Chapter 10: Adverse Reactions

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A. REPORTING

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

What:

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

How:

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

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

B. REACTION BY SYMPTOM

<table>
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<tr>
<th>Symptom</th>
<th>Consider</th>
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<td>Fever</td>
<td><strong>Management Algorithm Possible Reactions:</strong></td>
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<td></td>
<td>- Bacterial sepsis or contamination</td>
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<td>- Acute hemolytic transfusion reaction</td>
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<td>- Febrile non-hemolytic transfusion reaction (FNHTR)</td>
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<td>Dyspnea</td>
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<td></td>
<td>- Transfusion-related acute lung injury (TRALI)</td>
</tr>
<tr>
<td></td>
<td>- Transfusion-associated circulatory overload (TACO)</td>
</tr>
</tbody>
</table>
### Symptom | Consider
--- | ---
**Urticaria & Other Allergic Reactions/Anaphylaxis** | Management Algorithm
**Possible Reactions:**
- Anaphylaxis
- Minor allergic reaction – Urticaria

**Hypotension** | Management Algorithm
**Possible Reactions:**
- Bradykinin mediated hypotension

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

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

**Virus, Parasite, and Prion Infections** | - Viruses
- Parasites
- Prions
- Other transfusion-transmissible agents

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**FEVER**

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**Published:** Monday, March 27, 2017

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Fever (and/or Shaking Chills/Rigors)

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

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

Clerical error or serious symptoms?
Temperature ≥39 °C, hypotension/shock, tachycardia, shaking chills/rigors, anxiety, dyspnea, back/chest pain, hemoglobinuria/oliguria, bleeding from IV sites, nausea/vomiting

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must administer acetaminophen 325-650 mg</td>
<td>DO NOT RESTART TRANSFUSION</td>
</tr>
</tbody>
</table>
| Continue transfusion cautiously under observation; likely a febrile non-hemolytic transfusion reaction | SUSPECT
1. Hemolytic transfusion reaction; OR
2. Bacterial contamination
   • Collect blood bank specimen to re-check ABO-group
   • Clamp tubing, send unit to hospital blood bank along with attached IV solutions for bacterial cultures and gram stain
   • Send first post-transfusion urine specimen
   • Send blood cultures on patient taken from a different IV site
| Stop the transfusion if patient develops any of the above symptoms |
Bacterial Sepsis or Contamination

Etiology [reference 1]

Blood components may be contaminated by:

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

- Organisms
  - Serious morbidity and mortality occur most frequently with Gram-negative bacteria,² but are also reported with Gram-positive skin bacteria
  - A number of bacteria have been implicated, including:¹³

<table>
<thead>
<tr>
<th>Gram-negative</th>
<th>Gram-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>Staphylococcus epidermidis</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>Bacillus cereus</td>
</tr>
<tr>
<td>Pseudomonas speci</td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
</tr>
</tbody>
</table>

Incidence [references 1, 2, 4, 5, 6, 7]
Bacterial contamination | Symptomatic septic reactions | Fatal bacterial sepsis
---|---|---
Buffy coat platelet pool | 1 in 1,000 | 1 in 10,000 | 1 in 200,000
1 unit of RBC | 1 in 50,000 | 1 in 250,000 | 1 in 500,000

- Bacterial sepsis accounts for at least 10% of transfusion-associated fatalities. ³
- Bacterial sepsis occurs most frequently with platelets due to their storage at 20-24ºC for preservation of function
- About two thirds are Gram-positive and one third Gram-negative. ³

Clinical Presentation

- Clinical features of transfusion-associated sepsis may include: ⁵,⁸
  - 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 ⁷

Management [references 6, 8]

- If transfusion-transmitted bacterial infection is suspected:
  - Stop the transfusion!
  - Notify the hospital transfusion service (blood bank)
    - Hospital transfusion service (blood bank) will notify the supplier so that:
      - other products from the same donor(s) can be quarantined, cultured, and discarded AND
      - any recipients of other products can be identified and followed up

**ATTENTION**

Stop transfusion immediately if bacterial infection is suspected.

