Transfusion Reaction Module 3

Signs and Symptoms of Transfusion Reactions:

- Common Low-severity
- Delayed Transfusion Reactions
- Delayed Complications

Provincial Health Services Authority

BC Provincial Blood Coordinating Office

A program of the Provincial Health Services Authority

BC Transfusion Medicine Advisory Group

Speaker

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Disclosure:

Dr. Doyle reports receiving one consulting fee from CSL Behring for attending a meeting

Contents of Module 3

- Goals and Objectives of the module
- Introduction
- Transfusion Reaction Types Overview
- Common Low Severity Reactions
  - Febrile Non-Hemolytic Transfusion Reactions (FNHTR)
  - Allergic

Contents of Module 3

Delayed Transfusion Reactions

- Delayed Hemolytic Transfusion Reaction (DHTR)
- Delayed Serological Transfusion Reaction (DSTR)

Delayed Complications of Transfusion

- Immunomodulation
- Iron Overload
- Plasticizer Toxicity
- Transmission of Infectious Disease

Goal & Objectives of Module 3

Goal:

To review the signs, symptoms and management of the following transfusion reactions/ complications:

- Common Low-severity
- Delayed Transfusion Reactions
- Delayed Complications

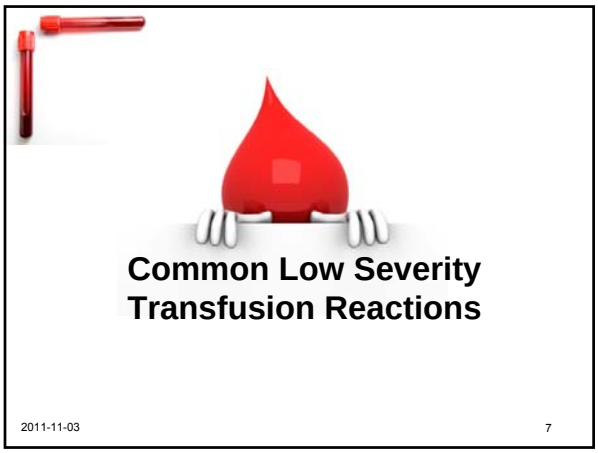
Objectives:

On completion of this module, you should be able to:

- recognize signs and symptoms of these reactions/complications
- apply appropriate management for these reactions/ complications
- direct the laboratory investigation of these reactions/complications
- correctly identify and report the reaction type

Key Points – Module 3

- Signs and symptoms (S/S) may overlap with early S/S of serious transfusion reactions.
- All transfusion reactions should be reported to the Transfusion Medicine Service (TMS/laboratory).
- It may be necessary to treat the patient and/or provide additional components/products before an investigation is completed.
- Low severity transfusion reactions may not require a laboratory investigation but do require a report.
- Remain aware that delayed transfusion reactions occur and present in the community.



Common Low Severity Transfusion Reactions

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Signs & Symptoms of Common Low-severity Transfusion Reactions

System	Signs and Symptoms
cutaneous	• urticaria • pruritus • flushing
inflammatory	• fever • chills • rigors
gastrointestinal	• nausea/vomiting
pain	• headache • joint/muscle pain

Oral temperature ≥38°C **AND** an increase of ≥1°C above pre-transfusion value

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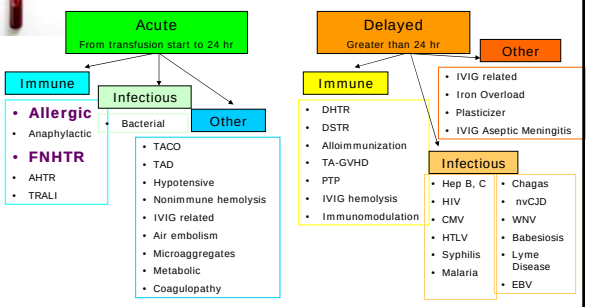
Transfusion Reaction Types

