

bloody easy 5

Blood Transfusions, Blood Alternatives and Transfusion Reactions

A Guide to Transfusion Medicine

Fifth Edition

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Preface to the Fifth Edition

Successive editions of the Bloody Easy guide to transfusion medicine have reflected the evolution of new knowledge in transfusion medicine while eliminating reference to obsolete and outmoded practices. The previous (4th) edition ushered in the concepts of “Patient Blood Management” (the promotion of the integrated and best use of transfusion and its alternatives and adjuncts)^{1,2} and the application of the objectives of the “Choosing Wisely” initiative as applied to transfusion³.

A recent international consensus conference⁴ has reviewed evidence to date and has provided recommendations regarding measures for Patient Blood Management (PBM) in respect of red blood cell transfusion and its options and adjuncts. These recommendations have been taken into account in formulating the transfusion guidance.

“Choosing Wisely” has formed the philosophical basis of the detailed Quality Improvement Plan (QIP) laid out by the Ontario Regional Blood Coordinating Network (ORBCoN) and is supported by the Canadian Society for Transfusion Medicine (CSTM)^{5,6}. The details of the QIP, the documentation associated with its implementation and the important role of transfusion medicine services in screening transfusion orders for appropriateness are presented in ORBCoN’s QIP Toolkit⁵.

The criteria guiding the relevant recommendations in Bloody Easy are essentially those implied by the PBM and Choosing Wisely initiatives.

Since the publication of the 4th Edition, estimates of transfusion rates in Ontario indicate decreases in *per capita* consumption between 2016 and 2020 of 10.6% for red blood cells, 17.2% for frozen plasma and 7.4% for platelets. These reductions, while encouraging, do not reflect the full potential for elimination of inappropriate transfusion and consequent avoidable hazard. Objective assessment of a successfully implemented multi-institutional patient blood management program has confirmed the potential for a significantly more substantial reduction in *per capita* consumption⁷.

Audits conducted as part of studies of the influence of pre-transfusion screening of orders for red blood cells for appropriateness confirm, that in the absence of such screening, transfusion rates are higher^{8,9}. Audits of frozen plasma use indicate continuing inappropriate transfusion^{5,10} and in practice pre-transfusion order screening has been very effective in reducing frozen plasma consumption^{11,12}. A recent audit of platelet transfusion in Ontario^{5,13} revealed that approximately 40% of platelet transfusions failed to meet criteria for appropriateness; while the criteria for determining appropriateness of platelet transfusion are necessarily more complex than those for red cells and plasma, there is clearly room for considerable improvement. In parallel with this new edition of Bloody Easy, ORBCoN has made available a Platelet Transfusion Toolkit incorporating Provincial guidelines for determining appropriateness of platelet transfusion orders to assist pre-transfusion screening and for promoting justifiable use, based on comprehensive guidelines.^{5,14-17}.

Other significant changes in content from the previous edition include:

Removal of the content on Cryoprecipitate since its role is being overtaken by the availability of purified specific products, Factor VIII, von Willebrand Factor and now Fibrinogen.

Additional content on pathogen-reduced platelets, treated with psoralens and UV-light to inactivate the nucleic acids of pathogens and, incidentally, inactivate residual leukocytes.

Incorporation of recommendations in the Massive Hemorrhage Protocol^{5,18} in the section on massive transfusion.

In the interests of maintaining bloody easy as a slim “pocket guide”, the references will no longer be included in the printed version but will be available as part of the electronic version posted at www.transfusionontario.org or you can access the references directly by scanning the QR code using your phone camera.



Ten Things Physicians and Patients Should Question⁶



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.

CHOOSE WISELY

For other Choosing Wisely Canada Recommendations including the new "Top Four Tests and Treatments to Question in Perinatal Transfusion Medicine" visit <https://choosingwiselycanada.org/recommendation/transfusion-medicine/>

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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- Dr. T. (Dorien) Ruijs
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- Laurie MacLeod, MLT

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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).
- Health Canada provides guidance to assist hospitals in complying with the blood regulations (<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/blood-regulations.html>).



National Standard

- Canadian Standards Association (CSA Group) publishes the national standard for all aspects of blood management (current version, CAN/CSA -Z902-20, available at https://webstore.ansi.org/standards/csa/csaz90210?gclid=Cj0KCQjwz7uRBhDRARIsAFqjulmb9GaQBIsUVkyfJVz7kyjd66V8aEKlae87kkQs1FCqdDpxAKI-x3caAju5EALw_wcB).
- Canadian Society for Transfusion Medicine (CSTM) publishes standards for Hospital Transfusion Services. These standards are consistent with the CSA national standard <https://www.transfusion.ca/Resources/Standards>.



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 hemoglobin

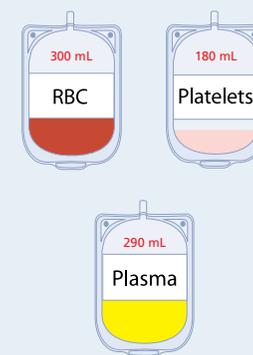
- Donor units tested for:

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

- All whole blood and apheresis donors at CBS and HQ are unpaid volunteers.
- In Canada, all plasma for fractionation is screened for parvovirus B19 and hepatitis A by nucleic acid testing. In Quebec, all blood components are also tested for parvovirus B19 and hepatitis A 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
- For pathogen-reduced platelets, the Buffy coat units from seven donors are combined with male plasma, platelet additive solution and separated into two platelet doses of 180mL each.
- For non-pathogen-reduced platelets, the buffy coat units from four donors are combined with male plasma and further processed to separate the platelets for a total volume of 350 mL.
- The red blood cell and platelet components are leukoreduced.



Whole blood processing (cont'd)

- At HQ one dose of platelets includes the buffy coat units from 5 donors, combined with the plasma from one of those donors.
- 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 67) for list of patient groups that need irradiated blood.

B Red Blood Cells and Components: Storage Conditions and Volumes¹⁹

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 pathogen reduced platelets (two doses from 7 units)	180 mL	5 days	20-24 °C	5 minutes
Buffy coat derived non-pathogen-reduced platelets (from 4 units)	350 mL	7 days	20-24 °C	5 minutes
Apheresis platelets	223 mL	7 days	20-24 °C	5 minutes
Frozen plasma	290 mL	1 year	-18 °C or colder	30 minutes
Apheresis plasma	250 mL	1 year	-18 °C or colder	30 minutes

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

Please see Circular of Information, Canadian Blood Services
<https://www.blood.ca/en/hospital-services/products/component-types/circular-information>

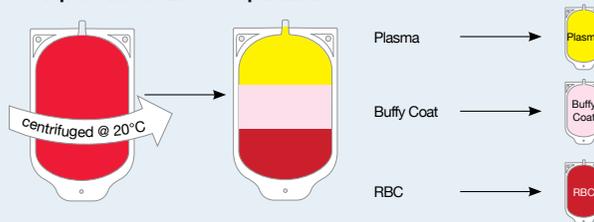


HQ provides buffy coat platelets from 5 units of buffy coat in 258 mL. HQ storage limit for platelets is 7 days and the product is currently not pathogen reduced.

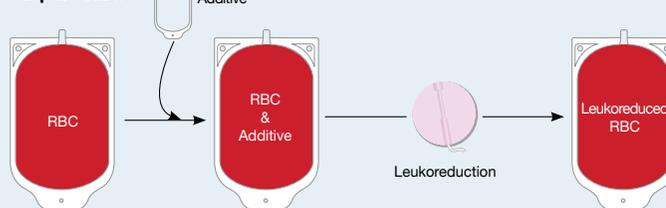
Some component manufacturing processes differ in HQ therefore volumes may differ slightly. Refer to Circular of Information, Héma-Québec
<https://www.hema-quebec.qc.ca/sang/professionnels-sante/notice/notice-lignes-directrices.en.html>

Process for Preparing Blood Components from Donated Units

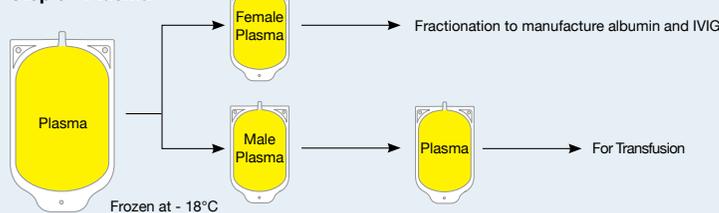
Step 1 - Whole Blood Separation



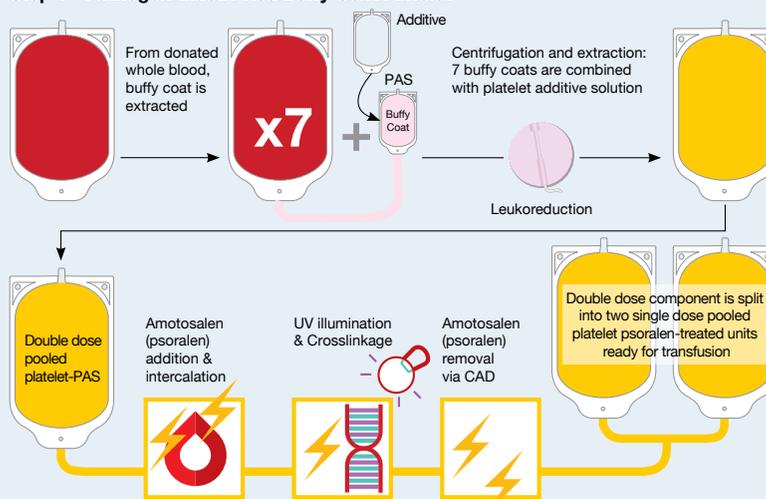
Step 2 - RBC



Step 3 - Plasma



Step 4 - Pathogen-inactivated Buffy Coat Platelet*



*Pathogen-inactivation process reduces the risk of microbial contamination and TA-GvHD

● Informed Consent

Consent is mandated by Transfusion Medicine Standards (ref CSA) and is identified as an important priority element to be incorporated into Patient Blood Management Programs.²⁰

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.²⁰



What²¹

- 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.



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, except for recipients with rare blood types.
- 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.



E Guideline Recommendations

Red Blood Cells^{4,22}

- The Association for the Advancement of Blood and Biotherapies (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 red blood cell (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 randomized trial evidence is not available for all categories of patients.”
- The 2018 Frankfurt guidelines advised a restrictive RBC transfusion threshold (hemoglobin concentration <75 g/L) in patients undergoing cardiovascular surgery.
- The 2018 Frankfurt guidelines advised a restrictive transfusion threshold (hemoglobin concentration 70-80 g/L) in hemodynamically stable patients with acute gastrointestinal bleeding.

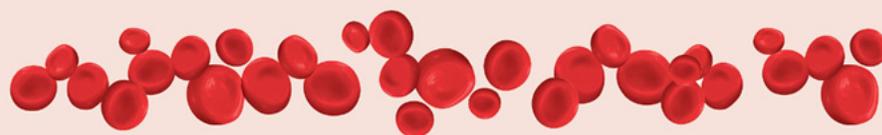
Platelets^{14,15}

- 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.

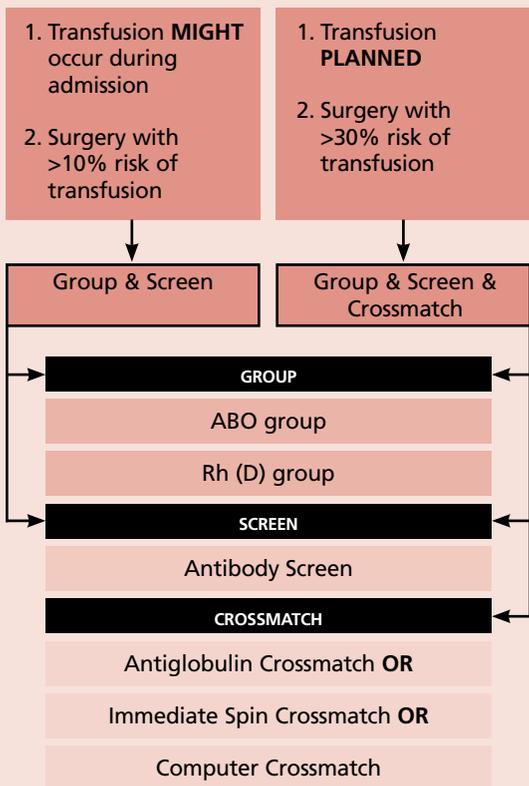
- For major elective non-neuraxial surgery, a threshold of less than $50 \times 10^9/L$ is recommended for prophylactic transfusion.
- Female children and people of child-bearing age/potential who are Rh(D) negative should receive Rh immunoglobulin before, after or within 72 hours of receiving an Rh(D) 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 do not require Rh immunoglobulin.

Imaging-guided Procedures¹⁷

- Low risk procedures (excluding patients with cirrhosis) – e.g., lumbar puncture, paracentesis, thoracentesis, central line placement, superficial biopsies – INR and platelet count not required but if performed INR<2-3 and platelet $>20 \times 10^9/L$ is sufficient.
 - ◆ Low risk procedures (with cirrhosis) – no need for plasma transfusion even for very high INR, and platelet count $> 20 \times 10^9/L$ is sufficient.
- High risk procedures (excluding patients with cirrhosis – e.g. solid organ biopsies and deep abscess drainage) – INR<1.5-1.8 and Platelet count $>50 \times 10^9/L$
 - ◆ High risk procedures (with cirrhosis) – INR<2.5 and platelet count $>30 \times 10^9/L$ is sufficient.



A When and How to Order Tests



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

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

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

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



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.

C Checking Identity of Patient

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

- When collecting a blood specimen:
 - Accurately label each specimen with patient's first and last names and unique identifier **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.



ATTENTION

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

ATTENTION

It is now considered best practice to employ electronic positive patient identification (e.g., barcode or radiofrequency tag) at the time of sample collection and unit transfusion²³

D 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

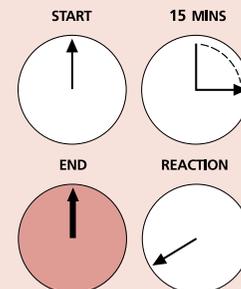
BLOOD COMPONENT/PRODUCT	IV ACCESS
Red blood cells – rapid transfusions in adults	16-18G (Gauge)
Red blood cells – routine transfusions in adults	20-22G
Other blood components/products	Any size is adequate
Pediatrics	22-25G
All components and products – adults and pediatrics	Central venous access devices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



Pediatrics^{19,21}
 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.

ATTENTION

Monitor patient closely for first 15 minutes.

D Monitoring & Infusion Practices (cont'd)

Transfuse

- Unless active hemorrhage, 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 hospital transfusion service.
- Consider a slower rate for patients at risk of circulatory overload and refer to prevention on page 57.
- 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.²⁴

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 specimens are taken near a site of IV infusion.
- Certain patients require irradiated products. Refer to page 67.

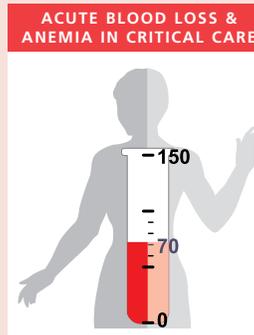
A T T E N T I O N

Record the order in the correct patient's chart or electronic record.

F Indications for RBCs

Acute blood loss

- Maintain **hemoglobin >70 g/L during active bleeding.**²⁵
 - ◆ 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.
- Liberal transfusion practices (**hemoglobin >90 g/L**) in the setting of gastrointestinal hemorrhage results in a higher rate of re-bleeding and mortality.²⁶
- It is unknown what the optimal transfusion threshold should be for patients with coronary artery disease and active bleeding.
 - ◆ A threshold of 80 g/L is non-inferior to 100 g/L in patients with acute myocardial infarction without bleeding.²⁷



F Indications for RBCs (cont'd)

Anemia in critical care and coronary care

- Consider a transfusion when the patient's hemoglobin is less than 70 g/L.²⁸
- Post-cardiac surgery, there is no benefit to a liberal transfusion strategy (when 75 g/L was compared to 95 g/L there was no difference in outcomes).²⁹
- In a patient with an acute coronary syndrome, threshold of 80 g/L results in similar outcomes to a threshold of 100 g/L.²⁷
- Unnecessary phlebotomy for laboratory testing is a major contributor to anemia in a critically ill patient.
- Recombinant erythropoietin reduces the risk of transfusion, but the impact on both mortality and thrombosis events is uncertain.^{30,31}
- The role of intravenous iron in the intensive care patient population has not been defined.^{32,33}

CHOOSE WISELY

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

ATTENTION

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 found to be as safe as a liberal transfusion strategy (95 g/L).³⁴
 - ◆ 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.

CHOOSE WISELY



Don't transfuse red blood cells for iron deficiency anemia in asymptomatic pediatric patients when there is no evidence of hemodynamic instability or active bleeding.

*American Society of Hematology - American Society of Pediatric Hematology/Oncology
<https://www.choosingwisely.org/clinician-lists/ash-aspho-avoid-packed-red-blood-cell-transfusions-for-anemia-in-asymptomatic-children/>



Pediatrics

Anemia in neonatal critical care

- Guidelines for the transfusion of neonates were published in 2016 by the British Committee for Standards in Haematology.³⁵
- Attention must be drawn to phlebotomy for laboratory testing since it is a significant cause of anemia in neonates.³⁶
- A restrictive practice results in similar outcomes for premature neonates.³⁷
- Suggested hemoglobin thresholds:

POST-NATAL AGE	RESPIRATORY SUPPORT	NO RESPIRATORY SUPPORT
1 week	110 g/L	100 g/L
2 weeks	100 g/L	85 g/L
≤ 3 Weeks	85 g/L	70 g/L

- Delayed cord clamping in premature neonates reduces morbidity including risk of transfusion.³⁸

F Indications for RBCs (cont'd)

Perioperative patients

- Manage patients undergoing elective surgery preoperatively, intraoperatively, and postoperatively with strategies to minimize the need for RBCs⁴ (see pages 80-95).
- Administer RBCs one unit at a time in non-urgent settings.³
- Assess patient prior to transfusing additional units (clinical exam and hemoglobin level).³
- 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.³⁹
- For patients undergoing cardiac surgery, a threshold of 75 g/L is non-inferior to a threshold of 95 g/L.²⁹
- 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.

ATTENTION

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.
<50 g/L	<p>Transfusion recommended^{3,40}</p> <ul style="list-style-type: none"> ◆ Young patients with low risk of ischemic cardiovascular disease can sometimes tolerate greater degrees of anemia. ◆ Patients with chronic iron deficiency should be managed with IV or PO iron alone. (PO iron works very well in children with iron deficiency anemia and hemoglobin level as low as 30 g/L in the absence of concerning symptoms of anemia and assurance of reliable follow-up.)