- 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

Published: Monday, March 27, 2017

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**Attention**

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

- DO NOT WAIT FOR RESULTS OF BLOOD CULTURES PRIOR TO STARTING ANTIBIOTIC THERAPY

**Attention**

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

### Prevention

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

**Attention**

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

### Acute Hemolytic Transfusion Reaction

#### Etiology

- Acute hemolytic transfusion reactions may be associated with:
  - ABO-incompatibility
  - Other blood group incompatibilities
    - There are 29 blood group systems and 346 known blood group antigens that may cause incompatibility (in addition to ABO)⁹
    - Rare cases when group O platelets with high titers of anti-A and/or anti-B are transfused to a non-group O recipient¹⁰
  - **ABO-incompatibility**
    - Is due to a clerical error or other error in patient identification
    - HALF of all errors are due to administering properly labelled blood to the wrong patient¹¹

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Other errors are the result of improper labelling of specimens or testing errors

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

### Incidence

- 1 in 38,000 RBC transfusions are ABO-incompatible due to transfusing the wrong blood to a patient.\(^{11}\)
- Less than 10% of ABO-incompatible transfusions result in a fatal outcome.\(^{11}\)
- Over 50% of patients have no morbidity from an ABO-incompatible transfusion.
- Risk of death correlates with the amount of incompatible blood transfused.\(^{12}\)

### Clinical Presentation [reference 13]

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

**ATTENTION**

Stop transfusion immediately if acute hemolytic reaction suspected.

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

Prevention

**ATTENTION**

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

- 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).

Febrile Non-Hemolytic Transfusion Reaction (FNHTR)

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Etiology

Attributable to:

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

Incidence [reference 15]

<table>
<thead>
<tr>
<th>Component</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Platelet pool</td>
<td>1 in 20</td>
</tr>
</tbody>
</table>

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

Management

**ATTENTION**

Fever is not a contraindication to continuing a blood transfusion!

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

Prevention

- Pre-medication with acetaminophen and diphenhydramine has not been shown to be effective in preventing FNHTR.\(^\text{16,17}\)
- In patients with significant and recurrent FNHTR, the following measures have been used but efficacy is unproven:
  - Acetaminophen, corticosteroids, fresh components, plasma-depleted components, washed red blood cells (washing platelets results in 50% loss of platelets)
  - Antihistamines are not effective.

**DYSPNEA**

(Anaphylaxis is described under Allergic Reactions/Anaphylaxis)
Transfusion-Related Acute Lung Injury (TRALI) [references 18, 19]

Definition of Acute Lung Injury (ALI)

- Acute onset.
- Hypoxemia:
  - $\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$; OR
  - Oxygen saturation is $< 90\%$ on room air; OR
  - Other clinical evidence
- Bilateral lung infiltrates on the chest radiograph.
- No evidence of circulatory overload.
Definition of TRALI

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

Definition of Possible TRALI

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

RISK FACTORS FOR ACUTE LUNG INJURY
Predisposing factors for ALI include:
- Direct Lung Injury
  - Aspiration
  - Pneumonia
  - Toxic inhalation
  - Lung contusion
  - Near drowning
- Indirect Lung Injury
  - Severe sepsis
  - Shock
  - Multiple trauma
  - Burn injury
  - Acute pancreatitis
  - Cardiopulmonary bypass
  - Drug overdose
Etiology

- Presently not fully defined. Two postulated mechanisms have been implicated:¹⁹,²⁰
  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).²¹,²²
     - 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.²³

Incidence

- True incidence of this syndrome is unknown two separate hospital-based reports estimate TRALI at 1 in 1,200 to 5,000 plasma-containing transfusions, respectively.²¹,²⁴ (Both studies were performed before TRALI reduction measures). ²¹, ²⁴
- The incidence of TRALI has decreased by approximately half with implementation of TRALI reduction measures with SHOT and American Red Cross reporting large reductions in cases (see Prevention).⁷⁶, ²⁵
- TRALI is known to be under-diagnosed and under-reported.