Common Low-severity…



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Case Study 1

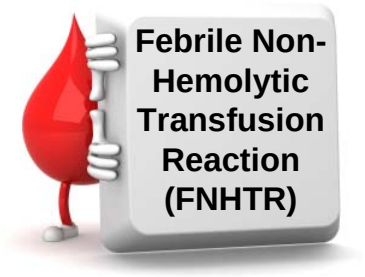
History	An 82 year old female 3 days post total hip arthroplasty with a hemoglobin of 72 g/L is ordered 2 units of RBCs. 10 minutes into the second unit of RBCs, she complains of chills and rigors. The attending nurse immediately stops the transfusion and assesses the patient.
Vital signs	Pre-transfusion: T: 36.2 °C, BP: 110/70 At the time of symptoms: T: 38.1 °C, BP: 115/80

Case Study 1

Bedside investigation	Clerical check of the patient's wristband identification and that of the units of RBCs reveals no errors. The patient appears stable. The attending physician is notified. Both units of RBCs are returned to the lab.
Lab investigations	Clerical check of the tubes and units of RBCs - ok Repeat forward and reverse grouping - ok Repeat cross match (serologic cross match) - ok Direct antiglobulin test (DAT) - neg Urinalysis - ok

Case Study 1

Assessment	Febrile non-hemolytic transfusion reaction (FNHTR).
Plan	Do NOT restart the transfusion.



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In 2010, approximately what percent of BC transfusion reactions were concluded as FNHTR?

1. 15%
2. 30%
3. 50%
4. 80%

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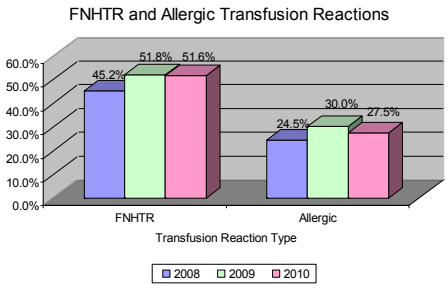
BC Data 2008 - 2010



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FNHTR Symptoms and Signs

Symptoms include:	Signs include:
• chills • general discomfort • sensation of cold • headache • nausea	• fever (±) • rigors • increase in diastolic BP

Oral temperature ≥38°C **AND** an increase of ≥1°C above pre-transfusion value

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Traditional definition FNHTR

- Characterized by an **isolated temperature increase of at least 1 degree C within 24 h of completion of the transfusion**, which is not explained by the patient's condition.
- However, current thinking dictates that a documented **temperature rise** is **NOT necessary to diagnose FNHTR**

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PHAC definition FNHTR

Recipient experiences **one or more** of:
- fever
- chills
- sensation of cold
- rigors

Note 1: ***Recipient may not have a fever.***
Note 2: *Symptoms may be accompanied by headache and nausea within four hours of transfusion completion without any other cause (such as AHTR, bacterial contamination or underlying condition).*

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FNHTR – Causes

Causes

Cytokines: (Biologic Response Modifiers)

- present in the donor unit
- released after a recipient antibody reacts with transfused donor antigen
- Include:
  - β-thromboglobulin
  - platelet factor 4
  - RANTES*
  - transforming growth factor β
  - macrophage inflammatory protein
  - CD 154 (CD40 ligand)
  - Interleukin-7 (IL – 7)

* Regulated upon Activation Normal T-cell Expressed and presumably Secreted

FNHTR – Causes

Causes

Ag-Ab reactions: result in stimulation and release of endogenous **pyrogens** by the donor leukocytes. Pyrogens include:

- Interleukin 1 β (IL - 1β)
- Interleukin 6 (IL – 6)
- Tumour necrosis factor α (TNFα)

Caveat

Pyrexia may be due to a cause other than an acute transfusion reaction, such as the patient's underlying condition.

FNHTR

Onset

- usually occurs at the end of the transfusion
- may occur up to 2 hours afterwards

Frequency

1/200 (platelets – leukocyte reduced)

1/500 (red cell unit – leukocyte reduced)

Results of reaction

- patient discomfort
- fever
- chills
- rigors

FNHTR - Suggested treatment and recommendations:

For all patients	**Stop the transfusion. Do NOT restart.** • Assess the patient's vital signs • Contact ordering physician • Provide symptomatic support • Return the unit to the TMS for investigation. • Send TRR form and samples to TMS/lab.