Chronic anemia^{41,42}

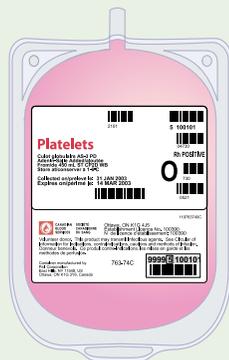
- Administer transfusions only when alternatives do not exist or have failed.⁴
- Administer RBCs at intervals to maintain the hemoglobin just above the lowest concentration that is not associated with symptoms of anemia.²⁵
- Patients at risk of iron overload (those on regular transfusions every three months or less) should be assessed for iron overload and complications of iron overload as part of their annual review.⁴³
- Chelation therapy should be considered in patients who are iron-overloaded, transfusion dependent, and who have a life expectancy of more than one year.
 - ◆ Chelation therapy should also be considered in non-transfusion dependent thalassemia patients who are iron overloaded. Screening by MRI when ferritin is higher than 300 ug/L.⁴⁴
- 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 at a minimum of every 3 months: tissue iron overload is likely if ferritin >1,000 ug/L and transferrin saturation >50%.⁴⁵
- Monitoring for end-organ damage from iron overload should be performed at baseline and repeated as per guidelines.⁴³
- 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 4 forms:

- ◆ Pathogen-reduced pool derived from 7 units of buffy coat platelets split in half.
- ◆ Pool of 4 units of buffy coat derived platelets (pools of 5 in Quebec).
- ◆ Single donor (collected by apheresis: non-pathogen-reduced).
- ◆ HLA selected 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 $10 \times 10^9/L$.^{14,15,46}
- In Canada, all non-pathogen-reduced 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.⁴⁷



CHOOSE WISELY

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

DOSE



A pooled pathogen-reduced platelet has a yield of 251 ± 32 ($\times 10E^9$) platelets/unit.



An Apheresis Platelet, has a yield of 333 ± 34 ($\times 10E^9$) platelets/unit.

B Monitoring & Infusion Practices

How

- Buffy coat derived pooled platelets from multiple donors or single donor apheresis platelets are supplied and considered equivalent.
- Platelets must be transfused through a blood administration filter (170-260 microns).
- Fresh blood administration filter preferred.
- Platelets are compatible **ONLY** with normal saline.
- Platelets can be infused through some blood warming device (licensed by Health Canada).⁴⁸

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 patients of childbearing potential require Rh immunoglobulin (RhIG) when Rh-positive platelets are transfused to avoid formation of anti-D antibody.
 - ◆ Each platelet unit contains less than 10×10^8 red blood cells.
 - ◆ 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.⁴⁹

Storage

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

ATTENTION

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



Pediatrics

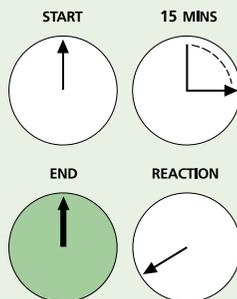
Dose: ^{50,51}

- Children and neonates: 8 mL/kg up to a maximum of 1 pool of pathogen-reduced buffy-coat platelets (10 mL/kg for all other platelet products).

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 x 10⁹/L.⁵²



ATTENTION
Monitor patient closely for first 15 minutes.

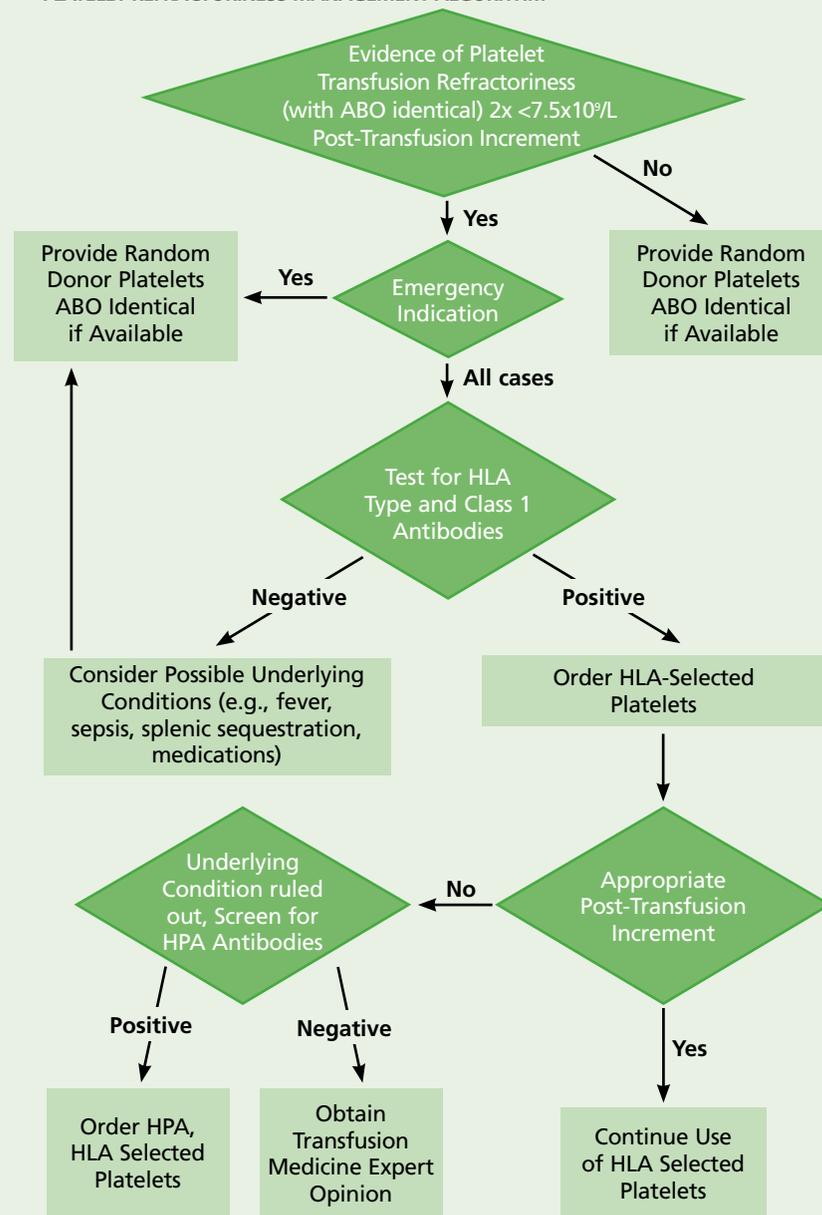
Transfuse

- 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 (<60 minutes) after infusion if patient suspected to be refractory (poor increments at 24 hours) to ensure adequate replacement and recognition of platelet refractoriness.⁵³
 - A platelet increment of <7.5 x 10⁹/L suggests refractoriness and requires investigation.⁵²
- If increments in platelet count are NOT adequate, special measures are required. Refer to the algorithm on page 31.

PLATELET REFRACTORINESS MANAGEMENT ALGORITHM^{5,54}



HLA – Human Leukocyte Antigen
HPA – Human Platelet Antigen

Indications & Infusion Recommendations

PLT (x 10 ⁹ /L)	CLINICAL SETTING	SUGGEST
<10	Non-immune thrombocytopenia	Transfuse 1 pool of platelets ¹⁵
<10	Non-immune thrombocytopenia & HLA-alloimmunized	Transfuse 1 unit of HLA selected platelets ¹⁶
<20	Low risk procedures (e.g., central line placement, lumbar puncture, paracentesis)	Transfuse 1 pool of platelets ¹⁷
<30	High risk procedures in patients with cirrhosis	Transfuse 1 pool of platelets ¹⁷
<30	Patient on anticoagulants that should not be stopped	Transfuse 1 pool of platelets ^{5,55}
<50	Procedures associated with blood loss or major surgery (>500 mL expected blood loss)	Transfuse 1 pool immediately before procedure ^{14,17,55}
<50	Immune thrombocytopenia	Transfuse platelets only with life-threatening bleeding ⁵⁶
<50-80	Epidural anesthesia	Transfuse 1 pool of platelets ^{57,58}
<100	Pre-neurosurgery or head trauma	Transfuse 1 pool of platelets ^{55,59}
Any	Platelet dysfunction and marked bleeding (e.g., post cardiopulmonary bypass). Exception: Transfusing platelets for intracranial hemorrhage (ICH) not requiring surgical management in patients on antiplatelet agents leads to increased morbidity	Transfuse 1 pool of platelets ^{14,60}

ATTENTION

The transfusion of platelets to non-operative patients with ICH on ASA/clopidogrel increases the risk of disability at 3 months.⁶⁰



Pediatrics – Platelet Transfusion Guidelines for Neonates

PLATELET COUNT (x 10 ⁹ /L)	CLINICAL INDICATION	DOSE
<25	Stable, non-bleeding ^{35,61,62}	8 mL/kg up to a maximum of 1 pool of pathogen reduced buffy-coat platelets (10 mL/kg for all other platelet products).
<30	Neonatal Alloimmune Thrombocytopenia without severe bleeding ⁶³	8 mL/kg up to a maximum of 1 pool of pathogen reduced buffy-coat platelets (10 mL/kg for all other platelet products).
<50	Bleeding, pre-surgery, coagulopathy ³⁵	8 mL/kg up to a maximum of 1 pool of pathogen reduced buffy-coat platelets (10 mL/kg for all other platelet products).
<50	Neonatal allo-immune thrombocytopenia with intracranial hemorrhage and/or previously affected sibling with ICH ⁶³	8 mL/kg up to a maximum of 1 pool of pathogen reduced buffy-coat platelets (10 mL/kg for all other platelet products) (raise to 100 and maintain over 50).
<100	Major bleeding, neuraxial or ocular surgery ³⁵	8 mL/kg up to a maximum of 1 pool of pathogen reduced buffy-coat platelets (10 mL/kg for all other platelet products).

CHOOSE WISELY

Don't transfuse platelets in the following situations:

- ◆ Platelet count above 10 x 10⁹/L with no bleeding in anticipation of a drop to less than 10 x 10⁹/L
- ◆ For patients with ITP without major hemorrhage, even when platelet count <10 x 10⁹/L
- ◆ For patients undergoing procedures more than 6 hours later (give as close to procedure as feasible)
- ◆ For minor procedures with platelet counts >20 x 10⁹/L (e.g., paracentesis or thoracentesis)

CHOOSE WISELY



ASH-ASPO 2019 CWC Pediatrics*

Don't transfuse platelets in an asymptomatic (i.e., non-bleeding) pediatric patient (e.g., aplastic anemia, leukemia, etc.), with a platelet count > 10x10⁹/L unless other signs and/or symptoms for bleeding are present, or if the patient is to undergo an invasive procedure.

*American Society of Hematology - American Society of Pediatric Hematology/Oncology <https://www.choosingwisely.org/clinician-lists/ash-aspho-avoid-packed-red-blood-cell-transfusions-for-anemia-in-asymptomatic-children/>

A Basics⁶⁴

- Frozen plasma can be derived from two sources:
 - ◆ Whole blood donor plasma (290 mL)
 - ◆ Apheresis donors (250 mL)



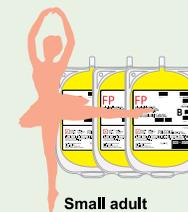
Notes:

- Frozen Plasma (FP) and Apheresis Frozen Plasma (AFP) are 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).
- Do not use FP or FFPA to replace fibrinogen when other coagulation factors are sufficient.⁶⁵

B Monitoring & Infusion Practices

How

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



Small adult

Dose⁶⁶

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



Large adult

When

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

Storage

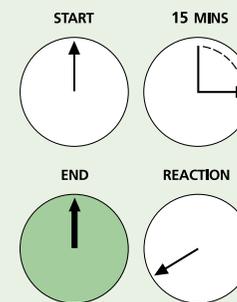
- Plasma is kept *frozen* for up to one year.
 - ◆ Once thawed, plasma can be stored at 1-6 °C for 5 days.
- After issue, plasma should be administered within 4 hours.
 - ◆ The biological half-life of plasma coagulation proteins is different for each protein:⁶⁷
 - 3-6 hours for factor VII
 - 8-12 hours 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.
- The PT/INR should be checked after infusion (<60 minutes) routinely.

ATTENTION

Half-life of plasma 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 Plasma

To determine if plasma 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 *Bloody Easy Coagulation Simplified, Second Edition*⁶⁸ 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., Plasma 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 often best managed with strategies other than plasma.
- Patients on anticoagulants are never appropriately managed with plasma.⁶⁸

1. Bleeding or prior to a significant operative procedure in patients INR ≥1.8 due to multiple factor deficiency when no coagulation factor concentrates or other alternative therapies are available.⁶⁹

- ◆ Repeat INR after infusion of plasma to ensure replacement is adequate.

ATTENTION

Plasma 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

Plasma is NOT indicated or effective for reversal of heparin, low molecular weight heparin, or direct oral anticoagulants

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
- ◆ Direct oral anticoagulant reversal
- ◆ High aPTT with normal INR

Note: 70,71,72,73

- 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 (5-10 mg i.v.) should also be given. See page 122 in this guide.
- For non-emergent reversal of warfarin or vitamin K deficiency, vitamin K alone should be used.
 - ◆ 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 Vitamin K is NOT recommended due to variable absorption: intravenous formulation can be used orally when required.



Pediatrics⁷⁴

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 Plasma (cont'd)

- 2. Microvascular bleeding or massive transfusion AND patient's clinical status precludes waiting 30-45 minutes for INR results.¹⁸
- 3. Thrombotic thrombocytopenic purpura.

ATTENTION

Ratio based replacement (i.e., 2:1 RBC:FP) with FP not indicated unless the massive hemorrhage protocol has been activated

INR	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 (see Transfusion Basics E, page 16)
Results not immediately available	Massive hemorrhage protocol activated AND patient's clinical status precludes waiting 30-45 minutes for INR/PT/PTT results
Any	Thrombotic thrombocytopenic purpura (TTP)

Solvent Detergent Treated Plasma (SD Plasma*):^{75,76,77}

- Pathogen reduced pooled plasma:
 - ◆ Effective against lipid-enveloped viruses.
 - ◆ Relatively ineffective against non-lipid-enveloped viruses (e.g., hepatitis A and parvovirus B19).
- Unit volume 200mL, groups O, A, B, AB.
- Labelled indications are detailed in the Octaplasma Product Monograph.⁷⁸

- Current funded indications include:
 1. Patients who require a high volume or chronic plasma transfusions (primary qualifier) because they have:
 - a) Congenital TTP or,
 - b) A need for plasmapheresis with plasma as a replacement fluid for conditions such as (but not limited to) acquired TTP and hemolytic uremic syndrome or,
 - c) Clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI).

AND who have one of the following secondary qualifiers:

- ◆ Have experienced a recurrent clinically significant allergic reaction to plasma.
 - ◆ Have an existing lung disorder that would make them more susceptible to effects of Transfusion-Related Acute Lung Injury (TRALI) reaction.
2. Any patient who requires plasma but a blood group compatible product is not available in a timely manner.
 3. Patients who have had a previous life-threatening reaction to plasma that could be avoided by the use of SD plasma, where no alternative therapies are available.
- Currently requests for SD plasma should be directed to CBS** and:
 - ◆ should be reviewed by a transfusion specialist prior to submission.
 - ◆ are subject to an approval process by CBS.

*Octaplasma™, Octapharma AG.

** HQ uses similar indications for prescribing SD plasma and can assist in the process for screening orders in Quebec.

RISK OF EVENT	EVENT
1 in 13	Red cell sensitization, increasing risk of hemolytic transfusion reaction and hemolytic disease of the fetus and newborn ⁷⁹
1 in 100	Febrile non-hemolytic transfusion reaction per pool of platelets ^{80,81,82}
1 in 100	Transfusion-associated circulatory overload per transfusion episode ⁸³
1 in 100	Minor allergic reactions (urticaria)
1 in 300	Febrile non-hemolytic transfusion reaction per unit of RBC
1 in 2,500	Delayed hemolytic transfusion reaction per patient transfused ⁸⁴
1 in 10,000	Transfusion-related acute lung injury (TRALI)
1 in 10,000	Symptomatic bacterial sepsis per pool of non-pathogen reduced platelets ⁸⁵
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 non-pathogen reduced platelets
1 in 250,000	Symptomatic bacterial sepsis per unit of RBC
1 in 354,000	ABO-incompatible transfusion per RBC transfusion episode ⁸⁶
1 in 500,000	Death from bacterial sepsis per unit of RBC
<1 in 1,000,000	Transmission of West Nile Virus
1 in 2,000,000	Residual risk of hepatitis B per unit ⁸⁷
1 in 4,000,000	Transmission of Chagas disease per unit
1 in 12,900,000	Residual risk of human immunodeficiency virus (HIV) per unit ⁸⁷
1 in 27,100,000	Residual risk of hepatitis C per unit ⁸⁷
<1 in 1,000,000,000	Transmission of HTLV per unit ⁸⁸

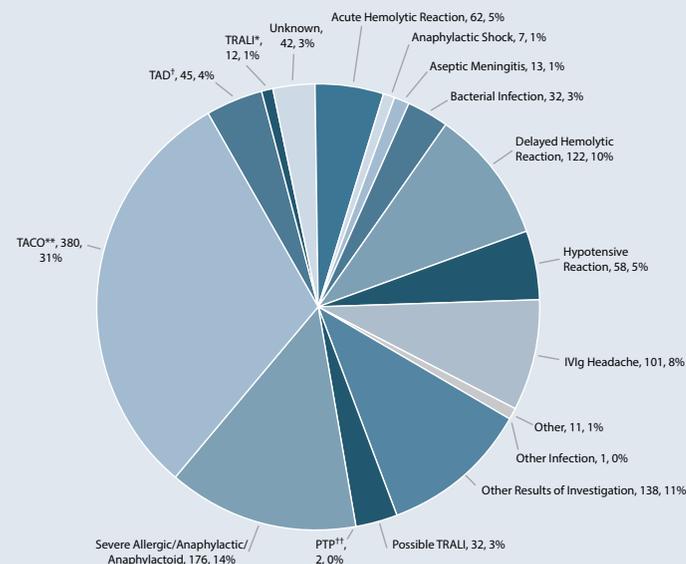
* All of these risk frequencies are likely to have quite wide confidence intervals.

Refer to HQ Circular of Information for residual risk for transfusion-transmitted infections in Quebec not in chart.

Risk of death per 1 unit component
(likely an under-estimate due to data from passive hemovigilance systems).

- 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) 2020.
 - ♦ 1 in 53,191 components issued possibly, probably or definitely related to patient death.⁸⁹
- United States (Food and Drug Administration) 2019.
 - ♦ 1 in 400,000 components transfused resulted in a death from transfusion possibly, probably or definitely.⁹⁰
 - ♦ Transfusion-associated circulatory overload was the most common cause of death from transfusion in 2019.