Presentation

- Dyspnea, hypoxemia, fever and hypotension.
- Chest X-ray reveals interstitial and alveolar infiltrates (pulmonary edema), without elevated pulmonary
pressures.
- Usually occurs with transfusion of RBCs, platelets and plasma, but rarely with other blood products (including cryoprecipitate and IVIG).
- Almost always within the first 1-2 hours after the start of transfusion but can be delayed for up to 6 hours.\textsuperscript{21}
- 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.\textsuperscript{21}
- Milder forms of TRALI are thought to exist and may present as transient hypoxia.\textsuperscript{26}
- Acute transient leukopenia may be observed after a TRALI reaction.\textsuperscript{27}

Management

- Supportive care, including mechanical ventilation when clinically indicated.
- Diuretics and steroids are not believed to be useful in treating TRALI.\textsuperscript{28}
- 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).

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

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{chest_x-ray.png}
\caption{Chest X-ray of a patient before and during an episode of transfusion-related acute lung injury (TRALI).}
\end{figure}
Prevention

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

Transfusion-Associated Circulatory Overload (TACO) [reference 29]

Etiology

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

Incidence

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

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

Management

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

Prevention


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

Preventative measures include:
- Avoid transfusing more than one unit at a time.
- Transfuse over longer periods (maximum 4 hours)
- Pre-emptive diuretics
- Components can be split into smaller aliquots to further reduce the speed of infusion without wasting product or increasing donor exposure

**URTICARIA AND OTHER ALLERGIC REACTIONS/ANAPHYLAXIS**
### MANAGEMENT ALGORITHM

#### Allergic Reaction

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

**Immediate Management:**
1. Interrupt the transfusion & maintain IV access
2. Take the patient’s vital signs
3. Re-check identification of patient and blood product
4. Physician assessment required
5. Notify hospital transfusion service (blood bank) even if transfusion restarted or already completed

#### Clerical error, anaphylaxis or serious symptoms?

- Hypotension
- Dyspnea/cough
- Tachycardia
- Generalized flushing or anxiety
- Nausea/vomiting
- Widespread rash >1/3 body

**Flowchart:**

- **No**
  - Consistent with minor allergic reaction
  - Give diphenhydramine 25-50 mg IV/po
  - Continue transfusion cautiously
  - Stop transfusion if patient develops any of the above symptoms

- **Yes**
  - DO NOT RESTART TRANSFUSION
    - Notify the patient’s physician STAT
    - Notify the hospital transfusion service (blood bank) immediately
  - SUSPECT ANAPHYLACTOID REACTION/ANAPHYLAXIS

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**Anaphylaxis**

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Etiology [reference 30]

- Vast majority of anaphylactic reactions are unexplained.
- The following mechanisms have been implicated in anaphylaxis/anaphylactoid reactions:
  - Anti-IgA in an IgA deficient recipient
  - Antibodies to polymorphic forms of serum proteins (IgG, albumin, haptoglobin, α-1-antitrypsin, transferrin, C3, C4, etc.)
  - Transfusing an allergen to a sensitized patient (e.g., penicillin, ASA, etc., consumed by donor)
  - Passive transfer of IgE (to drugs, food)
- 1 in 500 blood donors are IgA deficient (IgA <0.05 mg/dL), and 1 in 1,500 blood donors have anti-IgA, but most are NOT at risk of an anaphylactic transfusion reaction (reasons are not clear at this time).\(^3\)! \(^3\)
  - Anti-IgA as a cause of anaphylaxis from transfusion has recently been called into question due to the lack of evidence implicating IgA deficiency in this entity.\(^3\)
- Haptoglobin deficiency is not uncommon in Asian patients (1 in 1,000) and has been associated with anaphylactic reactions.\(^3\)

Incidence

- Transfusion-associated anaphylactic shock is rare.\(^3\)
- Anaphylaxis accounts for approximately 5% of transfusion associated fatalities.\(^3\)

Clinical Presentation [reference 30]

- 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
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ATTENTION

Stop the transfusion! Do not restart.