TMAG recommendations:
Restart of transfusions

Signs & Symptoms	Ongoing transfusion care
Urticaria or Pruritus with any blood component/product	**MAY** restart the transfusion **at** a slower rate **with** appropriate medication **and** frequent vital signs **if** ordered by the physician **after** consultation on the recipient's condition.
All other signs and symptoms	Do NOT restart

TMAG recommendations:
Restart of transfusions in context of fever

Signs & symptoms	Ongoing transfusion care
Fever in recipients where fever is related to their underlying condition	1. In facilities with specialized clinical care services such as Bone Marrow Transplantation and Hematology/Oncology, or other services with high blood and blood component/product usage, it will be at the discretion of the Medical Director of the Transfusion Medicine Service to authorize the clinical care unit(s) to incorporate clinical practice guidelines for the restarting of transfusions in the context of fever.

TMAG recommendations regarding restart of transfusions

Signs & symptoms	Ongoing transfusion care
Fever in recipients where fever is related to their underlying condition	2. Such authorization would be conditional on specialized education of the clinical personnel ordering and administering transfusions regarding the risks and conditions to be met when restarting a transfusion in the context of fever.

TMAG recommendations regarding restart of transfusions

Signs & symptoms	Ongoing transfusion care
Fever in recipients where fever is related to their underlying condition	3. Conditions that must always be met prior to orders being written to restart a transfusion are: • a bedside clinical assessment of the recipient by a physician, **and** • the fever is related to the recipient's underlying condition.

FNHTR - Suggested treatment and recommendations:

Recurrent reactions	For recurrent febrile non-hemolytic transfusion reactions, premedication with an antipyretic may be considered, but is not supported by literature evidence. Consultation with a Transfusion Medicine Pathologist may be helpful if the patient experiences recurrent febrile reactions.
Severe rigors	Consider the use of meperidine (25-50 mg IV) (Demerol®)
Differential diagnosis	Acute hemolytic transfusion reaction Bacterial contamination

Case Study 2

History	A 21 year old male with refractory acute myeloblastic leukemia with a failed BMT is being treated palliatively and receives 1 unit of RBCs to treat a hemoglobin of 66 g/L. 10 minutes into the transfusion, he complains of itchy, red skin over his arms and trunk. The attending nurse stops the transfusion and assesses the patient.
Vital signs	Pre-transfusion: T: 36.9 ºC, BP: 125/80 At the time of reaction: T: 37.1 ºC, BP: 120/80

Case Study 2

Bedside investigation	Clerical check of the patient's wristband and RBCs' identifiers reveals no errors. The patient appears stable and shows no other S/S. The attending physician is notified.
Lab investigations	None necessary

Case Study 2

Assessment	Allergic transfusion reaction.
Plan	CONSIDER using antihistamine and restarting the transfusion after consultation with the patient's physician.

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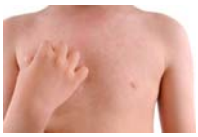
Allergic Symptoms and Signs

Symptoms include:	Signs include:
• itching • nausea	• urticaria • pruritus • localized angioedema (without respiratory distress) • flushing • cough • vomiting or diarrhea



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Allergic

Cause	• Most are unexplained. • Can be as a consequence of recipient responding to allergens in the blood component/product.
Onset	• Usually occurs at the start of the transfusion. • More commonly associated with frozen plasma or platelets.
Frequency	1/100 with plasma-containing components
Results of reaction	• itching • urticaria

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Allergic

Suggested treatment and recommendations:

For all patients:	**Stop the transfusion.** • Maintain IV access with N/S. • Assess vital signs & **c**ontact the physician. • Give diphenhydramine 25 – 50 mg. IV/PO if clinically appropriate. • Reassess the patient 20 minutes later. **MAY** restart the transfusion **at** a slower rate **with** appropriate medication **and** frequent monitoring of vital signs **if** ordered by the physician **after** consultation on the patient's condition. **Do not restart** if there are signs or symptoms of a more serious transfusion reaction.

Allergic

Suggested treatment and recommendations:

Recurrent reactions:	Premedication with an antihistamine may be considered, but is not supported by literature evidence.
Severe Allergic reactions:	Urgent consultation with a Transfusion Medicine Pathologist is suggested if the patient experiences a severe allergic or anaphylactic reaction.

Allergic

Suggested treatment and recommendations:

Laboratory investigation	Samples are not collected. Product/component is not sent to TMS/lab. TMS/lab serological investigation is usually not done.
Differential diagnosis	Reaction to other allergens, such as tape, latex or medications.

