?	Patient advised of risks of: <input type="checkbox"/> TACO 1 in 100 <input type="checkbox"/> Hemolytic reaction 1 in 7,000 <input type="checkbox"/> TRALI 1 in 10,000 <input type="checkbox"/> Major allergic reaction 1 in 40,000 <input type="checkbox"/> Bacterial infection 1 in 250,000
Female under 45?	<input type="checkbox"/> Order Kell-negative units <input type="checkbox"/> Inform recipient of the potential risk of transfusion causing hemolytic disease of the newborn in future pregnancies
At risk for FATAL transfusion-associated Graft vs. Host Disease?	Order irradiated blood if patient has any history of the following: <input type="checkbox"/> Hodgkin's lymphoma <input type="checkbox"/> Allogeneic or autologous stem cell transplant <input type="checkbox"/> Ever treated with fludarabine, cladribine, bendamustine, alemtuzumab, anti-thymocyte globulin (ATG) <input type="checkbox"/> Congenital immunodeficiencies
Diuretics?	Does my patient have a history of: <input type="checkbox"/> Age greater $\geq 70$ years <input type="checkbox"/> Renal dysfunction <input type="checkbox"/> Left ventricular dysfunction <input type="checkbox"/> Prior or current CHF <input type="checkbox"/> Severe euvolemic anemia (hemoglobin $< 50$ g/L)  <input type="checkbox"/> If YES to any of the above: prescribe PO/IV furosemide pre-transfusion ( <i>unless currently hypovolemic</i> )
Rate and Dose?	<input type="checkbox"/> Specify rate of infusion (default rate is over 2 hours per unit; inpatients and patients at risk for TACO (need diuretics) infuse over 3-4 hours) <input type="checkbox"/> Order 1 unit at a time (unless bleeding)

TACO: Transfusion-Associated Circulatory Overload, TRALI: Transfusion-Related Acute Lung Injury, CHF: Congestive Heart Failure