- 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.

ATTENTION

Epinephrine should be readily available whenever transfusion is carried out.

Prevention of Recurrent Anaphylaxis

- Pre-medication with intravenous steroids and diphenhydramine.
- If a patient is found to be IgA-deficient with anti-IgA, the following products are recommended:
  - IgA-deficient blood products from IgA-deficient donors, available from CBS/HQ.
  - Washed RBCs (2L normal saline in 6 wash cycles) or platelets.30,35

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.36


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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

**ATTENTION**

Interrupt transfusion.
Give diphenhydramine.
Restart transfusion slowly.

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

Prevention

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

HYPOTENSION [REFERENCE 37]
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Chapter 10: Adverse Reactions

**MANAGEMENT ALGORITHM**

**Hypotension**

>30 mmHg drop in systolic or diastolic blood pressure*

**Immediate Management:**
1. Stop the transfusion and maintain IV access
2. Take patient's vital signs
3. Re-check identification of patient & blood product
4. Consider differential diagnosis
5. Physician assessment required

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

**No**
unrelated to transfusion

Possibly resume transfusion after reassessing

**Yes**

Do not restart transfusion.
Refer to appropriate sections.

*Definition refers to adult patients only

**Pediatrics**

Hypotension in children is defined as:

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


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Bradykinin Mediated Hypotension

Etiology

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

Incidence

- Unknown.

Clinical Presentation

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

Treatment
CLINICAL GUIDE TO TRANSFUSION

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ATTENTION

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

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

Prevention

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

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, blood warmer malfunction)
  - Overheating of RBCs due to improper storage (e.g., RBCs placed on radiator)
  - Freezing of RBCs (e.g., transport of blood directly on ice or storage in freezer)
  - Transfusion of RBCs under pressure through a small bore needle
  - Transfusion of outdated or near outdated RBCs
  - Non-transfusion-related causes
- Most are benign, but life threatening hemolysis with severe anemia and renal failure may occur.

Delayed Hemolytic Transfusion Reactions

Etiology

- Results from the formation of antibodies in the recipient (to transfused red cell alloantigens or from RBC antigen exposure during a prior pregnancy) and below the level of detection on the initial antibody screen testing.
- Commonly implicated antigens are (in order of frequency): E, Jk", c, Fy", K.38
• 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. 77
• 1 in 6,715 units of RBCs transfused are associated with a delayed haemolytic transfusion reaction. 38

Clinical Presentation

• 3 days to 2 weeks after transfusion, the patient presents with hemolytic anemia (low hemoglobin, high bilirubin, reticulocytosis, spherocytosis, high LDH, positive antibody screen, and a positive direct anti-globulin test). 39

Complications

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

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

Prevention

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

Transfusion-Associated Graft vs Host Disease (TA-GvHD) [references 40, 41]

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.)
  - 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
Chapter 10: Adverse Reactions

Incidence

- Unknown; there were 13 cases reported in the UK SHOT program from 1996 to 2001; since 2001 there has been one case in 2012 attributed to failure to irradiate maternal blood for an intra-uterine fetal transfusion.76

Clinical Presentation

- Fever, rash, liver dysfunction, and diarrhea commencing 1-2 weeks post-transfusion followed by pancytopenia later.
- Overwhelming infections are the most common cause of death.
- Mortality is >90%.43
- Diagnosis can be made by biopsy of skin, liver, or bone marrow.
- Confirmation requires documentation of the presence of donor lymphocytes (e.g., HLA typing, short tandem repeat analysis).

Treatment

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

Prevention

- For patients at risk (see below), it is critical to irradiate cellular blood components (RBC and platelets).
- To avoid unacceptable high hemolysis (>0.8%) and elevated potassium levels from irradiation, adherence to the Council of Europe’s guidelines is advised. Red cells may be irradiated up to 28 days after collection and should be transfused as soon as possible, but no later than 14 days after irradiation, and no later than 28 days after collection.44,45

[Reference46]
Patients requiring irradiated blood

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

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

Post-Transfusion Purpura (PTP) [reference 47]
Etiology

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

Incidence

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

Clinical Presentation

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

Treatment

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

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

Warning

**ATTENTION**

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

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

Transfusion-Related Alloimmune Thrombocytopenia

- Uncommon cause of thrombocytopenia.
- Due to platelet specific donor alloantibodies to patient platelet antigens. ⁴⁹

Transfusion-Related Alloimmune Neutropenia [reference 50]

- Rare cause of neutropenia.