Transfusion Reaction Rate Comparison 2008, 2009, 2010
(Components)

	2008		2009		2010	
	N	Rate	N	Rate	N	Rate
Allergic	209	1 in 884	216	1 in 839	186	1 in 961
Febrile Non-Hemolytic	398	1 in 464	390	1 in 465	383	1 in 466

Rate: Transfusion reactions / units transfused

Data Source: Central Transfusion Registry

Transfusion Reaction Rate Comparison 2008, 2009, 2010
(Plasma Protein Products)

	2008		2009		2010	
	N	Rate	N	Rate	N	Rate
Allergic	14	1 in 3187	21	1 in 2133	33	1 in 1420
Febrile Non-Hemolytic	14	1 in 3187	19	1 in 2358	27	1 in 1735

Rate: Transfusion reactions / Plasma Protein Product (PPP) Event. PPP Event is defined as PPP products transfused to a specific patient, at a specific institution on a calendar day

Data Source: Central Transfusion Registry

Case Study 3

History	A 38 year old G3 P3 female received 2 units of RBCs 10 days ago for anemia of 61 g/L after a severe post-partum hemorrhage. She presents to her family MD with fatigue. Her husband has remarked on her yellow skin and eyes. Her pre-transfusion antibody screen had been negative.
Vital signs	T: 37.0 ^{0}C BP: 122/85
Clinic investigations	Careful physical examination done. MD orders CBC and reports a possible transfusion reaction.

Case Study 3

Lab investigations	CBC: Hgb of 65 g/L Bilirubin: elevated Repeat blood group: no change Repeat antibody screen: positive • Anti-Jk^a detected DAT: positive for IgG and C3d! Urinalysis: positive for "blood" on dipstick
Assessment	Delayed hemolytic transfusion reaction (DHTR).

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Delayed Transfusion Reactions

Delayed Complications of Transfusion

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Delayed Transfusion Reactions and Complications

Type	Examples
Transfusion reactions	• Delayed Hemolytic Transfusion Reactions (DHTR) • Delayed Serological Transfusion Reaction (DSTR)
Delayed complications (often not recognized or reported as transfusion reactions)	• Immunomodulation • Iron Overload • Plasticizer toxicity • Transmission of an infectious agent

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Delayed Transfusion Reactions Signs & Symptoms

Symptoms include:	Signs include:
• chills • pain • dyspnea • dizziness	• fever • anticipated rise in Hgb does not ocur • hemoglobinemia • jaundice/hyperbilirubinemia • hemoglobinuria

Oral temperature ≥38°C **AND** an increase of ≥1°C above pre-transfusion value

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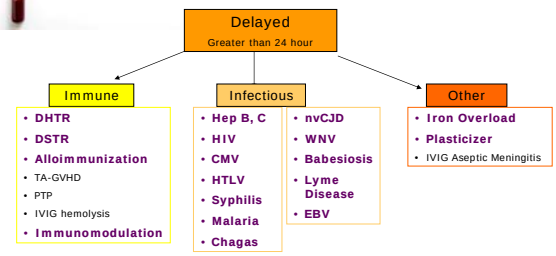
Delayed Transfusion Reaction Types Delayed complications



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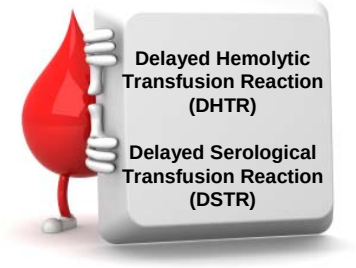

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DHTR

Cause	• Anamnestic alloantibody production • Patient was immunized to red cell antigen by a previous transfusion or pregnancy but antibodies were not detectable. Post-transfusion, antibody production is boosted leading to removal of donor red cells.
Onset	• 4-14 days post transfusion (as early as 2-3 days, but may be as late as 6 weeks) • It is rare for a primary immune response to cause DHTR.