TRANSFUSION TRANSMITTED INJURIES SURVEILLANCE SYSTEM (TTISS), ONTARIO.
Major Adverse Events Reported 2013-2020.⁹¹



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

A Reporting

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

A T T E N T I O N
Report all transfusion reactions to your hospital's transfusion service.

What

- The hospital transfusion service 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.
- If the reaction was attributable to an activity at the hospital that affected the safety or efficacy of the component, it must be reported to the Canada Vigilance Program (as required by the Health Canada Blood Regulations).

A T T E N T I O N
All serious adverse drug reactions to fractionated products (e.g., IVIG, albumin) that result in:

in-patient hospitalization or prolongation of hospitalization, congenital malformation, persistent or significant disability or incapacity, is life-threatening, or results in death.

Must be reported to Health Canada within 30 calendar days

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, PHAC, or Canada Vigilance Program.

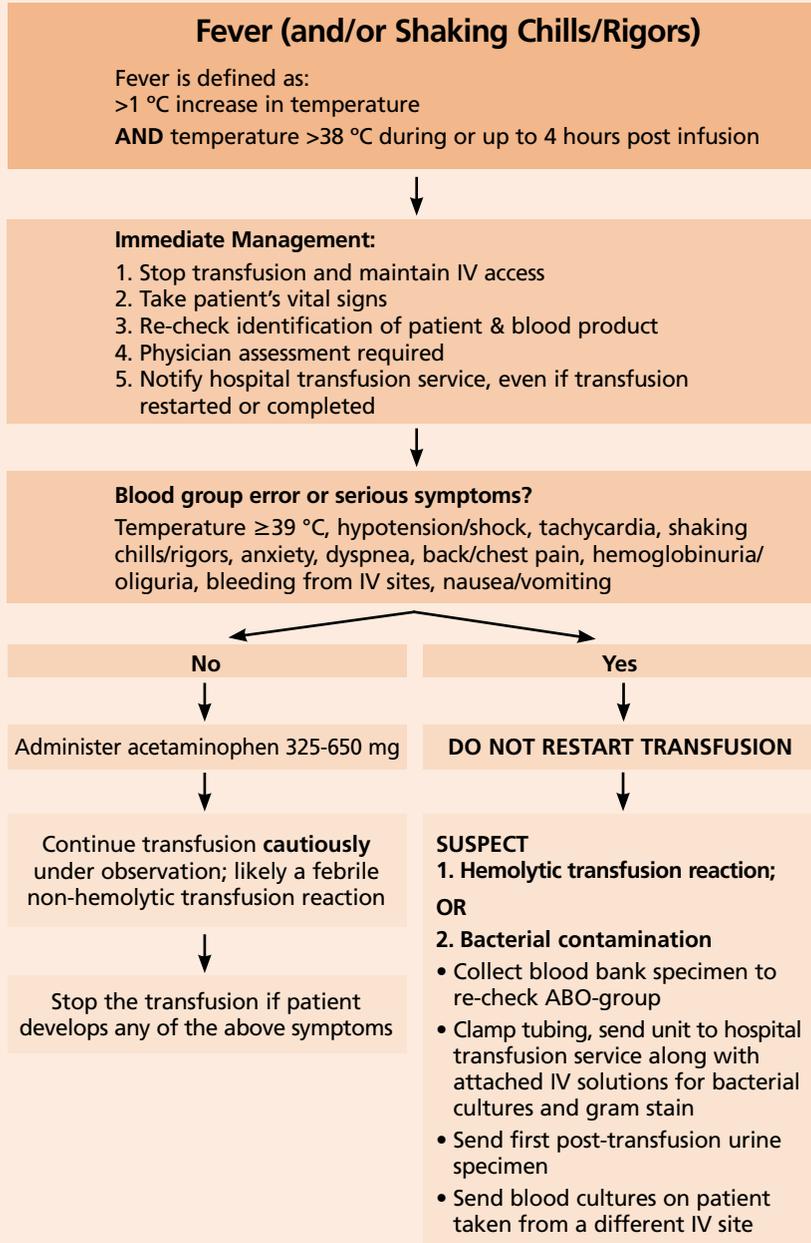
* <https://www.canada.ca/en/public-health/services/surveillance/blood-safety-contribution-program.html>

B Reaction by Symptom

SYMPTOM	CONSIDER	PAGE
Fever	Management Algorithm	44
	Possible Reactions:	
	◆ Bacterial sepsis or contamination	45
	◆ Acute hemolytic transfusion reaction	47
	◆ Febrile non-hemolytic transfusion reaction (FNHTR)	50
Dyspnea	Management Algorithm	51
	Possible Reactions:	
	◆ Transfusion-related acute lung injury (TRALI)	52
	◆ Transfusion-associated circulatory overload (TACO)	56
Urticaria & Other Allergic Reactions/ Anaphylaxis	Management Algorithm	58
	Possible Reactions:	
	◆ Anaphylaxis	59
	◆ Minor allergic reaction – Urticaria	61
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	Possible Reactions:	
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	◆ Acute hemolytic transfusion reaction	64
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Cytopenias After Transfusion	Possible Reactions:	
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Virus, Parasite and Prion Infections	◆ Viruses	70
	◆ Parasites	71
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Fever

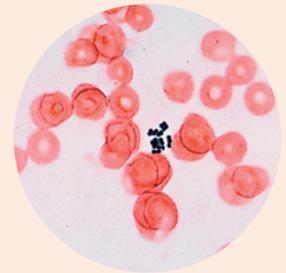
MANAGEMENT ALGORITHM



BACTERIAL SEPSIS OR CONTAMINATION

ETIOLOGY⁹²

- 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:
 - ♦ With the introduction of routine bacterial detection in platelet products, the vast majority of residual contamination is attributable to gram-positive organisms.⁸⁵
 - ♦ A number of bacteria have been implicated, including:⁹²



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

Gram-positive	Gram-negative
Bacillus species ^a	Klebsiella species
Streptococcus species	Serratia species ^a
Staphylococcus species ^a	Escherichia coli ^a
Propionibacterium acnes	Acinetobacter species
	Enterobacter species
	Providencia rettgeri
	Yersinia enterocolitica

^aSome of which are biofilm-producing species.

INCIDENCE^{85,93,94,95,96,97}

	BACTERIAL CONTAMINATION	SYMPTOMATIC SEPTIC REACTIONS	FATAL BACTERIAL SEPSIS
Non-pathogen reduced platelet unit	1 in 2,500	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.⁹⁸
- Bacterial sepsis occurs most frequently with platelets due to their storage at 20-24 °C for preservation of function.

CLINICAL PRESENTATION

- Clinical features of transfusion-associated sepsis may include:^{96,99}
 - ◆ 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.⁸⁵

MANAGEMENT^{97,99}

- If transfusion-transmitted bacterial infection is suspected:
 - ◆ **Stop the transfusion!**
 - ◆ **Notify the hospital transfusion service**
 - Hospital transfusion service 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).
- Pathogen reduced platelets were implemented in 2022 by CBS to reduce the risk of bacterial contamination.¹⁰⁰
- Apheresis and buffy coat non-pathogen reduced platelets are cultured by CBS/HQ prior to issue to hospitals.
- RBCs are stored at 1-6 °C in a monitored hospital transfusion service 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 36 blood group systems and 360 known blood group antigens that may cause incompatibility.¹⁰¹
 - ◆ Rare cases where group O platelets are transfused to a non-group O recipient, due to anti-A and anti-B in the residual plasma.
 - ◆ Implementation of platelet additive solution by CBS in 2022 may reduce the risk of ABO-hemolysis from platelet transfusion by reducing the volume of plasma in every unit.
- **ABO-incompatibility:**
 - ◆ Is due to a clerical error or the result of improper patient identification/labelling of specimens or testing error.
 - ◆ HALF of all errors are due to administering properly labelled blood to the wrong patient.¹⁰²

RBC alloantibodies (non-ABO):

- ◆ Result from patient immunization from a prior pregnancy, transfusion or IV drug abuse needle sharing.
- ◆ 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 3,046 in “wrong blood in tube” with manual/verbal patient identification and 1 in 14,606 with use of electronic positive patient identification (ePPID)* with potential for mis-transfusion.²³
- Near-miss events 79x more common than actual ABO incompatible transfusions.⁸⁹
- 1 in 64,806 transfusions given to the wrong patient before use of ePPID and 1 in 304,134 after ePPID introduced.¹⁰³
- 1 in 7.14 million RBC units transfused leads to death from ABO-incompatibility.⁸⁶

CLINICAL PRESENTATION¹⁰⁴

- 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.
- 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).
- **ePPID decreases the risk of blood collection errors**²³

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:¹⁰⁵
 - ◆ 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^{106,107,108,109}

	INCIDENCE
RBC	1 in 300
Non-pathogen reduced platelet	1 in 100
Pathogen-reduced platelet	1 in 200

CLINICAL PRESENTATION

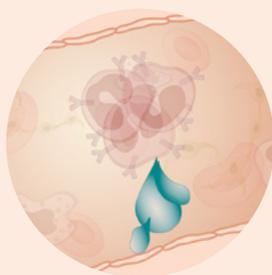
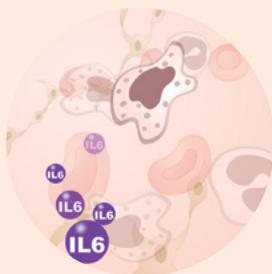
- Fever usually occurs during or up to 4 hours post transfusion.
 - ◆ May be associated with chills, rigors, nausea, vomiting and hypotension.
- Fever is not always present (i.e., only symptom is chills, nausea, etc., alone).

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 reduce FNHTR or allergic reactions.¹¹⁰
- 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 RBCs (washing platelets results in 50% loss of platelets).



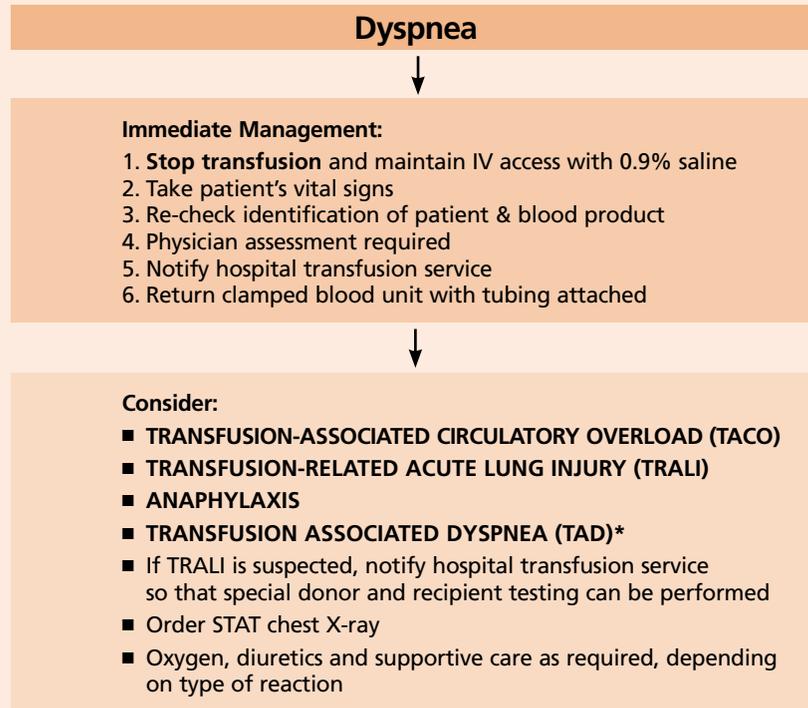
A T T E N T I O N
 Fever is **not** a contraindication to commencing a blood transfusion!

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



*TAD is characterized by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should be the most prominent clinical feature and should not be explained by the patient's underlying condition or any other known cause.¹¹¹

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

DEFINITION OF TRALI ¹¹²

- TRALI Type I - Patients who have no risk factors for ARDS and meet the following criteria:
 - a. i. Acute onset
 - ii. Hypoxemia (P/F \leq 300* or SpO₂ < 90% on room air)
 - iii. Clear evidence of bilateral pulmonary edema on imaging (e.g., chest radiograph, chest CT, or ultrasound)
 - iv. No evidence of left atrial hypertension (LAH)[†] or, if LAH is present, it is judged to not be the main contributor to the hypoxemia
- b. Onset during or within 6 hr of transfusion[‡]
- c. No temporal relationship to an alternative risk factor for acute respiratory distress syndrome (ARDS).

- TRALI Type II - Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F of 200-300), but whose respiratory status deteriorates[§] and is judged to be due to transfusion based on:
 - a. Findings as described in categories *a and b* of TRALI Type I, and
 - b. Stable respiratory status in the 12 hr before transfusion.

ARDS RISK FACTORS ACCORDING TO THE BERLIN DEFINITION ¹¹²

*(with slight modification due to consideration of the transfusion setting)**

- Direct
 - ♦ Pneumonia
 - ♦ Aspiration of gastric contents
 - ♦ Inhalational injury
 - ♦ Pulmonary contusion
 - ♦ Pulmonary vasculitis
 - ♦ Drowning
- Indirect
 - ♦ Nonpulmonary sepsis
 - ♦ Major trauma[†]
 - ♦ Pancreatitis
 - ♦ Severe burns
 - ♦ Noncardiogenic shock
 - ♦ Drug overdose

* Multiple (massive) transfusion is included in the Berlin definition of ARDS risk factors; however, we have removed it from this list because we recommend that ARDS occurring during or within 6 hours after multiple transfusions be classified as TRALI, provided no other ARDS risk factors (as listed in this table) are present. One example of a case scenario of multiple (massive) transfusion that fits the criteria for TRALI Type I is acute gastrointestinal bleeding without trauma or any other ARDS risk factors.

[†] Major trauma is defined as multiple fractures (two or more major long bones, an unstable pelvic fracture, or one major long bone and a major pelvic fracture). An alternate definition proposed by the Panel is an injury severity score of greater than 15.

* If altitude is higher than 1000 m, the correction factor should be calculated as follows: [(P/F) x (barometric pressure/760)]. P/F = PaO₂/FiO₂
[†] Use objective evaluation when left atrial hypertension (LAH) is suspected (imaging, e.g., echocardiography, or invasive measurement using, e.g., pulmonary artery catheter).
[‡] Onset of pulmonary symptoms (e.g., hypoxemia-lower P/F ratio or SpO₂) should be within 6 hours of end of transfusion. The additional findings needed to diagnose TRALI (pulmonary edema on a lung imaging study and determination of lack of substantial LAH) would ideally be available at the same time but could be documented up to 24 hours after TRALI onset.
[§] Use P/F ratio deterioration along with other respiratory parameters and clinical judgment to determine progression from mild to moderate or severe ARDS.

ETIOLOGY

- Presently not fully defined. Two postulated mechanisms have been implicated:¹¹³
 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).^{114,115}
 - 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.¹¹⁶



INCIDENCE

- True incidence of this syndrome is unknown; Incidence in published reports ranges from 1 in 1,333–270,000 per unit transfused.¹¹⁷
- The incidence of TRALI has decreased with the use of predominantly male plasma (RR 0.27, 95% CI 0.20-0.38; p< 0.001).¹¹⁸
- TRALI is known to be substantially 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 IVIG).
- Almost always within the first 1-2 hours after the start of transfusion but can be delayed for up to 6 hours.¹¹⁴
- 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.¹⁰⁴
- Milder forms of TRALI are thought to exist and may present as transient hypoxia.¹¹⁹
- Acute transient leukopenia may be observed after a TRALI reaction.¹²⁰

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.¹²¹
- 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:
 - ◆ RBC with minimal residual plasma
 - ◆ Plasma for transfusion only from male donors
 - ◆ Platelet pools suspended in male plasma
 - ◆ Plateletpheresis collected from male donors or never pregnant females
 - ◆ Platelets in platelet additive solution
- 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) ¹²²

ETIOLOGY

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

INCIDENCE

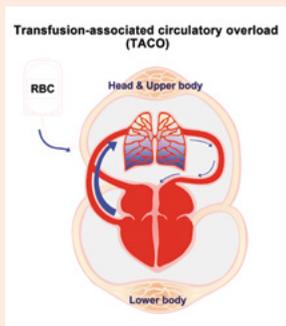
- Current estimate of the frequency of TACO ranges from 1 in 700 to 8% of transfusion recipients influenced by predisposing conditions.¹²³
- Patients over 70 years of age, infants, and patients with severe euvolemic anemia (hemoglobin <50 g/L), renal impairment, fluid overload, and cardiac dysfunction are particularly susceptible.

CLINICAL PRESENTATION

- Clinical presentation includes: dyspnea, orthopnea, cyanosis, tachycardia, increased venous pressure, and hypertension.
- May present with fever which should be investigated; fever does not exclude TACO if definition below met.

DEFINITION

- Acute or worsening respiratory compromise and/or evidence of pulmonary edema (A and/or B below) during or up to 12 hours after transfusion and presence of at least three of the below criteria:
 - A. Acute or worsening respiratory compromise
 - B. Evidence of acute or worsening pulmonary edema based on physical examination and/or chest imaging or other non-invasive assessment (e.g., echo)
 - C. Evidence for cardiovascular system changes not explained by the patient's underlying medical condition including tachycardia, hypertension, widened pulse pressure, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema



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

Transfusion-associated circulatory overload (TACO) surveillance case definition (2018) ¹²⁴

Acute or worsening respiratory compromise and/or evidence of pulmonary edema during or up to 12 hours after transfusion

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

- D. Evidence of fluid overload (e.g., positive fluid balance, response to diuretics, change in patient's weight)
- E. Elevated biomarker (BNP or NT-pro BNP) above the age group-specific reference range and greater than 1.5 times the pre-transfusion value.

MANAGEMENT

- Interrupt the transfusion.
- Administer oxygen and diuretics as needed.
- Measure cardiac biomarkers (NT-pro-BNP or BNP).
- Chest x-ray.
- Consider restarting transfusion at a reduced infusion rate if clinical status allows and product still viable.