VIRUS, PRION, AND PARASITE INFECTION

(Bacterial contamination is described under Fever)

Viruses

Risks
• Donating blood in the ‘window period’ - the interval between the time of infectivity and the appearance of detectable disease markers such as specific antibodies or viral nucleic acid sequences.

  • Current ‘window period’ estimates are: 51
    ○ 10 days for HIV
    ○ 8 days for HCV
    ○ 38 days for HBV

• Figures in chart below are risk per donor exposure: (i.e., 1 unit of RBC) 52, 53

<table>
<thead>
<tr>
<th>Virus</th>
<th>Risk per Donor Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Nile Virus (WNV)</td>
<td>&lt;1 in 1,000,000</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>1 in 7,500,000</td>
</tr>
<tr>
<td>Human T-cell lymphotropic virus</td>
<td>1 in 7,600,000</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>1 in 13,000,000</td>
</tr>
<tr>
<td>HIV</td>
<td>1 in 21,000,000</td>
</tr>
</tbody>
</table>

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 54

• 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. 55

• The current requirement for residual WBC after leukoreduction is <5.0 X 10^6 WBC/unit.

  • For fiscal year 2014/15 the mean monthly residual WBC far exceeded these requirements (data from CBS):
    ▪ Pooled platelet - 0.006 X 10^6 WBC/unit (fail rate 0.00%)
    ▪ RBCs - 0.063 X 10^6 WBC/unit (fail rate 0.15%)

• CMV serology must be drawn before allogeneic transfusions commence, otherwise false positive results may be found due to passive antibody detection.
West Nile Virus (WNV)

- No reported cases of transfusion transmitted WNV in Canada since nucleic acid testing of donations began in 2003.56
- Facts about transfusion-transmitted WNV:
  - The virus can be transmitted through RBCs, platelets, plasma, and cryoprecipitate, but not through manufactured blood products (e.g., albumin, IVIG, clotting factor concentrates)
  - The onset of symptoms post-transfusion has ranged from 3 to 13 days (median 7 days)
  - Symptomatic recipients were primarily immunocompromised patients; however, post-partum and post-operative patients have been affected

Parasites
Chagas Disease

- Chagas Disease is caused by the protozoan Trypanosoma cruzi found predominantly in Central and South America.
- There have been 7 reported cases of transfusion transmitted Chagas in U.S. and Canada, mostly with platelet products.57
- 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.58

Published: Monday, March 27, 2017

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Prions

Variant Creutzfeldt-Jakob Disease (vCJD)

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

Other Transfusion-Transmissible Agents [references 57, 61, 62]

- 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, Simiam foamy virus and Zika virus
  - Protozoal – Malaria, Babesiosis, Leishmaniasis, Toxoplasmosis
  - Helminthic – Filariasis
  - Spirochetal – Treponema pallidum (Syphilis)
  - Rickettsial – R. rickettsii (Rocky Mountain Spotted Fever), R. burnetii (Q fever), Ehrlichia (Ehrlichiosis)
- It is extremely important to report cases of the above infections in transfusion recipients and recent blood
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.\(^\text{63}\)

[references 67,68]

Complications [reference 64]

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

1. Dilutional coagulopathy
50% of massively-transfused patients develop an INR >2.0 and about 33% have thrombocytopenia with a platelet count <50 x 10^9/L.\(^{65}\)

- Number of RBCs transfused does not accurately predict the need for platelet and FP transfusion; frequent laboratory measurements are required to guide transfusion decisions.
- In one large randomized controlled trial, resuscitation of trauma patients with 1:1:1 was not found to be superior to resuscitation with a ratio of 2:1:1 (RBC:FP:PLT).\(^{56}\)
  - Only patients with extremely rapid hemorrhage were enrolled in this trial and formula-driven resuscitation should not be applied to less extreme hemorrhage situations.\(^{66}\)