DHTR

Frequency	• 1/7,000 units of RBC transfused • commonly implicated antigens are: E, Jk^a, c, Fy^a, K.[88]
Results of reaction	• usually signs of extravascular hemolysis • anemia, jaundice • rarely – severe anemia or renal failure

DHTR

Suggested treatment and recommendations:

Clinician	Recognize as a possible transfusion reaction. Report to TMS for investigation.
Differential Diagnosis	• Auto-immune hemolysis • Delayed hemolysis due to malaria or babesiosis
Hemolysis work-up	Test CBC and blood chemistry for: – spherocytes, increased WBC, – decreased Hgb – decreased haptoglobin – increased LDH and/or bilirubin
TMS Investigation	Repeat Antibody Screen (If positive do Antibody Investigation) DAT (If positive, confirm antibody with an eluate)

DHTR

Suggested treatment and recommendations:

Clinical Management:	• DHTR usually well tolerated – observation is required. • Usually do not need to fluid load unless intravascular hemolysis is occurring. • Avoid further transfusion, if possible, until specificity of the antibody has been determined and antigen-negative blood is available. • Requires excellent communication between clinician and Transfusion Medicine Medical Director
TMS/lab Management:	• Should provide antigen-negative red cells.

DSTR - Delayed Serological Transfusion Reaction

Cause	Patient forms a new alloantibody to a red cell antigen following transfusion.
Onset	within 28 days post-transfusion
Frequency	rare

DSTR

Common Presentation:

TMS/lab Investigation	• New allo-antibody is detected within 28 days of a previous transfusion • DAT may be positive • Patient has NO clinical or laboratory signs of hemolysis.

DSTR

Suggested treatment and recommendations:

Future transfusions	• If allo-antibody is clinically significant, antigen-negative red cells should be transfused.

Clinical and Lab Distinguishing Features

Type	Serologic Incompatibility	Evidence of Clinical Hemolysis	Time of discovery from transfusion	Response
DHTR	Yes DAT Positive	Yes	3-14 days	anamnestic
DSTR	Yes DAT may be positive	No	within 28 days	new allo-antibody
Allo-immunization	Yes DAT negative	No	> 28 days	new allo-antibody

Immunomodulation

Immunomodulation

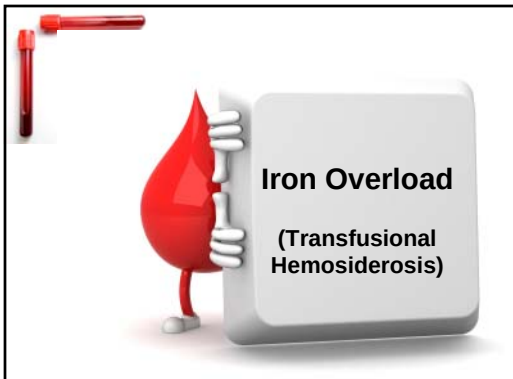
Observations in transfused patients include:

Positive	Negative
• Fewer rejection events after renal transplantation • Reduced recurrence rates of spontaneous abortion and inflammatory bowel disease • May enhance engraftment and survival in BMT patients	• Increased post-operative infection and mortality, but the evidence is inconclusive • Increased tumour spread or recurrence – causality not proved • Recipients who have been transfused have poorer outcome.

Leukoreduction should hypothetically minimize immunomodulation.

Immunomodulation

Cause	Exact mechanism is not clear, but likely relates to a decreased cell-mediated immunity.
Onset	delayed post-transfusion
Frequency	Unknown
Result of Reaction	Conflicting results suggest: • immunosuppression increases the likelihood of infections and/or cancer recurrence • improved survival of renal allografts



Iron Overload Symptoms and Signs

Symptoms include:	Signs include:
• dyspnea • ankle swelling	• jaundice • heart failure • skin hyperpigmentation

Iron Overload

Cause	Patient clinical condition requires multiple transfusions of red cells, in the absence of chronic blood loss. – 1 unit of RBC's contains 250 mgs of elemental iron which cannot be excreted – Excess, unbound, circulating iron is toxic to tissues/organs.
Onset	Adults: usually begins after 20 units invariably after 100 units Child: Chronic transfusion therapy for > 1 year Total transfused volume of 150 ml/kg

Iron Overload

At Risk	Occurs in patients with thalassemia, hemoglobinopathy, Myelodysplastic Syndrome (MDS) and marrow failure who do not receive curative therapy
Results of Reaction	progressive cardiac, liver, pancreatic, and endocrine damage leading to eventual failure

Iron Overload – Chelation

Suggested treatment and recommendations:	
Chelation therapy	Thalassemia and hemoglobinopathy patients requiring lifelong RBC transfusion therapy should start chelation therapy as early as possible.