PREVENTION

- Pre-transfusion assessment is important to identify patients at risk and management should be adjusted accordingly.
- The following have been hypothesized to reduce TACO but are unproven¹²⁵
 - ◆ Restrictive transfusion practice
 - ◆ Transfusing one RBC unit at a time
 - ◆ Slowing rate of transfusion
 - ◆ Transfusing split RBC units
 - ◆ Washing RBC units
 - ◆ Pre-transfusion diuretics
 - ◆ Volume reduced products

A T T E N T I O N

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

A T T E N T I O N

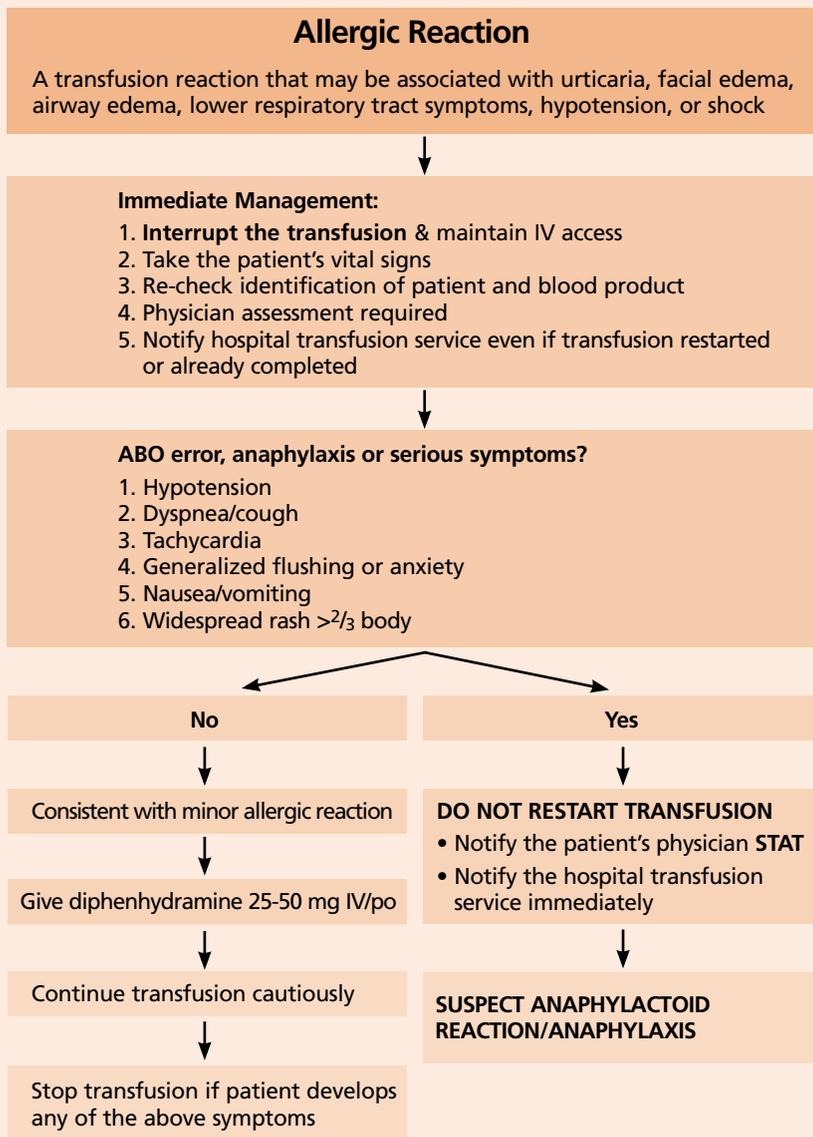
In patients at risk, avoid transfusing more than one unit at a time.

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

ETIOLOGY¹²⁶

- 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 to cause anaphylactic transfusion reaction (reasons are not clear at this time).¹²⁷
 - ◆ 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 entity¹²⁸
- Haptoglobin deficiency is not uncommon in Asian patients (1 in 1,000) and has been associated with anaphylactic reactions.¹²⁹

INCIDENCE

- Transfusion-associated anaphylactic shock is rare.¹³⁰
- Anaphylaxis accounts for approximately 10% of transfusion associated fatalities.⁹⁰

CLINICAL PRESENTATION¹³¹

- 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 who had an anaphylactic reaction, the following products are recommended:
 - ◆ IgA-deficient blood products from IgA deficient donors, available from CBS/HQ
 - ◆ Washed RBCs or platelets.¹³²

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.¹³³

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, or other antihistamine.
- **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

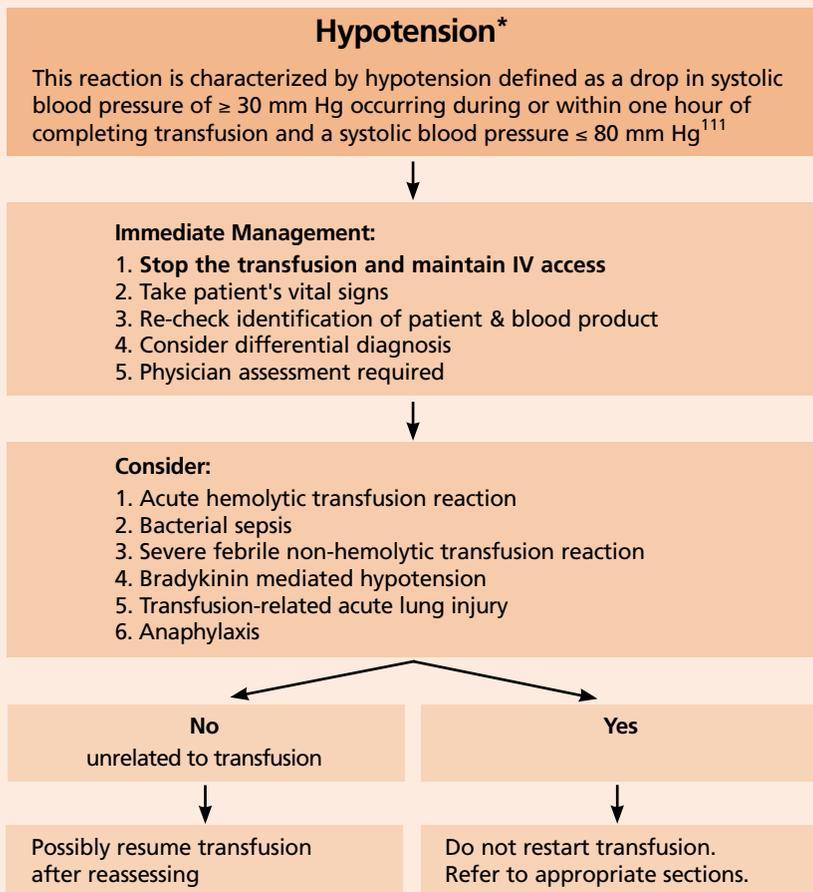
- If the urticarial reactions are recurrent, the following precautionary measures may be used although their efficacy is unknown:
 - ◆ Pre-medication with diphenhydramine and/or corticosteroids
 - ◆ Plasma depletion of RBCs or platelets
 - ◆ Washed RBCs or platelets

A T T E N T I O N

Interrupt transfusion. Give diphenhydramine. Restart transfusion slowly.

Hypotension¹³⁴

MANAGEMENT ALGORITHM



Pediatrics¹³⁵

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

- 3.2 for 100,000 blood units transfused.¹³⁶

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 may be 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 or technical limitations of the assay.
- Commonly implicated antigens are (in order of frequency): E, Jk_a, c, Fy_a, K.¹³⁷
- 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.⁷⁹
- 1 in 2,500 units of RBCs transfused are associated with a delayed hemolytic transfusion reaction.⁸⁴

CLINICAL PRESENTATION^{135,138}

- 24 hours to 28 days 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).

COMPLICATIONS

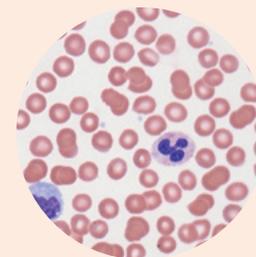
- Most are benign, but life-threatening hemolysis with severe anemia and renal failure may occur.

TREATMENT

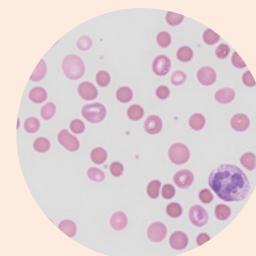
- Transfuse compatible blood ('antigen negative'; i.e., if the offending antibody is anti-Jk^a, then the hospital transfusion service will provide units that do not carry the Jk^a antigen).

PREVENTION

- Avoid RBC transfusions.
- Use of antibody screening methods with maximal sensitivity.
- Regional electronic registry of alloimmunized patients should be used to minimize the risk of delayed hemolytic transfusion reactions.¹³⁹
- Notify patient and provide an antibody card for the patient to carry in their wallet.
- For females of child-bearing potential, matching for Kell (K) reduces the incidence of K-immunized pregnancies from 68 to 20 per 100,000 and except in emergency situations, this is now current practice in Canada.¹⁴⁰



Normal Blood Film



Spherocytes

Normal blood film and spherocytes pictures reproduced with permission, courtesy of Dr. David Good, Kingston Health Sciences Centre.

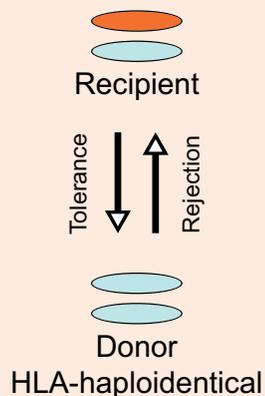
Antibody Card	
Blood Bank:	Date: June 11, 2011
Name: Mary Bloodworthy	Date of Birth: Oct 25, 1981 Hospital File # 1175380
ABO/Rh: O NEG	
Special Requirements:	ANTIBODY (IES) ANTI-E

Cytopenias After Transfusion

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GvHD)^{141,142}

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.)^{143,144}
 - ◆ 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

- 1 in 25,439,401 transfusions⁸⁹

CLINICAL PRESENTATION

- Fever, rash, liver dysfunction, and diarrhea commencing 2 days to 6 weeks post-transfusion followed by pancytopenia later.¹³⁵
- Overwhelming infections are the most common cause of death.
- Mortality is >90%.¹⁴⁴
- 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) or provide pathogen-reduced 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.^{145,146}

PATIENTS REQUIRING IRRADIATED BLOOD¹⁴⁷

- ◆ First and second degree family members or HLA-selected donors.
- ◆ Intra-uterine or neonatal exchange transfusion.
- ◆ Congenital T-cell immunodeficiency.
- ◆ Autologous stem cell transplant recipients from 7 days prior to stem cell collection to 3 months post-transplant (6 months if total body irradiation is part of the conditioning regimen).
- ◆ Allogeneic stem cell transplant from initiation of conditioning regimen and continued until over 6 months post-transplant and lymphocyte count >1x10⁹/L and patient free of chronic GvHD and off all immunosuppressive agents (otherwise continue indefinitely).
- ◆ CAR-T cell infusion from 7 days prior to collection and for 3 months after infusion.
- ◆ All patients with Hodgkin's Disease.
- ◆ Certain therapeutics in select patient populations (see box to right).

ATTENTION

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

Alemtuzumab (anti-CD52)
Anti-thymocyte globulin (ATG)
Bendamustine
Cladribine (2-CDA)
Clofarabine
Deoxycoformicin
Fludarabine
Nelarabine

Special Needs Card	
Blood Bank	Date: June 11, 2011
Name: Mary Bloodworthy	Date of Birth: Oct 25, 1981 Hospital File # 1175380
ABO/Rh: O NEG	
Special Requirements:	REQUIRES IRRADIATED PRODUCTS

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

POST-TRANSFUSION PURPURA (PTP)^{148,149}

ETIOLOGY

- Transfusion of platelet antigen-positive RBCs, plasma, or platelets to a patient who lacks the same platelet antigen.
 - ◆ Antibodies to HPA-1a, HPA-1b, and HPA-5b account for 60% of antibodies.
- 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 2012.¹⁵⁰

CLINICAL PRESENTATION

- There are 5 times as many female transfusion recipients with PTP as males, as a consequence of sensitization in a previous pregnancy.
- Usually presents 5-12 days post-transfusion.¹³⁵
- 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.

- Corticosteroids are often employed, but effectiveness unknown.
- Platelet transfusions (even if matched for the HPA antibody) are rarely effective and should only be administered for life-threatening bleeding.

PREVENTION

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

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.¹⁵¹

TRANSFUSION-RELATED ALLOIMMUNE NEUTROPENIA¹⁵²

- 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:¹⁵³
 - ◆ 6 days for HIV
 - ◆ 3 days for HCV
 - ◆ 19 days for HBV
- Figures in chart below are risk per donor exposure: (i.e., 1 unit of RBC).^{87,88,154}



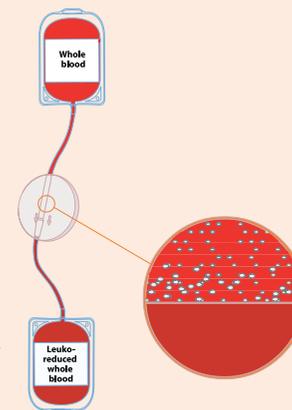
HIV Virus

West Nile Virus (WNV)	<1 in 1,000,000
Hepatitis B virus (HBV)	1 in 2,000,000
Human Immunodeficiency Virus (HIV)	1 in 12,900,000
Hepatitis C virus (HCV)	1 in 27,100,000
Human T-cell lymphotropic virus (HTLV)	<1 in 1,000,000,000

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 13,575,000.¹⁵⁵
- 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.¹⁵⁶

- CMV serology must be drawn before allogeneic transfusions commence, otherwise false positive results may be found due to passive antibody transfusion.
- The National Advisory Committee on Blood and Blood Products recommends the sole indication for CMV seronegative (in addition to leukoreduction) is for intrauterine transfusions.¹⁵⁷
- In addition, the Comité consultatif national de médecine transfusionnelle (CNNMT) recommends CMV seronegative granulocytes in recipients who are CMV seronegative.¹⁵⁸



West Nile Virus (WNV)

- No reported cases of transfusion transmitted WNV in Canada since nucleic acid testing of donations began in 2003.¹⁵⁹
- Facts about transfusion-transmitted WNV:
 - ◆ The virus can be transmitted through RBCs, platelets, and plasma, but not through manufactured blood products (e.g., albumin)
 - ◆ 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.

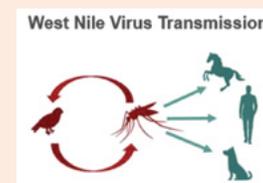


Image reprinted with permission. Source: O'Brien S. Surveillance Report 2020 [Internet]. Ottawa: Canadian Blood Services; 2020. Available from: Surveillance report | Professional Education (blood.ca)

PARASITES

Chagas Disease

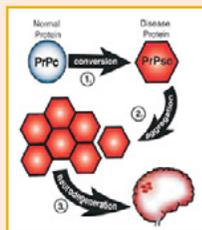
- Chagas Disease is caused by the protozoan *Trypanosoma cruzi* found predominantly in Central and South America.
- There have been 7 reported cases of transfusion transmitted Chagas in US and Canada, mostly with platelet products.¹⁶⁰
- Since May 2010, at risk donors in Canada are tested for Chagas Disease.
- The current risk of transfusion-transmission is estimated to be 1 in 4 million, based on U.S. data.¹⁶¹



PRIONS

Variant Creutzfeldt-Jakob Disease (vCJD)

- 4 suspected cases of transfusion-associated transmission have been reported in the U.K.¹⁶²
- 1 suspected case of transmission from U.K.-derived Factor VIII concentrate.¹⁶³
- At present, high risk blood donors (a cumulative total of 3 months or more in the U.K. between 1980 and 1996 or a cumulative total of 5 years or more in France and/or Ireland between 1980 and 2007) are deferred in Canada.



Public Health Agency of Canada

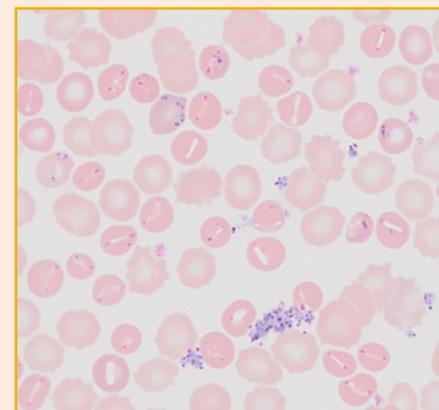
- It is extremely important to report cases of the above infections in transfusion recipients and recent blood donors.

OTHER TRANSFUSION-TRANSMISSIBLE AGENTS^{160,163,164,165}

- 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), Anaplasma (Anaplasmosis)



Blood film pictures "Anaplasmosis". Reproduced with permission, courtesy of Dr. David Good, Kingston Health Sciences Centre.



Blood film picture "Babesiosis". Reproduced with permission, courtesy of Dr. David Good, Kingston Health Sciences Centre.

Travel Deferrals

Protecting the blood from insect and food borne infections

 	<p>Dengue Chikungunya Zika</p>	<p>2 week deferral Any travel outside USA or Canada</p>
 	<p>Malaria</p>	<p>3 month deferral Travel to risk area 3 year deferral Living in risk area</p>
 	<p>Variant Creutzfeldt Jakob Disease</p>	<p>Indefinite deferral 3 months UK or France 1980 -1996 5 years in Western Europe 1980-2007 6 months Saudi Arabia 1980-1996</p>

Travel Deferrals. Reproduced with permission, courtesy of Dr. Sheila O'Brien, Canadian Blood Services.

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.¹⁶⁶

Complications¹⁶⁷

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

1. Coagulopathy

- 24% of trauma patients present with coagulopathy prior to transfusion and this acute traumatic coagulopathy is associated with higher mortality rates.¹⁶⁸
- Number of RBCs transfused does not accurately predict the need for platelet and plasma 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).¹⁶⁹
 - ◆ Only patients with extremely rapid hemorrhage were enrolled in this trial and formula-driven resuscitation should not be applied to less extreme hemorrhage situations.¹⁶⁹

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^{170,171}

- Transfusion support to replace ongoing blood loss of >10% Total Blood Volume (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

There is no threshold of units of group O red blood cells above which a switch to group-specific red blood cells is prohibited. The switch to group-specific red blood cells and plasma should be done as soon as possible.¹⁸

- 60% of trauma patients are hypothermic and failure to monitor the temperature is associated with higher mortality rates.¹⁷²
- Every 1 °C drop in temperature increases blood loss by 16% and the risk of transfusion by 22%.¹⁷³
- Consequences of hypothermia:¹⁷⁴
 - ◆ Platelet dysfunction
 - ◆ Decreased coagulation factor activity
 - ◆ Reduced clearance of citrate
 - ◆ Decreased cardiac output
 - ◆ Hypotension
 - ◆ Arrhythmias (especially if cold blood is transfused rapidly through a central line).

