Safety-Related Adverse Transfusion Reactions

What Reactions are Reportable to Health Canada?

Mélanie Derry, PhD
Scientific Evaluator
Marketed Health Products Directorate
Health Canada
Declaration of conflict of interest

I do not have an affiliation (financial or otherwise) with a pharmaceutical, medical device, or communications organization, or other for-profit funder for this program.
Outline

• Hemovigilance in Canada
  – Health Canada and the Public Health Agency of Canada/Transfusion-Transmitted Injury Surveillance System (TTISS)

• Oversight of blood safety in Canada
  – Roles and responsibilities under the Blood Regulations

• Reportable adverse reactions
Hemovigilance in Canada

Health Canada and the Public Health Agency Of Canada
# Health Canada and Public Health Agency of Canada

## Roles and focus

<table>
<thead>
<tr>
<th>Focus</th>
<th>Health Canada</th>
<th>Public Health Agency of Canada/TTISS</th>
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</table>
| Regulatory oversight of safety of blood supply including risk mitigation actions | Scientific data on transfusion reactions:  
  • Incidence  
  • Mechanisms  
  • Risk factors |
| Goal | Regulatory compliance with *Blood Regulations* | Identification, characterization, management of transfusion-related injuries |
| Reporting | Mandatory | Voluntary |
| Data capture | • Reported as narratives including summary of medical events, investigations  
  • Reported using TTISS forms  
  • Captured as MedDRA terms  
  • Captured as standardized TTISS adverse reaction categories | |
| Key partners | Blood establishments (operators, transfusing establishments) | Provincial/territorial health authorities |
Oversight of blood safety in Canada

Roles and responsibilities under the *Blood Regulations*
Overview of blood safety in Canada

- *Blood Regulations* implemented in October 2014 post-Krever

- Shared responsibility:
  - Blood establishments
    - Blood operators
    - “Downstream” blood establishments, e.g., hospitals
  - Health Canada
    - Marketed Health Products Directorate (MHPD)
      - Reports of recipient adverse reactions to blood
    - Biologics and Genetic Therapies Directorate (BGTD)
      - Reports of donor adverse reactions, processes/materials, etc.
    - Regulatory Operations and Regions Branch (RORB)
      - Compliance and enforcement, including errors and accidents
Key definitions under *Blood Regulations*

- **Adverse reaction**: serious/unexpected reaction associated with the safety of the transfused blood, indicating a risk to human safety or the safety of the blood

- **Serious adverse reaction**: results in:
  - Hospitalization or its prolongation
  - Persistent/significant disability or incapacity
  - Medical/surgical intervention required
  - Life-threatening condition
  - Death

- **Unexpected adverse reaction**: is not identified in the circular of information or any other information provided to recipient

- **Blood establishment**: conducts importation, processing, distribution, transformation, or transfusion of blood
Adverse reactions: reporting requirements

• Initial report: 24 hours (fatal); 15 days (non-fatal) (section 113)
  • Adverse reaction
    – Is this quality/safety-related?
  • Risk management: quarantine, notifications, donor deferral, etc.
  • Any other pertinent information, e.g., process deviations, other adverse reactions associated with the implicated donor(s) (Guidance document)

• Final report (section 115)
  • Results of investigation
  • Final disposition of the implicated blood, including a rationale
  • Any corrective actions or other changes implemented
When you do report to Health Canada?

• Reports required from the investigating institution (section 113)
Blood establishment learns of a serious/unexpected adverse reaction

- **IMMEDIATELY** identify and quarantine all implicated blood *(section 110)*
- **IMMEDIATELY** launch a preliminary investigation to determine root cause of adverse reaction *(section 110)*

If root cause is an activity conducted by **this** blood establishment

- **IMMEDIATELY** notify “downstream” blood establishments *(section 110)*
- Investigate adverse reaction and share results *(sections 110, 114)*
- **Report** adverse reaction to Health Canada *(initial and final reports)* *(section 113, 115)*
Reporting an adverse reaction: a flow chart

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If root cause is an activity conducted by **another** blood establishment

- **IMMEDIATELY** notify “upstream” and “downstream” blood establishments *(section 110)*
- Cooperate with investigation *(section 112)*
Reportable adverse reactions

Quality or safety of the blood
## Reportable adverse reactions: quality/safety of blood