### 2. Hypothermia

- Rapid infusion of cold blood can result in cardiac arrhythmias.
- Prevention is critical – if massive transfusion is likely, use an approved and properly maintained blood warmer.
- Mortality after massive transfusion is inversely related to core temperature (data from 1987):\(^{69}\)
  - <34ºC – 40%
  - <33ºC – 69%
  - <32ºC – 100%
- Every 1 ºC drop in temperature increases blood loss by 16% and the risk of transfusion by 22%.\(^{70}\)
- Risk of clinically important hypothermia is significantly increased by infusion of 5 or more units of blood.\(^{69}\)
- Consequences of hypothermia:
  - Platelet dysfunction
  - Decreased coagulation factor activity
  - Reduced clearance of citrate
  - Decreased cardiac output
  - Hypotension
  - Arrhythmias (especially if cold blood is transfused rapidly through a central line)
3. Hypocalcemia/Hypomagnesemia/Citrate toxicity

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

4. Metabolic acidoses

- 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 and tissue hypoperfusion.

5. Hyperkalemia

- 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.
- Order bloodwork q1h (e.g., CBC, INR, PTT, fibrinogen, calcium, arterial blood gas, potassium).
KEY COMPONENTS OF A HOSPITAL
MASSIVE HEMORRHAGE PROTOCOL

Every hospital must have a Massive Hemorrhage Protocol to ensure standardized care is delivered.73

- Prompt use of measures to prevent hypothermia, including use of a blood warmer for all IV fluids and blood components.
- Monitor core temperature and maintain above 36 °C.
- Watch for dilutional coagulopathy with q1h blood work.
  - While patient is actively bleeding, transfuse to keep:
    - Platelet count >50 x 10^9/L
      (with head injury >100 x 10^9/L)
    - INR <1.8
    - Fibrinogen >2.0 g/L
  - Institute ratio-based resuscitation if the required rate of transfusion exceeds 4 units of RBC per hour
  - Administer tranexamic acid 1 gram IV bolus and then 1 gram IV over 8 hours74
- Watch for hypocalcemia, acidosis and hyperkalemia.
- Blood tubing must be changed every 2-4 units and within the number of hours specified by your hospital policy. In massive transfusion this may be impractical so an add-on filter can be used to minimize the frequency of tubing changes. Rapid infusers with large blood filters may allow for less frequent tubing changes.

POSTPARTUM HEMORRHAGE (PPH)

- The above Massive Hemorrhage protocol also applies to the patient with a massive postpartum hemorrhage
- All postpartum females should be closely monitored for early signs of hemorrhage
- Protocols for rapid administration of uterotonics must be in place at all hospitals with obstetrical patients
- Use of intrauterine balloons should be a key part of the early management while a decision is being made

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regarding definitive therapy (i.e., hysterectomy vs. uterine artery embolization).
- RBC transfusion, when indicated clinically, should NOT be delayed while waiting for pre-transfusion testing and uncrossmatched blood should be administered.
  - uncrossmatched blood must be available within 10 minutes of the onset of a postpartum hemorrhage at all hospitals with obstetrics
- Maintain fibrinogen level above 2.0 g/L with early and aggressive use of cryoprecipitate.  

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) Program can claim the reading of the Clinical Guide to Transfusion as a continuing professional development (CPD) activity under Section 2: Self-learning credit. The reading of one chapter is equivalent to two credits.

We’re here to answer your questions about the Clinical Guide to Transfusion. We’d also appreciate your ideas on how to improve the Guide. Please contact us through the Clinical Guide feedback form.

REFERENCES

6. Blajchman MA. Bacterial Contamination and Proliferation During the Storage of Cellular Blood Products. Vox
Chapter 10: Adverse Reactions

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Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podlosky L, Clarke G, Ambruso DR.


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