3. Hypocalcemia/Hypomagnesemia/Citrate toxicity

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

ATTENTION

Every 1 °C drop in temperature increases blood loss by 16% and the risk of transfusion by 22%.¹⁷³

- Clinical symptoms of hypocalcemia 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.
 - ♦ Patients with severe hypocalcemia have higher mortality and require more blood components.¹⁷⁵

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. Hyperkalemia¹⁷⁶

- 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.¹⁷⁷
- Order bloodwork q1h (e.g., CBC, INR, fibrinogen, ionized 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.¹⁸

- 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 coagulopathy with q1h blood work.
 - ♦ While patient is actively bleeding, transfuse to keep:
 - Platelet count >50 x 10⁹/L (with head injury >100 x 10⁹/L)
 - INR <1.8
 - Fibrinogen >1.5 g/L (>2.0 g/L for post-partum hemorrhage and cardiac surgery)
 - ♦ Institute ratio-based resuscitation until lab-guided hemostatic resuscitation can be provided.
 - ♦ Administer tranexamic acid (TXA), preferably within 60 minutes of injury or onset of hemorrhage.
 - There is no role for TXA in the management of gastrointestinal bleeding¹⁷⁸
- Monitor for hypocalcemia, acidosis and hyperkalemia.
- Blood filter/tubing must be changed every 4 units and within the number of hours specified by your hospital policy. New blood filter/tubing is recommended for every platelet transfusion. In massive transfusion, an add-on filter can be used to minimize the frequency of changes. Rapid infusion device tubing/filters often allow for less frequent tubing changes (refer to the operators manual for the device used at your hospital).

Ontario's Top 10 Recommendations for Massive Hemorrhage Protocol

- 1 All hospitals shall have a protocol to guide the management of a massively bleeding patient
- 2 The protocol shall be called "The Massive Hemorrhage Protocol"
- 3 Participating team members should have access to formal training and drills
- 4 The protocol should specify how the lead clinician at the bedside is designated
- 5 Tranexamic acid (TXA) should be administered as soon as possible
- 6 All patients should receive interventions to prevent hypothermia
- 7 The protocol shall state the reversal strategy for commonly used oral anticoagulants
- 8 The transport service(s) should be promptly notified if the decision is made to transfer the patient to another hospital for definitive hemorrhage control
- 9 Laboratory testing should be done at baseline and at a minimum hourly until the protocol is terminated
- 10 The protocol shall consider the available resources at the institution

This achieves standardization and better outcomes for patients
For more information on the provincial MHP visit www.transfusionontario.org

Postpartum Hemorrhage (PPH)

- The principles above for the management of massive hemorrhage also apply to the patient with a massive postpartum hemorrhage.
 - ◆ The risk for post-partum hemorrhage should be assessed antenatally to identify higher risk individuals.
- All postpartum females should be closely monitored for early signs of hemorrhage.
- Protocols for the management of bleeding and rapid administration of uterotonics must be in place at all hospitals with obstetrical patients.¹⁷⁹
- 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.
- If blood group is unknown, transfuse uncrossmatched O Rh D negative Kell negative RBCs.
 - ◆ 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 fibrinogen concentrate.¹⁸



A T T E N T I O N

If blood group is unknown, transfuse uncrossmatched group O Rh D negative, Kell negative RBCs.

MHP Quality Metrics¹⁸

Included in the Massive Hemorrhage Protocol (MHP) are 8 Quality Metrics for local hospital and/or provincial reporting using an electronic survey/database for data entry.

The reporting of quality metrics promotes improvement and increases transparency within the healthcare system. Standardized quality metrics have been developed for the Provincial Massive Hemorrhage Protocol to help assess and improve specific activities over time at individual hospitals and will allow for peer benchmarking.

The following should be tracked on all activations of the MHP and the data reviewed quarterly at your organizations hospital transfusion committee and the Medical Advisory Committee.

	Quality metric
Q1	The proportion of patients receiving tranexamic acid within 1 hour of protocol activation.
Q2	The proportion of patients in whom RBC transfusion is initiated within 15 minutes of protocol activation.
Q3	The proportion of patients (of patients requiring transfer for definitive care) with initiation of call for transfer within 60 minutes of protocol activation.
Q4	The proportion of patients achieving a temperature >35°C at termination of the protocol.
Q5	The proportion of patients with hemoglobin levels maintained between 60-110 g/L during protocol activation, excluding certain pediatric populations (e.g., neonates) that may require higher hemoglobin values.
Q6	The proportion of patients transitioned to group specific RBCs and plasma within 90 minutes of arrival/onset of hemorrhage.
Q7	The proportion of patients with appropriate activation (>6 RBC units in first 24 hours; > 40 ml/kg/24 hours of RBCs in pediatric patients) or before this level in patients dying due to hemorrhage within 24 hours.
Q8	The proportion of patients without any blood component wastage (including plasma that is thawed and not used within the 5 day limit on another patient).

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.^{4,180}

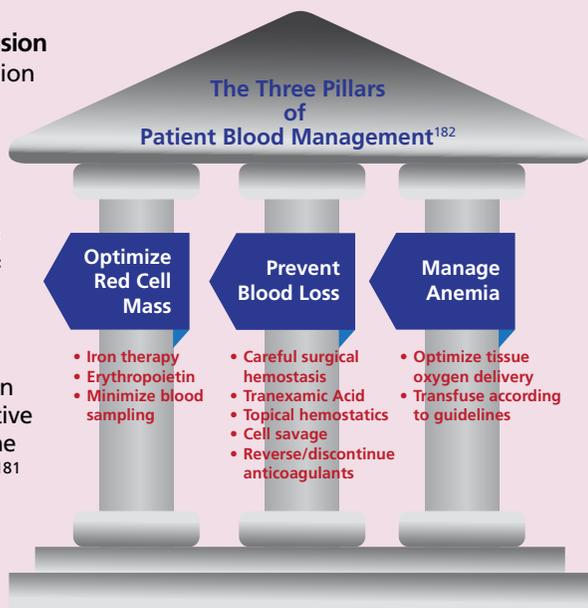
- There are currently multiple perioperative blood conservation strategies available to patients.
- Patients that are at high risk of perioperative transfusions (>10% chance of allogeneic RBC transfusion) need to be identified as early as possible to investigate the cause of anemia and offer treatments to correct the anemia. This may require rescheduling of surgery where appropriate.
 - ◆ As transfusion risk varies from institution to institution and surgeon to surgeon for the same procedure, each institution must determine the target patient populations for patient blood management.

A T T E N T I O N

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

Likelihood of Transfusion

- The risk of transfusion is increased by the following factors: lower hemoglobin, older age, lower weight, female sex, type of surgery, urgency of surgery, and renal dysfunction.
- There is a strong association between patients' preoperative hemoglobin and the risk of transfusion.¹⁸¹



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
>10 days	◆ Investigate and treat anemia	–
	◆ Delay surgery (if possible) until anemia corrected	–
	◆ Iron	86
	◆ Erythropoietin	90
<10 days before surgery	◆ Delay surgery (if possible) until anemia corrected	–
	◆ Stop anticoagulants	–
Intraoperative	◆ Attention to surgical hemostasis	82
	◆ Antifibrinolytics	92
	◆ Intraoperative cell salvage	88
	◆ Regional anesthesia	94
	◆ Topical hemostatic agents (e.g., fibrin sealants)	94
	◆ Adherence to transfusion guidelines and validated, goal-directed transfusion algorithms	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
 - ◆ Minimize tissue trauma
 - ◆ Optimal use of electrocautery
 - ◆ Meticulous attention to surgical hemostasis
 - ◆ Utilize avascular tissue planes
 - ◆ Appropriate use of topical hemostatic agents
 - ◆ Employ minimally invasive surgical techniques where available

Consider stopping anti-platelet agents and anticoagulants before major surgery

- **Acetylsalicylic acid (Aspirin®), clopidogrel (Plavix®), Ticagrelor (Brilinta®) and prasugrel (Effient®):**¹⁸³
 - ◆ In most clinical situations, withholding ASA before non-cardiac surgery is not associated with an increase in adverse cardiac events.¹⁸⁴

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)
- recent cardiac ablation
- coronary stent in last 12 months

RECOMMENDATIONS FOR PRE-OPERATIVE MANAGEMENT OF ANTIPLATELET AGENTS ¹⁸⁵

<p>DIAGNOSTIC TESTING, ARTHROCENTESIS, AND MINOR DENTAL, SKIN AND EYE PROCEDURES</p>	<p>Patients can continue ASA without interruption. Less is known about the safety of continuing P2Y12 inhibitors (clopidogrel, ticagrelor, prasugrel) around minor procedures when taken as monotherapy. It is reasonable to interrupt them for a short period (3-4 days) before the procedure. If patients are also taking ASA (dual antiplatelet therapy), the P2Y12 should be interrupted for 7-10 days.</p>
<p>MANAGEMENT OF PATIENTS UNDERGOING ELECTIVE OR NON-URGENT NONCARDIAC SURGERY</p>	<p>ASA should be discontinued 7 to 10 days prior to elective or non-urgent non-cardiac surgery except in patients undergoing carotid endarterectomy or with recent coronary artery stenting (6 weeks for BMS*, 3 to 12 months for DES**). In patients with an indication for chronic ASA, this medication should be resumed when the risk of bleeding related to surgery has passed, usually between 8-10 days after major noncardiac surgery.</p>
<p>MANAGEMENT OF PATIENTS WITH CORONARY STENTS UNDERGOING ELECTIVE OR NON-URGENT NONCARDIAC SURGERY Percutaneous coronary intervention patients with a Bare Metal Stent or drug-eluting stent</p>	<p>ASA should be continued perioperatively. Clopidogrel and ticagrelor should be withheld 5-7 days preoperatively, and prasugrel 7- 10 days preoperatively, P2Y12 inhibitor should be restarted as soon as it is deemed safe by the surgeon.</p>

* bare-metal stent (BMS)
 ** drug-eluting stent (DES)

RECOMMENDATIONS FOR PREOPERATIVE MANAGEMENT OF ANTICOAGULANTS

- **Dabigatran (Pradaxa®):**¹⁸³
 - ◆ **MINIMAL-BLEED-RISK procedure:** In patients who require a minor procedure (dental, cataract, or skin procedures) it is likely safe not to interrupt anticoagulation. An alternative approach would be to hold dabigatran on the day of the procedure or to delay that day's dose for 4-6 hours after the procedure.
 - ◆ **LOW/MODERATE-BLEED-RISK surgery/procedures:** For patients with normal renal function or mild impairment (Creatinine Clearance (CrCl) > 50 mL/min), last dose of dabigatran 2 days before the surgery/procedure (i.e., skip 2 doses before a surgery/procedure).
 - ◆ **HIGH-BLEED-RISK (includes any neuraxial [i.e. spinal or epidural] anesthesia or procedure):** Depending on renal function, last dose of dabigatran 3 to 5 days before surgery/procedure (i.e., skip 4 to 8 doses). This ensures minimal (3-6%) residual anticoagulant effect at the time of surgery. If renal function is moderately impaired (CrCl 30-49 mL/min), 1-2 additional days of interruption is required to ensure elimination of any residual anticoagulant effect.
- **Rivaroxaban (Xarelto®), Apixiban (Eliquis®) and Edoxaban (Lixiana):**¹⁸³
 - ◆ **MINIMAL-BLEED-RISK procedure (see above):** It is likely safe not to interrupt anticoagulation. An alternative approach would be to hold apixaban on the day of the procedure or to delay that day's dose for 4-6 hours after the procedure.
 - ◆ **LOW/MODERATE-BLEED-RISK surgery/procedure:** Last dose of apixaban 2 days before surgery/procedure.
 - ◆ **HIGH-BLEED-RISK surgery/procedure (includes any neuraxial [i.e., spinal or epidural] anesthesia or procedure):** Last dose 3 days before surgery/procedure.

- **NSAIDs:**
 - ◆ Caution is warranted regarding the use of perioperative NSAIDs as impact on bleeding and other important clinical outcomes are unclear.¹⁸⁶
 - ◆ Consider stopping therapy 4-7 days before major surgery.
 - ◆ Celecoxib does not inhibit platelet aggregation at usual doses.
 - ◆ Pre-operative use of NSAIDs may increase the risk of acute kidney injury.¹⁸⁷

Minimize blood sampling and loss¹⁸⁸

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

Preoperative patients on Warfarin:¹⁸⁹

- For very low risk procedures (dental, cataract, skin procedures): no need to interrupt warfarin anticoagulation.
- If low risk of thromboembolic events (e.g., primary prophylaxis of atrial fibrillation):
 - ◆ Stop warfarin 4-5 days preoperatively; repeat INR day minus 1.
 - ◆ If INR >1.5 on day minus 1, give 1-2 mg oral vitamin K.
 - ◆ Then repeat INR preoperatively.
- If high risk of thromboembolic events (see list in box):
 - ◆ Consider bridging to low molecular weight heparin; consult with hematology on timing and preferred regimen or consult recommendations at <http://thrombosiscanada.ca/>

Emergency reversal of anticoagulants

- See page 125.

HIGH THROMBOEMBOLIC RISK
(bridging anticoagulation suggested)

- Any mechanical prosthetic mitral valve
- Older generation (cage-ball, tilting disc) mechanical aortic valve
- Chronic atrial fibrillation (valvular or non-valvular) with a CHADS2 score of 5-6
- Recent (within 3 months) arterial thromboembolism (stroke, systemic embolism, transient ischemic attack [TIA])
- Recent (within 3 months) venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Prior arterial or venous thromboembolism during appropriate interruption of warfarin
- Severe thrombophilia with history of venous thromboembolism (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid syndrome)

IRON

- All patients undergoing major operative procedures should be evaluated for iron deficiency and where present corrected preoperatively.¹⁹⁰
- Choice of iron formulation and route of administration should be based on degree of anemia, time to surgery, and patient's ability to tolerate or absorb iron.
 - ◆ Perioperative intravenous iron reduces the risk of transfusion and improves hemoglobin levels.^{191,192}
 - ◆ Post-operative oral iron has not been shown to be effective.¹⁹³

A T T E N T I O N

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

ORAL IRON

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 decrease compliance, and higher doses cause decreased fractional iron absorption by increasing the hormone hepcidin.)¹⁹⁴

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).

Common Adverse Events*

- **GI upset** (diarrhea, nausea, constipation) was twice as frequent with oral iron as with placebo.¹⁹⁵
- **Dark stools.**
- Patient compliance with oral treatment is about 50%.¹⁹⁶

* See product monograph for details

COMMONLY USED IRON REPLACEMENT THERAPIES	DOSE MG	ELEMENTAL MG
Ferrous gluconate	300	35
Ferrous sulfate	300	60
Ferrous fumarate	300	100

A T T E N T I O N

Heme-based iron and polysaccharide-iron complexes in randomized controlled trials appear less effective, less tolerated, and are substantially more expensive.^{197,198}



Pediatric Dose 4-6 mg/kg elemental iron (max 60 mg of elemental iron)

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

INTRAVENOUS IRON

- Patients with **iron deficiency anemia** (whose surgery should not be delayed to allow for oral iron therapy to correct the anemia) should be treated with **intravenous iron**.¹⁹⁹ IV iron restores iron stores and hemoglobin levels more rapidly than oral iron.^{191,200}

Dosage

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

GENERIC NAME	BRAND NAME	DOSE	DAILY ESTIMATED COST ²⁰⁰
Iron sucrose	Venofer	200-300 mg in a single dose over 2 hrs	373
Ferric derisomaltose	Monoferric	500-1500 mg in a single dose over 30 to 60 mins	450-900

Adverse reaction

- ◆ Reactions may include hypersensitivity reactions (including anaphylaxis), hypophosphatemia (transient pain, muscle weakness, fatigue), and hypotension.²⁰¹

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.²⁰²

Evidence

- Meta-analysis of 75 studies:²⁰³
 - ◆ 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).²⁰⁴

Indications²⁰⁵

- Collection of blood for potential cell salvage ('collect only' mode) should be considered for surgical procedures where blood loss may exceed 500 ml (or > 8 ml/kg for children).
 - ◆ Heparin is used to prevent clotting of collected blood, but is washed out during processing.
- The use of leukoreduction filters should be considered during re-infusion of salvaged blood in cancer surgery (there is mixed evidence of the benefit of leukocyte depletion filters in obstetrics).
- When the use of cell salvage is proposed in surgery for malignancy or infection, an explanation should be given to the patient of the potential risks and benefits and specific consent should be obtained.

- Current evidence does not support the routine use of cell salvage during caesarean section. Cell salvage should be considered in the 'collect only' mode in women undergoing caesarean section who are anemic before surgery, in women anticipated to be at high risk of hemorrhage or if unanticipated bleeding develops during surgery.²⁰⁶

Complications

- Complications include:
 - ◆ **Air embolism – ensure air is removed from bag prior to re-infusion**
 - ◆ Thrombocytopenia and dilutional coagulopathy
 - ◆ Bacterial contamination (rare)
 - ◆ Tumour dissemination in cancer surgery
 - ◆ Hemolysis – ensure correct wash fluids are used

Clinical Practice

- Re-infusion of salvaged blood should be completed within the manufacturers' recommended time frame; usually 4 h after the completion of processing for intraoperative cell salvage. Patient identification and checks before transfusion should be the same as for allogeneic blood. Standard blood administration tubing/filter should be used to transfuse cell salvage blood.
- A formal maintenance program is required for equipment.
- Hospitals must have both a clinical lead and a coordinator for cell salvage who oversee a training program for involved staff, along with ongoing data collection and audit.

Cautions

- Malignant cells in operative field (risk may be mitigated by leukoreduction filter).
- Bacterially-contaminated operative field.
- Do not use hypotonic solutions in the operative field.
- Do not use topical thrombogenic agents in the operative field.
- Do not use heparin if history of HIT.

A T T E N T I O N

Air embolism is a risk of intraoperative cell salvage.

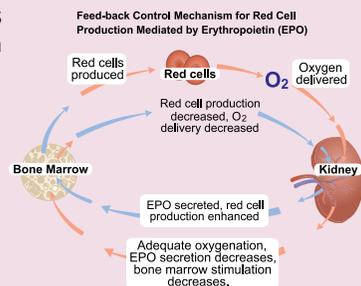
A T T E N T I O N

Do NOT use heparin if history of HIT

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.
 - ◆ Expected rise in hemoglobin is 10-20 g/L.



Evidence²⁰⁷

- 32 randomized controlled trials (n = 4750 patients) comparing preoperative erythropoietin (n = 2482 patients) to placebo (n = 2268 patients).
- Preoperative erythropoietin is associated with a significant decrease in incidence of allogeneic blood transfusions amongst all patients (n = 28 studies; risk ratio, 0.59; 95% CI, 0.47-0.73; P < 0.001) as well as patients undergoing cardiac (n = 9 studies; risk ratio, 0.55; 95% CI, 0.37-0.81; P = 0.003) and elective orthopedic (n = 5 studies; risk ratio, 0.36; 95% CI, 0.28-0.46; P < 0.001) surgery compared to placebo, respectively.
- Preoperative erythropoietin was also associated with fewer red blood cell transfusions.

Eligibility and Dosage

- Short acting Erythropoiesis Stimulating Agents (ESAs) in conjunction with iron should be considered in adult pre-operative patients with hemoglobin levels less than 130 g/L undergoing elective major orthopedic surgery.⁴
 - ◆ Consider factors such as the probability of transfusion, expected blood loss, etiology of anemia and risk of thromboembolic complications in decision-making.
 - ◆ Risk-benefit of ESAs outside of orthopedic surgery is less clear and consideration of use should be on a case-by-case basis.
- Suggested dose (Eprex®): 600 U/kg sc qwk for up to 4 doses commencing 28 days before surgery.^{208,209,210}
 - ◆ e.g., 30,000 or 40,000 U sc qwk x 4 weeks, start 28 days pre-op.