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Example of issue relating to safety/quality of blood</th>
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<tbody>
<tr>
<td>TRALI</td>
<td>• <strong>Immune</strong>: passive transfusion of donor antibodies (anti-HLA/-HNA)</td>
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<tr>
<td></td>
<td>• <strong>Non-immune</strong>: infusion of BRMs (cytokines, neutrophil-priming lipids, etc.)</td>
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<tr>
<td>Infections: bacterial, viral, fungal, etc.</td>
<td>• <strong>Donor-transmitted</strong></td>
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<td></td>
<td>• Contamination during processing, transformation, thawing, etc.</td>
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<td></td>
<td>• Incorrect storage conditions</td>
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<tr>
<td>Hypersensitivity/ anaphylaxis</td>
<td>• <strong>Donor-derived</strong>: passive transfer of IgE/allergen</td>
</tr>
<tr>
<td></td>
<td>• Prolonged/improper storage, transformation, etc. → anaphylatoxins</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>• Labelling error causing ABO incompatibility</td>
</tr>
<tr>
<td></td>
<td>• Improper storage conditions, transformation (irradiation)</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>• Improper irradiation, improper labelling of irradiated component</td>
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<tr>
<td>Metabolic complications</td>
<td>• Improper irradiation/storage of component, e.g., hyperkalemia</td>
</tr>
<tr>
<td>Hypotensive reaction</td>
<td>• Donor-derived vasoactive substances in component</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>• Degradation from transformation, prolonged or improper storage, etc.</td>
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Example 1
Hyperkalemia

F, 6 days, receives irradiated, plasma-reduced red blood cells

Hyperkalemia leading to life-threatening cardiac arrest

Preliminary investigation

Blood bag & syringe → high levels of K

Investigation by blood operator

- Donor had normal serum K
- Other irradiated units of similar age had normal K levels

NO ROOT CAUSE IDENTIFIED
Blood establishments’ responsibilities

Hyperkalemia

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Example 1
The ideal: transfusing establishment investigates

F, 6 days, receives irradiated, plasma-reduced red blood cells

Hyperkalemia leading to life-threatening cardiac arrest

Preliminary investigation

Blood bag & syringe → high levels of K

Investigation by establishment that transformed blood

- Irradiation/washing procedures followed?
- All other procedures followed?
- Contributing factors in patient Hx or medical decisions?

ROOT CAUSE IDENTIFIED?
Example 2
Undiagnosed reaction

M, 69, receives RBC

Dyspnea, $O_2$ desaturation

Results of preliminary investigation not provided

Insufficient info for diagnosis or root cause analysis

Blood operator request for additional data from transfusing establishment

No response from hospital

NO ROOT CAUSE IDENTIFIED
Example 2
Undiagnosed reaction

Blood establishment learns of a serious/unexpected adverse reaction

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Example 3
TRALI

M, 82, receives RBCs

Dyspnea, O2 desaturation, bilateral pulmonary infiltrates, death

Preliminary investigation

No volume overload, cardiac dysfunction; no effect of diuretic: Possible TRALI

Investigation by blood operator

- Donor 1: No HLA antibodies detected
- Donor 2: HLA class I and II detected, cognate with patient HLA

ROOT CAUSE: donor-derived reaction
- Donor 2 permanently deferred
Example 3
TRALI

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14 days
Example 4
Anaphylaxis

F, 70, massive transfusion protocol

Dyspnea, angioedema, death

Preliminary investigation

Anaphylaxis

Investigation by blood operator

- Patient: no hx of allergy; had received piperacillin/tazobactam ~ 3h pre-transfusion
- One donor reported mild allergy to penicillin/amoxicillin; serious allergy to seafood

- ROOT CAUSE: possible passive transfusion of anaphylaxis from donor
- Surveillance code applied to RBC donors
Summary: investigating transfusion reactions

• **Tell us what you think!**

• Investigating and reporting reactions:
  – Investigate root cause: what could have caused the reaction?
  – Consider quality/safety of blood
  – Consider activities carried out by your establishment
  – Notify early
  – Cooperate with investigation – share what you know/suspect/question
Contact us

**Adverse reactions:**
Marketed Health Products Directorate

mhpdp_dpsc@hc-sc.gc.ca

**Errors/accidents, inspections:**
Regulatory Operations and Regions Branch

**NEW** bpcp-pcpb@hc-sc.gc.ca