Contraindications (in elective surgery patients)

- Uncontrolled hypertension.
- Hypersensitivity to mammalian-derived cell products, albumin, or other components of the product.
- History of pure red cell aplasia from ESAs.
- Patients who can not receive anti-thrombotic treatment.

For more details, refer to product monograph.

Adverse Effects

- Elective surgical patients: no difference between patients treated with ESAs, as compared to placebo in incidence of thromboembolic events (n = 28 studies; risk ratio, 1.02; 95% CI, 0.78-1.33; P = 0.68).²⁰⁷

For more details, refer to product monograph.

ANTIFIBRINOLYTICS

General Principles^{211,212}

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

Indications**1. Antifibrinolytics in Cardiac Surgery**^{211,213}

- Prophylactic administration is preferred rather than at time of marked hemorrhage.
- Tranexamic acid reduces bleeding and transfusion rates.²¹⁴
- ◆ The dose of tranexamic acid evaluated in large randomized trials has varied from 20-100 mg/kg.^{211,214,215}
- ◆ Suggest considering a total dose of 20-25 mg/kg for low risk of bleeding surgical cases (e.g., isolated coronary bypass grafting or single valve replacement with short pump run) and a maximum of 50-100 mg/kg for cases with high risk of bleeding.
- ◆ The higher dose is associated with lower rates of transfusion but higher rates of seizures.

2. Tranexamic Acid in Non-Cardiac Surgery²¹⁶

- Evidence suggests a high degree of efficacy and safety:
- ◆ 69 trials, including 6157 patients: TXA reduces the proportion of patients transfused RBCs (relative risk (RR) 0.59; 95% CI 0.48 to 0.72 and the volume of RBC transfused (MD -0.51 RBC units; 95%CI -0.13 to -0.9 units;) when compared to placebo or usual care.
- ◆ The POISE-3 randomized, placebo controlled trial in 9535 patients undergoing non-cardiac surgery found a reduction in bleeding (433 of 4757 patients (9.1%) in the tranexamic acid group and in 561 of 4778 patients (11.7%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.67 to 0.87)), without an increase in cardiovascular outcomes.²¹⁷
- ◆ The dose used in the POISE-3 trial was 1 gram at the start and end of the procedure.

- ◆ TXA for surgical patients is not associated with differences in deep vein thrombosis, pulmonary embolism, all-cause mortality, hospital length of stay, need for re-operation due to hemorrhage, myocardial infarction, stroke or seizure.
- ◆ The use of topical tranexamic acid in knee and hip joint replacement is equally effective as intravenous use.²¹⁸

3. Tranexamic acid for Traumatic Injury

- 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).²¹⁹
- Since the publication of the CRASH-2 study, several studies have published on the efficacy and safety of bolus infusions in trauma (e.g., two 1 gram boluses or 2 gram bolus) reducing the complexity of providing tranexamic acid in trauma.^{220,221}

Adverse Effects

- Tranexamic acid: GI upset, seizures.
- ◆ Data from meta-analyses do not suggest an increased risk of thrombosis in surgical patients.²¹⁶

Not indicated

- Gastrointestinal hemorrhage: The HALT-IT trial randomized 12,009 patients to tranexamic acid compared to a placebo infusion and found no difference in the mortality rate or other important outcomes, and tranexamic acid was found to increase the risk of thromboembolic complications.¹⁷⁸

Contraindicated:

- Subarachnoid hemorrhage, due to risk of cerebral edema and cerebral infarction.
 - Active intravascular clotting.
 - Severe hypersensitivity reactions to tranexamic acid or any of the ingredients.
- Refer to product monograph for more details.

A T T E N T I O N

Tranexamic acid saves 1 in 67 traumatically injured patients from death if administered within 3 hours of injury!

REGIONAL ANESTHESIA

- A systematic review of the literature found that the use of **neuroaxial blockage with epidural or spinal anesthesia** reduced the risk of:²²²
 - ◆ Transfusion in total hip arthroplasty OR 0.84, 95% CI 0.83 to 0.86; Total knee arthroplasty OR 0.91, 95% CI 0.90 to 0.92.
 - ◆ Other complications were also reduced, including: cognitive dysfunction, respiratory failure, cardiac complications, surgical site infections and thromboembolic events.
- The following have been hypothesized for the physiologic reasons that neuraxial anesthesia might decrease blood loss: a decrease in arterial and venous blood pressure leading to less bleeding and absence of controlled ventilation (controlled ventilation may lead to higher venous pressure).²²³

TOPICAL AGENTS^{213,224}

- Fibrin sealants and topical thrombin in cardiac and vascular surgery:
 - ◆ Meta-analysis of 13 RCTs showed a statistically significant decrease in blood loss (mean difference 120.7 mL (95% CI -150.6 - -90.7)).
 - ◆ Post-operative blood transfusions, re-operation due to bleeding, and 30 day mortality were not significantly different.
 - ◆ Current evidence supports selective rather than routine use of fibrin and thrombin sealants in vascular and cardiac surgery.²²⁵
- There is currently insufficient evidence to support routine use of topical agents in liver resection.²²⁶

TRANSFUSION PROTOCOLS AND ALGORITHMS

- Goal directed transfusion algorithms which include point-of-care testing, such as viscoelastic testing, are recommended to reduce bleeding and transfusion requirements.^{227,228,229}

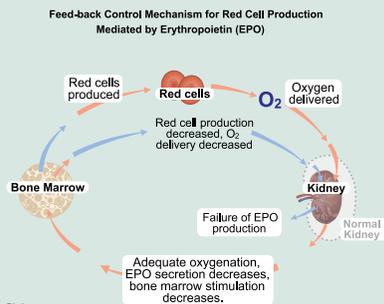
OTHER BLOOD CONSERVATION STRATEGIES UNDER CLINICAL INVESTIGATION

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

- Pre-operative autologous blood donation.
- Hemoglobin-based oxygen carriers.²³⁰
- Recombinant factor VIIa.²³¹
- Hypervolemic hemodilution.
- Acute normovolemic hemodilution.
 - ◆ May be of benefit for patients undergoing high blood loss cardiac surgery but is logistically complicated to perform and therefore is infrequently applied.²³²

General Principles

- 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 non-myeloid malignancies undergoing chemotherapy.

Contraindications²³³

1. History of pure red cell aplasia from erythropoietin stimulating agents
2. Uncontrolled hypertension
3. Hypersensitivity to any component of the product
4. Cannot receive anti-thrombotic agents

Refer to product monograph for more details.

CHRONIC RENAL FAILURE (CRF)

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).²³⁴

Eligibility

- Patients with clinically and biochemically established CRF with a hemoglobin <90-100 g/L should be considered.^{235,236,237}
- Usually erythropoietin is considered when the creatinine clearance is <60 mL/min/1.73 m².²³⁸
- 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 90-110 g/L.²³⁷

Iron²³⁷

- Assess iron status every 3 months.
 - Sufficient iron should be administered to maintain the serum ferritin >500 ug/L AND iron transferrin saturation >30%.
 - Intravenous iron is frequently utilized for patients who fail oral iron.
 - Intravenous or oral iron are 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

- Initial dose should be based on patient's starting hemoglobin, patient weight, and clinical circumstances.
 - ◆ Dose adjustments based on current hemoglobin, rate of change in hemoglobin, current dose, and clinical circumstances.^{237,239}

ANEMIA ASSOCIATED WITH MALIGNANCY

Eligibility^{240,241}

- 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).²⁴²
 - ◆ 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).²⁴²
 - 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).²⁴²

Dosage

- Iron status should be assessed and iron deficiency treated.
- Concurrent iron therapy recommended unless there are concerns of iron overload.²⁴³
- 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).²⁴⁴
- 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 2020-2021, 9 million grams of albumin were used in Canada, at a cost of about \$22 million dollars (excluding Quebec).

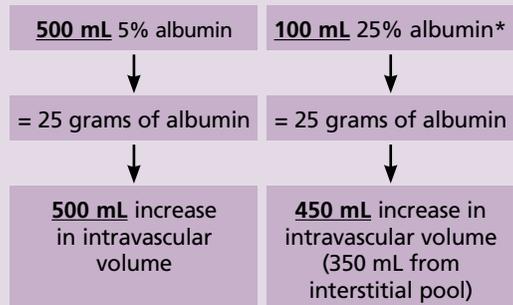
A T T E N T I O N
 Albumin is a blood product. Consent required.

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 cirrhosis

Administration ^{245,246}

- No blood bank sample required.
- Use vented IV tubing, no filter required.
- Fluid compatibility: all IV solutions.
- Record lot number and volume of albumin administered in patient chart.
- The infusion rate of 5% albumin should not exceed 5ml/min and the infusion rate for 25% albumin should not exceed 2ml/min.

Adverse reactions / Risks

- Anaphylaxis – rare.
- Circulatory overload.²⁴⁷
- Hypotension – rare case reports of transient hypotension in patients on angiotensin-converting enzyme inhibitors.²⁴⁸
- 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 paracentesis induced circulatory dysfunction in the management of tense ascites by paracentesis.²⁴⁹
- For paracentesis of <5 litres – albumin is unnecessary.²⁵⁰
- For large volume paracentesis, albumin should be considered as the replacement fluid of choice.

VOLUME OF ASCITES	25% ALBUMIN*
<5 L	0
5-6 litres	100 mL
6-8 litres	200 mL
>8 litres drained	300 mL

* 6-8 grams of albumin per L of fluid removed for paracentesis >5 L

- There is preliminary evidence that midodrine²⁵¹ and terlipressin²⁵² may be alternative therapies to intravenous albumin in this setting, but have not been shown to be superior to albumin.²⁵³
- **Malignant ascites** – there is no evidence to support the use of albumin in patients with malignant ascites post-paracentesis.²⁵⁴

A T T E N T I O N

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).²⁵⁵
 - ◆ 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.
 - ◆ Use dry-weight of patient for dosing.
 - ◆ Consider dose reduction or administering over 3 days if patient at risk for transfusion-associated circulatory overload.
 - ◆ 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** terlipressin²⁵⁶ or midodrine/octreotide²⁵⁷ may be effective for type 1 hepatorenal syndrome. 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.²⁵⁸
 - ◆ This therapy has not been shown to change mortality rates in hepato-renal syndrome.
 - ◆ Albumin alone, without terlipressin or other agent is ineffective.²⁵⁹

A T T E N T I O N

Use of Intravenous albumin alone is ineffective for hepatorenal syndrome.

DOSAGE

- 1 g/kg of 25% albumin on day 1 to a maximum of 100 g (400 mL of 25%) and then 25 g (100 mL) daily thereafter for a maximum of 14 days.²⁵⁶

4. Plasma exchange

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

THE CURRENT MEDICAL LITERATURE CANNOT CONFIRM ANY BENEFIT OF INTRAVENOUS ALBUMIN IN THE FOLLOWING SUBGROUPS OF PATIENTS:

1. Resuscitation

- Current evidence: **albumin is not superior to crystalloid for resuscitation in intensive care.**
- A systematic review from 2019 identified 55 randomized controlled trials comparing crystalloid with various colloids in intensive care patients. Data on mortality were available for 26,329 patients from 46 studies. There was no mortality benefit when albumin was compared with crystalloid (Relative Risk (RR) 1.02 (95% CI 0.96-1.10)).²⁶⁰
- A systematic review published in 2014 included 16 randomized trials totaling 4,190 patients with sepsis who received crystalloid or intravenous albumin and found no difference in all-cause mortality (RR 0.94, 95% CI 0.87-1.01).²⁶¹

2. Hypoalbuminemia

- Current evidence: **albumin is NOT superior to crystalloid for treatment of hypoalbuminemia.**
- An RCT (n=777) evaluated the role of albumin as compared to no albumin in hospitalized patients with decompensated cirrhosis and hypoalbuminemia (albumin <30 g/L); there was no difference in the primary endpoint (composite of new infections, kidney dysfunction, or death between days 3 and 15) between groups (OR 0.98, 95%CI 0.71-1.33) and more severe or life-threatening serious adverse events were reported in the albumin treated patients.²⁴⁷
- 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 ²⁶²	1.69	1.07-2.67	69% (7 to 167%)
Wilkes et al ²⁶³	1.59	0.91-2.78	59% (-9 to 178%)

3. Severe burns

- A systematic review of randomized trials failed to show an improvement in mortality with intravenous albumin (Odds Ratio 1.41 (95% CI 0.27-7.38)).²⁶⁴
- There is currently a wide variation in fluid resuscitation practice in burn patients.²⁶⁵
- 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.^{266,267}
- Intravenous albumin should only be commenced after transfer to a specialized burn centre.

PARKLAND FORMULA

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

ATTENTION

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

4. Hypotension during dialysis

- There are currently insufficient data to support the routine use of albumin in the treatment of hypotension during dialysis.
 - ◆ There are 4 small trials comparing albumin to alternative fluids with uncertain benefits found in patients with intradialytic hypotension.^{268,269,270,271}

5. Cardiac surgery²⁷²

- 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

6. Acute Lung Injury

- A systematic review from 2014 evaluated the impact of intravenous albumin, as compared to crystalloid, in patients with acute respiratory distress syndrome. Three small randomized trials totaling 204 patients were included; no difference in mortality was found (RR 0.89, 95% CI 0.62-1.28).²⁷³
- A large RCT (1386) in patients undergoing cardiac surgery with albumin, as compared to Ringer’s lactate solution, did not find a reduction in adverse outcomes.
 - ◆ Patients randomized to albumin had higher rates of bleeding, re-sternotomy, and infections.²⁷⁴

A Basics

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



Products Available

- 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.

IG PRODUCTS LICENSED IN CANADA*

PRODUCT	IGIVNEX	GAMUNEX	PRIVIGEN	GAMMAGARD LIQUID	GAMMAGARD S/D	HIZENTRA	OCTAGAM	PANZYGA	CUVITRU	CUTAQUIG
%	10%	10%	10%	10%	5–10%	20%	10%	10%	20%	16.5%
Manufacturer	Grifols	Grifols	CSL Behring	Takeda	Takeda	CSL Behring	Octapharma	Octapharma	Takeda	Octapharma
Plasma Source	Canada	United States	Canada/ United States	United States	United States	United States	United States	United States	United States	United States
IgG (g/L)	98 ± 20	100 ± 10	100	100	>90	200	100	100	200	165
IgA mcg/mL	46 mcg/mL (average)	46 mcg/mL (average)	<25 mcg/mL	≤140 mcg/mL	≤2.2 mcg/mL (for 5% preparation)	≤50 mcg/mL	106 mcg/mL (average)	Not specified	80 mcg/mL (average)	Not specified
Sugar content	Contains no carbohydrate stabilizers	20 mg/mL glucose (in 5% solution)	Contains no carbohydrate stabilizers	Maltose 90 mg/mL	Contains no carbohydrate stabilizers	Contains no carbohydrate stabilizers	Maltose 79 mg/mL			
Osmolality (mOsmol/kg)	258	258	320	240-300	Not indicated	Not indicated	310-380	240-310	280-292	310-380
Form	Liquid	Liquid	Liquid	Liquid	Lyophilized	Liquid	Liquid	Liquid	Liquid	Liquid
Route of administration	IV/SC	IV/SC	IV	IV	IV	SC	IV	IV	SC	SC

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

Cost

- IVIG costs \$60 per gram, depending on US\$ exchange rate.
 - ◆ A single course of treatment for a 70 kg patient with the commonly prescribed dose of 1 g/kg each day for 2 days, costs \$8,400.

In 2021-2022

Canada (minus Quebec) used 6,809 kg at a cost of 450 million dollars.

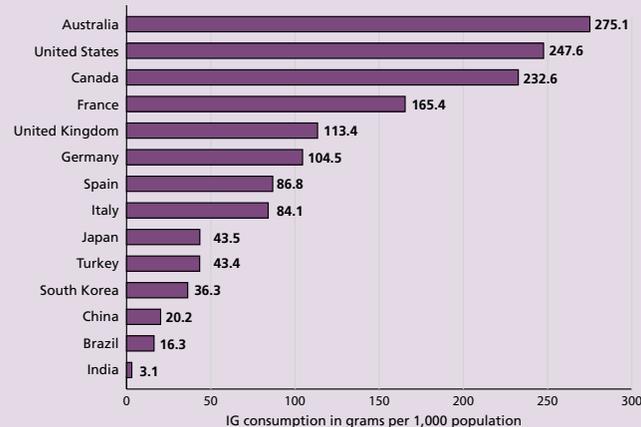
Availability & Consumption

- Approximately 10-15% of the IVIG used in Canada is derived from Canadian plasma.²⁷⁵
- The rest is derived from paid U.S. donors.
- Canada has one of the highest *per capita* consumption rates of IVIG in the world.²⁷⁶

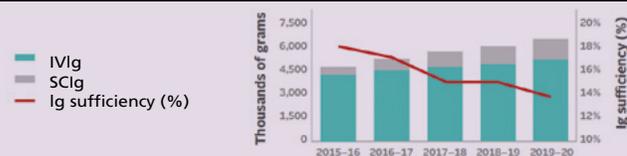
IN ONTARIO

In Ontario, requests for IVIG for infusion are required to be made on a MOH – mandated request form. The IVIG request form can be found at <https://transfusionontario.org/en/category/ivig-scig/ordering-ig-in-ontario/>

IMMUNOGLOBULIN CONSUMPTION IN SELECT COUNTRIES IN 2017 (IN GRAMS PER 1,000 POPULATION)



FIVE-YEAR UTILIZATION TREND IN CANADA



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), hepatitis A 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.²⁷⁷

B Administration & Infusion Recommendations

Administration

- For detailed recommendations for infusion of IVIG, refer to “Intravenous Immune Globulin Toolkit for Ontario”.²⁷⁸
- Administered as 5%, 10%, 16.5% or 20% solution as per brand specifications, dispensed by the Hospital Transfusion Service.
- Safe for use in pregnancy.
Refer to package insert for further details.

General Principles

- Refer to Institution specific policies.
- Use Adjusted Body Weight Dosing Calculator²⁷⁸, check every 6 months or if significant weight change.
- Round dose to nearest vial size.

DOSE CALCULATOR

<https://ivig.transfusionontario.org/bmi/>

Pre-infusion

- Verify documentation of order, clinical indication and consent.
- Identify patients at risk for complications, especially TACO (see page 56) and thromboembolic events.
- Assess patient and check vital signs.

Infusion

- Slow initial rate for first 30 minutes refer to “IVIG and SCIG infusion rates” table.
- Assess patient and 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 hospital transfusion service any unused or defective vials, and any vials associated with an adverse event.

IVIG AND SCIG INFUSION RATES*

PRODUCT	INITIAL RATE	MAXIMUM RATE	COMMENT
IGIVnex	0.6-1.2 mL/kg/hour 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 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™	0.5 mL/kg/hour for 30 minutes	Increase gradually to a maximum rate of 4.0 mL/kg/hour if initial dose is tolerated	Use filter supplied with product
GAMMAGARD® Liquid	0.5 mL/kg/hour 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	Increase gradually to maximum rate of 7.2 mL/kg/hour	Product monograph recommends not exceeding 4.8 mg/kg/min for patients receiving >1 g/kg
OCTAGAM	0.6 mL/kg/hour for 30 minutes	Increase gradually to 7.2 mL/kg/hour	
Panzyga	0.6 mL/kg/hour for 30 minutes	Increase gradually to a maximum rate of 4.8 mL/kg/hour for first infusion, then if tolerated, to a maximum of 8.4 mL/kg/hour	Maximum rate after 3 infusions 7.2 mL/kg/hour and after 6 infusions 8.4 mL/kg/hour. For chronic ITP, maximum dose 4.8 mL/kg/hour
Hizentra	20 mL/hour/site	50 mL/hour/site	No limit to the number of injection sites used in parallel
Cuvitru	10-20 mL/kg/hour/site for first 2 infusions	Subsequent infusion rate may be increased to 60 mL/hour/site if tolerated	Use up to 4 sites simultaneously
Cutaquig	First 6 infusions: 15-20 mL/hour/site	Subsequent infusions: 25 mL/hour/site	Maximum flow rate per hour for all sites: – first 6 infusions 30 mL/hour for all sites – from infusion 7, a gradual increase to 50 mL/hour for all sites, subsequently 80 mL/hour for all sites and, if tolerated, up to 100 mL/hour for all sites

* Refer to IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for further information at <https://transfusionontario.org/en/category/ivig-scig/infusion-guide-and-adverse-events/>

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 ^{278,279,280,281}

REACTION	SEVERITY	FREQUENCY**	COMMENT/TREATMENT
Anxiety, chills/fever, rash, flushing, headache, chest, back or abdominal pain, nausea/vomiting, tachycardia, hypo- or hypertension	Mild-moderate	21% ²⁸²	Slow or pause IVIG treatment. Symptomatic treatment. Recurrent reactions – pre-medicate and/or change to another manufacturer’s IVIG product or where appropriate change to SCIG
Aseptic meningitis	Moderate	7 in 10,000 ²⁸³	Stop infusion. Administer analgesics. Usually resolves spontaneously in 24-48 hours. Pre-medicate and/or change to another manufacturer’s IVIG product or where appropriate change to SCIG
Migraine headache	Mild-moderate	3-6% ²⁸⁴	Manage with acetaminophen and/or NSAIDs. For recurrent reactions consider pre-medication with acetaminophen, changing to another manufacturer’s IVIG product, or where appropriate switching to SCIG.
Anaphylaxis	Severe	Rare	Stop infusion. May require epinephrine promptly. Consider testing for IgA and anti-IgA (see page 60)
Acute kidney failure	Severe	Rare	Usually with sucrose-containing product (none currently licensed in Canada). Predisposing factors: age >65, diabetes mellitus, pre-existing renal insufficiency
Hemolysis	Mild-Severe	20% of non-group O patients develop grade 2 or higher hemolysis ²⁸⁵	Occurs within 10 days of infusion. Non-group O patients should have their hemoglobin levels monitored post-infusion, between 5-10 after infusion.
Thrombo-embolic events	Severe	0.5-1% ²⁸⁶	Causative relationship not clearly established. Possibly related to increases in viscosity
Neutropenia	Mild-moderate	Uncommon	Occurs 2-4 days after infusion and usually persists for 2 weeks ²⁸⁷
Infectious disease transmission	Severe	No reported case since HCV in 1995. ²⁸⁸ 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/23518142.²⁸⁹
 - ◆ Treatable conditions to which antibody deficiency may be secondary must be excluded.
- Subcutaneous immunoglobulin is the preferred replacement strategy as it has several advantages (better tolerated, more convenient for patients, and is economically superior). Consult a transfusion medicine specialist or immunologist for additional information.

CHOOSE WISELY

Immunoglobulin 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.

FACTORS IN CHOOSING IVIG OR SCIG

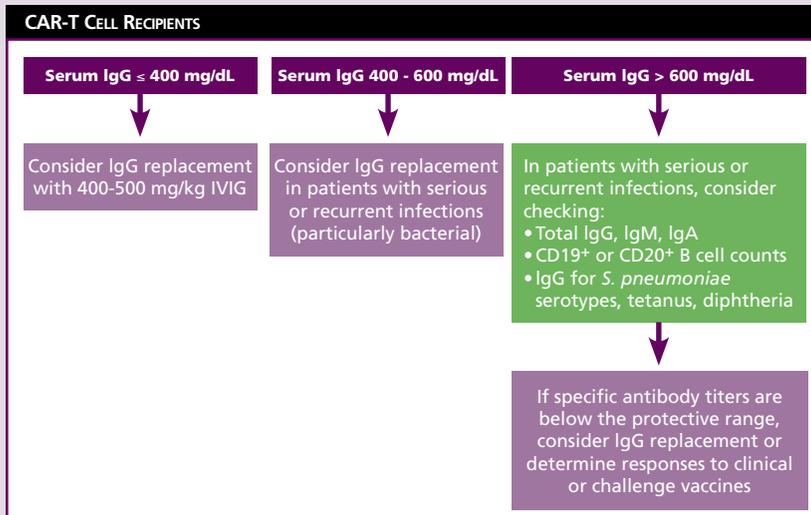
INTRAVENOUS IMMUNOGLOBULIN (IVIG)	SUBCUTANEOUS IMMUNOGLOBULIN (SCIG)
<ul style="list-style-type: none"> ◆ Good maintenance of clinical benefit ◆ Local reactions to SCIG ◆ Patient uncomfortable with home or self-medication 	<ul style="list-style-type: none"> ◆ Clinical response not well maintained ◆ Adverse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

IVIG IN IMMUNOGLOBULIN DEFICIENCY^{290,291}

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Primary Immune Deficiency ²⁹² Secondary Immune Deficiency (SID) ²⁹³	IVIG is recommended in hypogamma globulinemia (total IgG or IgG subclasses reduced) with recurrent bacterial infections	Adult: 0.4-0.6 g/kg/ every 3-4 weeks Pediatric: 0.3-0.6 g/kg/ every 3-4 weeks Monitor IgG trough level to maintain low range
Hematopoietic Stem Cell Transplant in primary immunodeficiencies ²⁹⁴	IVIG is recommended in PID patients undergoing stem cell transplant	0.4-0.6 g/kg/every 3-4 weeks; requirements may increase and should be based on clinical outcomes
CAR-T cell recipients ²⁹⁵	See Figure below for recommendations on when to replace	0.4-0.6 g/kg/every 4 weeks; requirements may increase and should be based on clinical outcomes

IVIG IN SOLID ORGAN TRANSPLANTATION²⁹⁶

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Kidney transplant from living donor to whom the patient is sensitized ²⁹⁶	IVIG is recommended to decrease donor-specific sensitization	2 g/kg/month for 4 months
Pre-Transplant (heart) ²⁹⁶	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) ^{297,298,299,300}	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 ^{296,297,298,299,300}	Acute antibody-mediated rejection in a solid-organ transplant recipient – first-line agent Chronic antibody-mediated rejection in a solid-organ transplant recipient	1 g/kg/dose, can give as divided doses if in association with a course of plasmapheresis 1 g/kg/month



Hematology

IVIG IN HEMATOLOGICAL DISORDERS AND BONE MARROW/STEM CELL TRANSPLANTATION^{290,301,302}

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Immune Thrombocytopenic (ITP) refractory to standard treatment, platelet count <20 x 10 ⁹ /L	Benefit established	1 g/kg for 1 day. Repeat if platelet count not >30 x 10 ⁹ /L
ITP with persistent or life-threatening bleeding and platelet count <50 x 10 ⁹ /L	Benefit established	1 g/kg for 1-2 days
Thrombocytopenia associated with HIV unresponsive to antiviral therapy, platelet count <20 x 10 ⁹ /L or <50 x 10 ⁹ /L with bleeding	Benefit established	1 g/kg for 2 days
ITP in pregnancy <ul style="list-style-type: none"> platelet count <10 x 10⁹/L platelet count 10-30 x 10⁹/L in 2nd or 3rd trimester platelet count <30 x 10⁹/L and bleeding at any stage in pregnancy 	Appropriate initial treatment	1 g/kg; longest inter-treatment interval consistent with maintaining adequate platelet count
Chronic ITP unresponsive to alternatives (e.g., splenectomy, rituximab, thrombopoietin receptor agonists, immunosuppressive agents)	Use in consultation with an expert in ITP	1 g/kg q3-4 months
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) ³⁰³	Considered standard first-line antenatal treatment. Considered adjunctive therapy for newborn with F/NAIT. Appropriate consultation advisable with high-risk pregnancy and neonatal unit	Maternal: 1 g/kg weekly (In non-group O patients monitor closely for hemolytic anemia) ³⁰⁴ Infant: Give IVIG if platelet transfusion not immediately available <u>or</u> there is no response to platelet transfusion <u>or</u> prolonged thrombocytopenia (>7 days). Dose 1 g/kg and reassess

Pediatrics



- Transfuse platelets to maintain platelets over 30 x 10⁹/L.
- Transfuse platelets in the setting of life-threatening hemorrhage (intracranial or GI bleeding) to maintain platelets >50 (raise to 100, maintain >50)⁶³

CHOOSE WISELY

Don't give IVIG as first line treatment for patients with asymptomatic immune thrombocytopenia (ITP).³⁰⁵

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Pure red cell aplasia (PRCA) (viral or immunologic) ^{291,301}	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) including hyperhemolysis in Sickle Cell Disease ²⁹¹	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) ^{290,301,306}	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 ³⁰⁷	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) ³⁰¹	Not recommended for routine use. Option in severe life threatening VAHS	Determine in consultation
Rare cases of auto-immune hemolytic anemia or neutropenia, auto-antibodies to factor VIII or von Willebrand factor ^{290,291,301}	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 ^{290,308,309}	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*^{290,310}

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Guillain-Barre Syndrome (including Miller-Fisher syndrome and other variants) ³¹¹	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 ^{312,313,314,315}	Benefit established; Front-line treatment is corticosteroids, consider IVIG as front-line treatment for motor CIDP	<p>IVIg: Total dose 2 g/kg divided over 2-5 days as induction and then two to five repeated doses of 1 g/kg IVIG every 3 weeks may be required before either the patient improves or it can be decided that IVIG is ineffective.</p> <p>Maintenance: The most commonly used IVIG maintenance regimen in clinical trials is 1 g/kg every 3 weeks, but in clinical practice lower doses and longer treatment intervals maintaining maximal sustained improvement should be considered (eg, 0.4-1 g/kg every 2-6 weeks)</p> <p>SCIg: Dose: 0.4 g/kg qweek</p> <p>When CIDP patients switch from IVIG to SCIg, it is reasonable to start using the same mean dose (1:1) per week. If the treatment effect is insufficient, the dose should be adjusted using reliable outcome measures.^{315,316}</p>
Multifocal motor neuropathy ³¹⁷	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: 1 g/kg q2-4 weeks ³¹⁷
Myasthenia gravis ³¹⁸	Consider for refractory myasthenia gravis, life-threatening presentations	2 g/kg over 2 days; maintenance therapy should be individualized ³¹⁹

* 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) ^{290,310,320}	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	<p>Adults: Total dose of 2 g/kg divided over 2-5 days</p> <p>Pediatric: Total dose of 2 g/kg divided over 2 days</p>
Lambert-Eaton Myasthenic Syndrome (LEMS) ^{290,310}	IVIg is an option for treatment of LEMS. Objective evidence of clinical improvement is needed for sustained use of IVIG.	<p><i>Initial treatment:</i> Total dose of 2 g/kg divided over 2-5 days</p> <p><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</p>
Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS) ^{290,310}	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
Autoimmune encephalitis ³²¹	IVIg is an option for the management of autoimmune encephalitis; if no or inadequate response to front-line treatment (corticosteroids and IVIG) at 2-4 weeks, second line immunosuppressive agents should be considered (rituximab, cyclophosphamide) ³²¹	<p>Adults: Total dose of 2 g/kg divided over 2-5 days</p> <p>Pediatric: Total dose of 2 g/kg divided over 2 days</p> <p>IVIg not recommended as maintenance therapy³²¹</p>

Neurology

IVIG IN NEUROLOGICAL DISORDERS* (cont'd)

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Stiff Person's syndrome ^{290,310,322}	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> Adults: Total dose of 2 g/kg divided over 2-5 days Pediatric: 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 ³²³	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-myoclonus syndrome ³²⁰	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 ^{324,325,326}	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** ³²⁷	Current evidence does not support use	
Kawasaki disease ³²⁸	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 ³²⁹	No reliable evidence to support benefit or lack of benefit; if used, it should be under the supervision of a specialist in toxic epidermal necrolysis ^{330,331}	2-3 grams per kg divided over 2-3 days ^{331,332}
Pemphigus vulgaris and variants ³³³	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 ³³⁴	Anecdotal evidence 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 ³³⁵	IVIG may be considered as third line therapy if patient has failed conventional immunosuppressants and rituximab; recommended for patients at high risk of adverse events from first and second line treatments	Total dose of 2 g/kg divided over 2-5 days. Maintenance treatment should be individualized

Obstetrics and Gynecology

IVIG IN OBSTETRICS AND GYNECOLOGY³³⁶

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Anti-phospholipid syndrome ^{337,338}	Uncertain benefit	Determine in consultation with high-risk pregnancy specialist
Recurrent spontaneous abortion	Ineffective ³³⁹	Not indicated
<i>In Vitro</i> fertilization/implantation procedures	Ineffective ³⁴⁰	Not indicated

Infectious Diseases

IVIG IN BACTERIAL INFECTION^{290,291}

DIAGNOSIS	EFFICACY/COMMENT	DOSE
Septic/Toxic Shock Syndrome (Group A streptococcal sepsis with hypotension and multi-organ failure) 341,342,343,344,345,346,347,348	Uncertain benefit; use in consultation with experts in infectious diseases	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 ³⁴⁹	No benefit	Not recommended for use
Sepsis in patients in critical care ^{345,346}	No 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: <https://professionaleducation.blood.ca/en/immune-globulin-products> (see package insert for details)
 - ◆ Varicella-Zoster Immune Globulin (VZIG)
 - ◆ Hepatitis B Immune Globulin (HBIG; BayHepB)
 - ◆ Anti-RSV Immune Globulin (Respigam®)
 - ◆ Cytomegalovirus Immune Globulin (CMVIG, Cytogam®).

Dosing of IVIG for Obese Patients³⁵⁰

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

A tool which assists with the calculation of the appropriate dose of IVIG based on the patient's sex, height and weight is available at <https://transfusionontario.org/en/category/ivig-scig/dosing-using-adjusted-body-weight/>.

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.

DOSE CALCULATOR

<https://transfusionontario.org/en/category/ivig-scig/dosing-using-adjusted-body-weight/>

ATTENTION

IVIG in Ontario can only be requested using the prescribed request form.

A Basics ^{351,352}

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.
- PCCs are a blood product and informed consent is required.
- 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 ³⁵²

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	22.2	12.0	0.1	6.0
Beriplex [®]	CSL Behring	31.0	16.2	28.9	41.3	21.6	17.9	0.6	0.5

B Monitoring & Infusion Practices for Octaplex[®] and Beriplex[®] ³⁵¹

How

- Lyophilized powder must be reconstituted for administration.
- Final volume is either 20 mL per vial which contains 500 IU of factor IX or 40 mL per vial which contains 1000 IU of factor IX.
- Can be prepared in syringe or minibag for intravenous infusion.

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.

WARFARIN REVERSAL AND TREATMENT OF VITAMIN K DEFICIENCY

- Emergency reversal of warfarin effect.
 - ◆ For patients with INR ≥ 1.5 AND
 - ◆ "Life or limb" threatening bleeding OR
 - ◆ Emergency surgery within 6 hours
- Give:
- ◆ Vitamin K 10 mg IV
 - ◆ PCC

Dose³⁵¹

- 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 1000 IU per 5 minutes.

A T T E N T I O N

Giving plasma for warfarin reversal is associated with a 3-fold higher risk of TACO.³⁵³

A T T E N T I O N

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

<https://www.nacblood.ca/resources/guidelines/PCC.html>

Storage

- Store between +2 to +25°C.
- Freezing and light exposure may affect product quality.
- PCCs should NOT be administered if:
 - ◆ INR ≤ 1.5 as individual coagulation factors are not below the level needed to maintain hemostasis.
 - ◆ Patients with known HIT (Beriplex® and Octaplex® both contain heparin).
- Clinical situations where vitamin K alone will suffice are shown in the "Choosing Wisely" box to the right.

REVERSAL OF OTHER ANTICOAGULANTS

- Reversal of anti-Xa inhibitors.
 - ◆ Currently specific reversal agents are not available in Canada.
 - ◆ 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 observational and uncontrolled studies.³⁵⁴
- Reversal of anti-IIa inhibitors (Dabigatran).³⁵⁵
 - ◆ 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.

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

A Basics

How

- Lyophilized powder must be reconstituted for administration.
- Final volume is 50 mL per vial which contains 1 gram of fibrinogen.
- Can be prepared in a syringe or minibag for intravenous infusion.
- Cryoprecipitate is also a source of fibrinogen replacement but fibrinogen concentrates are clinically equivalent and the preferred product for both congenital and acquired hypofibrinogenemia.
- Fibrinogen concentrates have a superior safety profile as a pathogen inactivated product, and logistical advantages with respect to dosing, storage and administration.

Dose

- **Adults:** 4 grams infused over 10 minutes for bleeding patients.³⁵⁶
- **Neonates and Children:** 50 mg/kg infused over 10 minutes for bleeding patients.¹⁸

Storage

- Store between +2 to +25C for Fibryga® (for up to 36 months) +2 to +8C for RiaSTAP® (for up to 60 months).
- Ideally give immediately following reconstitution; may be stored at room temperature and infused.

Monitoring

- Monitor patient for signs and symptoms of allergic transfusion reactions.
- Repeat fibrinogen level immediately post-infusion.



B Indications

- For major or massive hemorrhage from surgery or trauma when fibrinogen <1.5 g/L.^{18, 357}
- For acute phase of acute promyelocytic leukemia with fibrinogen <1.5 g/L.³⁵⁸
- Hemorrhage after cardiac surgery or peripartum with fibrinogen <2.0 g/L.¹⁸
- Intracranial hemorrhage secondary to treatment with Tissue Plasminogen Activator with fibrinogen <2.0 g/L.
- Congenital afibrinogenemia or hypofibrinogenemia for bleeding or prior to procedures.

CHOOSE WISELY

Don't transfuse Fibrinogen concentrates for:

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

MASSIVELY BLEEDING PATIENTS WHERE PLASMA IS UNAVAILABLE

- Some smaller/remote organizations may be unable to provide plasma in bleeding patients.
- Can be given concurrently as a substitute for plasma, where plasma is not available.
- Dosing strategies are inconclusive: with 2000 IU (or 25 IU/kg rounded up for pediatric patients) of PCC suggested.

Rh(D) Immune Globulin (WinRho®) 359,360,361

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 Pathologists' on line calculator at <https://uchicagomedlabs.testcatalog.org/catalogs/367/files/7215>)
 - ♦ 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 cephalic 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, e, K, 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%.^{49,362}

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

A Principles of Transfusion in Sickle Cell Disease³⁶³

Decisions regarding the transfusion of patients with sickle cell disease are made very differently from those of other patients and are rarely determined by the hemoglobin alone. In addition, patients with sickle cell disease are at increased risk of serious transfusion reactions. For this reason, consultation with a hematologist is strongly recommended before blood products are administered.

Three principles of transfusing patients with sickle cell disease can be summarized as follows:

1. The primary benefit of transfusion is from decreasing the HgbS% (as determined by hemoglobin electrophoresis) rather than increasing the total hemoglobin.
2. Transfusing above a hemoglobin threshold of 100 g/L is likely to worsen oxygen delivery due to hyperviscosity.
3. While a hemoglobin < 50 g/L is a strong indication for transfusion in sickle cell patients, several conditions that can cause anemia of this severity (aplastic crisis, sequestration crisis and hyperhemolysis) also increase the risk of serious transfusion reactions.

B Special Transfusion Requirements

- To prevent dangerous hemolytic transfusion reactions, blood products for patients with sickle cell disease must be selected with greater care than is expected with other patients.
- Specifically, RBC units should be selected on the basis of the patient's extended antigen phenotype (supported whenever possible by genotyping studies), and the presence of any RBC antibodies which may have developed in the past. In some cases, this information will reveal that RBC units of rare phenotype will need to be ordered from the blood supplier.

ATTENTION

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

ATTENTION

In the absence of symptoms, transfusion should be avoided unless the hemoglobin has decreased to <50 g/L.³⁶⁴

ATTENTION

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

ATTENTION

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

- ◆ As the above steps may introduce delays in care, it is important that the hospital transfusion service be notified, even if there is not an immediate plan to transfuse, every time a sickle cell patient presents for acute care. This notification should include a list of other hospitals the patient has received care at previously (this information may be included within the 'comments' section attached to a request to perform a blood group and screen).
- ◆ Note that the above considerations apply to all forms of sickle cell disease (ie., HgbSS, HgbSC and HgbS- β -thalassemia). No special precautions are required, however, for patients with sickle cell trait (ie., Hgb AS).

The role of genotyping

- While serologic techniques can identify common minor blood group antigens (D,C,c,E,e,Fya,Fyb,M,N,S and s) they cannot identify the partial variants of these antigens which are common in these patients.
 - ◆ For example, studies have found that nearly a quarter of sickle cell patients who phenotype as C-positive only express a partial form of this antigen. Transfusing these patients C-positive RBC units therefore risks provoking an anti-C antibody, which is capable of causing life-threatening transfusion reactions.³⁶⁵
- Genotyping can also identify patients who may be safely challenged with antigens they don't express on their own RBCs. For example, a large majority of sickle cell patients who phenotype as Fyb-negative are actually Fyb-positive by genotype, but with expression limited to non-erythroid cells. These patients can be safely transfused Fyb-positive RBCs.³⁶⁶

ATTENTION

Notify hospital transfusion service immediately about sickle cell disease patients.

ATTENTION

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 # 1175380	
ABO/Rh: O NEG	
Special Requirements:	
ANTIBODY (RES) ANTI-E	

B Special Transfusion Requirements (cont'd)

- Genotyping studies are available at no charge from Canadian blood suppliers (Canadian Blood Services and HemaQuebec).

Sicklelex®-negative blood

- RBC units which test positive by Sicklelex® test are from donors with sickle cell trait (HgbAS). This blood would be 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.³⁶⁷

C Exchange Transfusion

- Depending upon a patient's initial hemoglobin, it may not be possible to achieve a specific target HgbS% by top-up transfusion without exceeding a total hemoglobin of 100 g/L.
- Exchange transfusion may therefore be required to meet the desired target of HgbS% <30% (Note: in patients with HgbSC, this goal may be reframed as targeting a HgbA > 70%).³⁶⁸
- 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):³⁶⁹
 1. Phlebotomize 1st 500 mL of whole blood (for patients who are very anemic at baseline [e.g., hemoglobin <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;

Indications for top-up transfusion

1. Hemoglobin < 50 g/L unless secondary to hyperhemolysis
2. Mild-moderate acute chest syndrome
3. Pre-operative prophylaxis in patients with hemoglobin < 90 g/L, without high-risk features, undergoing low-moderate risk surgery

Indications for exchange transfusion:

1. Severe acute chest syndrome (e.g., accompanied by multiorgan failure)
2. Treatment of acute ischemic stroke
3. Secondary stroke prophylaxis
4. Primary stroke prophylaxis in patients at high risk (e.g., high-flow transcranial doppler ultrasound)
5. Pre-operative prophylaxis in high-risk patients or patients undergoing high-risk procedures
6. Progressive cholestasis
7. Post-solid organ transplant
8. High-risk pregnancy
9. Other complications (e.g., pulmonary hypertension, priapism, acute renal failure, malleolar ulceration) failing to respond to more targeted therapy
10. Patients with progressive complications despite top-up transfusion
11. Prevention of pain crises or acute chest syndrome in patients failing or with contraindication to hydroxyurea.
12. Patients requiring top-up transfusions with hemoglobin > 90 g/L

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 hemoglobin from exceeding 110 g/L.

D Primary indications for Transfusion**THERAPEUTIC TRANSFUSION****Aplastic Crisis³⁷⁰**

- Most commonly due to parvovirus B19 infection, with profound reticulocytopenia.
- Transfusion support may be required if symptomatic anemia, or if hemoglobin <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 hemoglobin.

**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.³⁷¹

ATTENTION

Due to decreased lifespan of sickle RBCs (16-20 days), significant fall in hemoglobin will occur before the reticulocyte count recovers.³⁷²

ATTENTION

In people with hypovolemia due to severe acute splenic sequestration, immediately provide IV fluid resuscitation.

In consultation with a sickle cell expert, transfuse people who have acute splenic sequestration and severe anemia to raise the hemoglobin to a stable level, while avoiding over-transfusion.

In consultation with a sickle cell expert, address the performance and timing of splenectomy in people with recurrent acute splenic sequestration or symptomatic hypersplenism.³⁷³

- Less commonly, patients may present with hepatic sequestration crisis, characterized by a rapidly enlarging liver accompanied by a decrease in hemoglobin, a rise in reticulocyte count, and a conjugated hyperbilirubinemia.
 - ◆ This type of sequestration is generally less severe than splenic sequestration but can have first onset in adulthood.
 - ◆ Transfusions should also be administered cautiously due to the risk of autotransfusion and hyperviscosity. Recurrences are common.³⁶⁴

Acute chest syndrome³⁷⁴

- Transfusion is advised in patients with moderate to severe acute chest syndrome; exchange transfusion rather than a top-up transfusion is indicated in patients with severe disease (e.g., rapid deterioration or evidence of multiorgan dysfunction) or in those with a baseline hemoglobin > 90 g/L. Otherwise, a top-up transfusion to a maximum of 100 g/L may be considered as initial therapy.
- In patients with milder disease (e.g., chest x-ray infiltrates without hypoxemia), supportive care without transfusion may be considered.
- In all cases, supportive care should include antibiotics with coverage for atypical organisms, and consideration for incentive spirometry and/or bronchodilators.
- Any sickle cell patient requiring invasive ventilatory support should be referred to a centre capable of providing apheresis exchange transfusion support.

ATTENTION

Acute chest syndrome is defined as new pulmonary infiltrates on chest x-ray in a patient with sickle cell disease, accompanied by respiratory symptoms, chest pain or fever. Acute chest syndrome cannot be easily distinguished from, and is often accompanied by, community-acquired pneumonia.

Progressive cholestasis (aka sickle hepatopathy)

- 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 progress to fulminant liver failure.³⁷⁴
 - ◆ Avoid liver biopsy due to high risk of complications.

Acute ischemic stroke or retinal artery occlusion

- All patients should be initiated on a program of monthly transfusions with the goal of keeping HgbS < 30%.
- The same practice should be followed with adult patients, although there is less supporting evidence and consideration should be given to other potential causes of ischemic stroke (e.g., cardioembolism).
- In patients with hemorrhagic stroke secondary to underlying vasculopathy, implementation of regular transfusion support may be beneficial for secondary stroke prevention once the bleeding has resolved.

PROPHYLACTIC

Perioperative

- Due to high rates of perioperative complications (e.g., 10% rate of acute chest syndrome typical onset 2-3 days post-operatively) aggressive supportive care and close observation is indicated.^{375,376}
 - ◆ Avoid surgery during vaso-occlusive episodes
 - ◆ IV fluids if NPO \geq 2 hours pre-op and continue post-op until oral fluids tolerated
 - ◆ Maintain SpO₂ >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
- The type and intensity of pre-operative transfusion depends upon three variables: (see table)
 - ◆ the risk of the procedure
 - ◆ the patient's baseline comorbidities
 - ◆ the patient's baseline hemoglobin.
- Pre-operative transfusions (whether top-up or exchange) should be performed within 10 days of the surgical procedure.

SURGICAL PROCEDURE	TRANSFUSION MANAGEMENT
Low risk: Skin, minor dental, perineal, or distal extremity surgery	Transfusion likely not necessary
Moderate risk: Abdominal, oropharyngeal or orthopedic surgery	Hgb <90 g/L top up to 100 g/L; Hgb >90 g/L exchange to HgbS<60%
High risk of serious co-morbidities: Intracranial, cardiovascular, or intrathoracic procedures; scleral buckle Note: in patients with HgbSC, the goal of transfusion is better expressed as a target HgbA%. For example, the goal for a high-risk procedure is to achieve a HgbA > 70 g/L	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 hemoglobin <120 g/L results in a 92% reduction in stroke incidence.³⁷⁷
- 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.³⁷⁸
 - ◆ Transfusion and hydroxyurea need to be overlapped by 4-9 months.³⁷⁹
 - ◆ A safe alternative to transfusion has not yet been established in children who have already experienced a stroke.
- Little evidence to guide initiation of transfusions for either primary or secondary stroke prophylaxis in adults.
- Patients with silent ischemic strokes may also benefit from transfusion, with management advised on a case-by-base basis in consultation with hematology and/or neurology. (e.g., strokes that do not lead to apparent focal neurological symptoms and can only be detected neuroimaging techniques).³⁸⁰

⑤ Supplemental indications for transfusion

For the following indications a trial of transfusion therapy may be considered if non-transfusion therapies (e.g., localized treatment, disease-modifying medications, treatment of comorbidities) have been unsuccessful.

1. Recurrent pain episodes/acute chest syndrome³⁸¹

- In patients who have failed an adequate trial of hydroxyurea or other disease-modifying medication, chronic transfusion support may be considered as a means of decreasing recurrence of vaso-occlusive pain episodes or acute chest syndrome.^{380,382}
- 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).^{371,383}

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.^{384,385}

3. Malleolar ulcers

- Transfusion may speed healing if no response to bed rest, wound care, antibiotics, hyperbaric oxygen.³⁸⁶

4. Pregnancy^{363,387}

- 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 hemoglobin <60 g/L accompanied by a reticulocyte response of <3%.³⁸² However, maternal sickle cell complications were nonetheless decreased.³⁸²

ATTENTION

While the American Society of Hematology acknowledges there is insufficient evidence to recommend a strategy of prophylactic transfusion rather than standard care in pregnant sickle cell patients, prophylactic transfusion at regular intervals at the onset of pregnancy should nonetheless be considered for women with: a history of severe sickle cell-related complications before the current pregnancy (including during previous pregnancies) with the goal of reducing recurrent pain episodes or other complications in the mother, and additional features of high-risk pregnancy (e.g., nephropathy), with the goal of improving fetal outcomes. Moreover, women who develop SCD-related complications during the current pregnancy may benefit from initiating regular transfusion.

5. Pulmonary hypertension³⁸⁸

- Defined as a resting mean pulmonary pressure (mPAP) > 20 mmHg on right heart catheterization. An increased tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/sec is associated with increased morbidity and mortality but is only a screening tool for pulmonary hypertension, which requires a pulmonary artery catheterization to both confirm the diagnosis and to distinguish pre- from post-capillary causes.
- In patients with TRV of >2.5 m/s, NT-pro-BNP >160 pg/ml, or pre-capillary pulmonary hypertension (i.e., pulmonary arterial hypertension) confirmed by right heart catheterization, chronic transfusion therapy should be considered if lack of response (or contraindication) to treatment with hydroxyurea.³⁸⁸

ATTENTION

Priapism, pulmonary hypertension and malleolar ulcers may represent complications of chronic intravascular hemolysis (e.g., nitric oxide depletion) rather than acute vaso-occlusion.³⁸⁸

F Transfusion Complications

Delayed hemolytic transfusion reactions

- Without prophylactic phenotypic matching, alloimmunization rates of 19 to 43% have been reported in transfused sickle cell disease patients, with the majority of antibodies directed towards the C, E and K1 antigens.³⁷¹
 - Alloimmunization is due in part to genetic differences in the antigens expressed on RBCs in the donor population (primarily Caucasians) vs. 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.³⁶⁷
- Prophylactic matching for antigens therefore advised when selecting RBCs for sickle cell patients; advance notification of hospital transfusion service required.
 - Prophylactic matching decreases the rate of alloimmunization (from 3.0% to 0.5%/unit) but it remains an issue.³⁸⁹
- Due to the high frequency of variant RBC antigens in individuals of African ethnicity, genotyping of patients with sickle cell disease is highly recommended.³⁶³

ATTENTION

Alloimmunized sickle cell patients require an antibody card.

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

Hyperhemolysis^{390,391}

- Defined as post-transfusion RBC destruction accompanied by fall in hemoglobin to below pre-transfusion levels.
 - Hemolytic indices increased from baseline, occasionally accompanied by relative reticulocytopenia.
 - Acute: occurs less than 7 days after transfusion, often with no new antibodies detectable.
 - Delayed: occurs between 1 and 4 weeks following transfusion and often accompanied by new RBC antibodies.
- Enhanced hemolysis appears to involve both transfused and autologous RBCs, and may be exacerbated by further transfusion of even crossmatch compatible/antigen-negative RBCs.

ATTENTION

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

- Patients requiring emergency transfusion support who are at high-risk of hyperhemolysis should be considered for administration of pre-transfusion rituximab.
- Avoid further transfusions, if at all possible:**
 - Treat with IVIG 2 g/kg over 2-5 days and high dose steroids (e.g., Prednisolone 1 mg/kg/d x 7 days).³⁹²
 - Consider brief course of erythropoietin if relative reticulocytopenia.³⁹²
 - If accompanied by acute organ failure, or if first line therapies have failed, eculizumab may be indicated.³⁶³

Hyperviscosity³⁹³

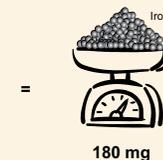
- Sudden onset hypertension during or shortly after transfusion, accompanied by signs of congestive heart failure and profound alterations in mental status, including stupor, coma, seizures, or features of intra-cerebral infarct or hemorrhage.³⁹⁴
- Risk increases if hemoglobin transfused above 100-110 g/L in patients with SCD and HgbS% >25%, particularly if patient dehydrated and hypoxemic.³⁹⁵
 - May also occur secondary to auto-transfusion following transfusion support of sequestration crises.
- Manage with emergency phlebotomy.

ATTENTION

Patients with a hemoglobin > 110 g/L may require phlebotomy to decrease viscosity effects

Transfusional iron overload

- Each transfused unit of RBCs delivers 180 mg of iron.¹⁹
- Significant iron overload therefore likely after repeated top-up transfusions: may eventually result in hepatic injury, particularly when serum ferritin > 2500 µg/mL or when calibrated MRI measures a liver iron concentration > 7 mg/g dry weight.³⁹⁶
- Patients with transfusional iron overload should be followed by a hematologist with expertise in sickle cell disease for iron overload and iron chelation therapy initiated where indicated.



Appendix A

Price List³⁹⁷

ITEM	PRICE
1 unit red blood cells*	\$421
Pooled platelets (dose)**	\$192
Apheresis platelets (dose)	\$480
4 units frozen plasma***	\$504
Fibrinogen Concentrates <i>per gram</i>	\$424
IG <i>per gram</i>	\$60
Albumin <i>per 25 gram equivalent</i>	\$61
Blood group (ABO, Rh D)	\$10
Antibody screen	\$10
Crossmatch (no antibody)	\$25
Crossmatch (antibody positive patient)	\$30
Prothrombin Complex Concentrates 1,000 IU	\$558
Recominant Factor VIIa/mg	\$1,222
Anti-D 300 ug	\$86

* 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).³⁹⁸

** This cost refers only to the acquisition cost of a platelet unit.
The total cost of a platelet is \$1359.99 per unit.³⁹⁹

*** 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.⁴⁰⁰

A complete list of references for this pocket guide can be found on the ORBCoN website at <https://transfusionontario.org/en/category/bloody-easy-e-tools-publications/bloody-easy-for-healthcare-professionals/>

Check out these other Bloody Easy Handbooks available:

Bloody Easy Blood Administration



Bloody Easy Blood Administration handbook is designed 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 Simplified



Bloody Easy Coagulation Simplified 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 bleeding disorders.

Design and layout by Hope Creative Inc., Toronto, Ontario

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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: <ul style="list-style-type: none"> <input type="checkbox"/> TACO 1 in 100 <input type="checkbox"/> Delayed reaction 1 in 2,500 <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: <ul style="list-style-type: none"> <input type="checkbox"/> Hodgkin's lymphoma <input type="checkbox"/> Allogeneic or autologous stem cell transplant or CAR-T cell infusion <input type="checkbox"/> Ever treated with Alemtuzumab (anti-CD52), Anti-thymocyte globulin (ATG), Bendamustine, Cladribine (2-CDA), Clofarabine, Deoxycoformicin, Fludarabine, Nelarabine <input type="checkbox"/> Congenital immunodeficiencies
Diuretics?	Does my patient have a history of: <ul style="list-style-type: none"> <input type="checkbox"/> Age greater ≥ 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