May be considered for	Transfusion of red cells:	Serum ferritin levels reach
adult	20 -30 units	1000-2000 ng/mL
child	10 units	1000 ng/mL

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Harmful Effects - Plasticizer (DEHP) Toxicity

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Risks to use of Plasticizer DEHP

Issue:

- DEHP (di-2-ethylhexyl phthalate) leaches from plastic used to store medical fluids or from IV lines/administration sets
  - associated with liver tumours and reduced sperm count in rats
  - effects not confirmed in humans
- At-risk patient populations include:
  - all infants, particularly newborn males
  - pregnant woman carrying male fetus
  - patients with prolonged exposure to plastics such as dialysis, transfusion, cardiac bypass, ECLS (extracorporeal life support)

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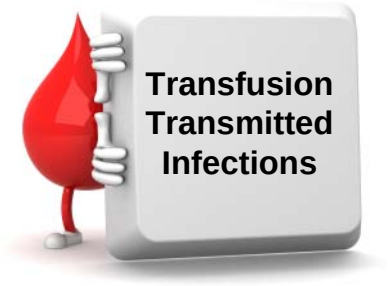
Risks of Plasticizer DEHP:
Component bags and administration sets

Blood Components/Products:

- DEHP has been used for many years as a blood bag plasticizer, but there is no record of it being associated with major side effects in recipients.
- Potential risk as DEHP leaches into "older" red cells:
  - **may be an issue for newborns/infants with strategies to minimize donor exposure being used**
  - **possible risk for adults receiving multiple units of "older" red cells.**
- An alternative product that maintains the current life-span of red cells is not available at present.

DEHP (blood bag plasticizer)

Component/ Product	Risk
Red blood cells (more DEHP in older units)	• may be a risk to newborns and infants receiving 3 - 4 transfusions from "older blood" • possible risk for adult receiving multiple transfusions (no clinical evidence)
Platelets	• none – DEHP plasticizer not used in platelets bag.
Albumin	• limited exposure in extraction
Plasma	• minimal risk – for adults, thawed plasma storage limit is 5 days – for children, thawed plasma storage limit is 12 hours
IVIG	• unknown
Recombinant factors	• none – Product is usually in glass vials, therefore no risk.



Delayed Infections Transmitted by Transfused Component or Product

Key Points:

- Infections can be transmitted by a blood component/product.
- These may be either recognized or novel infections.
- All infections possibly related to transfusion MUST be reported to CBS and to a surveillance system.

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Known Transfusion Transmitted Infections:

- Viral
  - Hepatitis B, C, A, D
  - HIV
  - HTLV
  - WNV
  - EBV
  - Parvovirus B19
  - CMV
    - risk in pregnancy, neonates, immunocompromised patients
- Parasitic/Protozoal
  - Malaria
  - Chagas Disease
  - Babesiosis
- Prion – nvCJD
- Bacterial
  - Syphilis
  - Lyme Disease

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Infections

Cause	Infectious organism is transmitted through donated blood
Onset	Delayed - weeks or months to many years post-transfusion.
Frequency	Rare as donor samples are screened for known infectious agents.
Results of reaction	Transfer of disease to a recipient, their sexual partner or to an infant by vertical transmission.

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Course Contributors – Advisory Panel

Thanks to:	Health Authority	Advisory Group
Dr. Kate Chipperfield	VCH	TMAG
Dr. Jason Doyle	IH	TMAG
Dr. Doug Morrison	FH	TMAG
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Included are members of:

- BC Transfusion Medicine Advisory Group (TMAG)
- BC Transfusion Transmitted Injuries Surveillance System Working Group (BC TTISS WG)
- Technical Resource Group (TRG)
- Nursing Resource Group (NRG)

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Questions?

Upcoming Live Webinars

Date / Time	Topic	Speaker
November 17, 2011 12:00 to 1:00pm	Immunoglobulin Related Reactions	Dr. Doug Morrison MD FRCPC Medical Director, Transfusion Medicine Lab, FH
December 1, 2011 12:00 to 1:00pm	Transfusion Reaction Reporting and Surveillance	Dr. Louis Wadsworth MB FRCP(C) FRCPath, Clinical Professor, Department of Pathology, UBC
December 15, 2011 12:00 to 1:00pm	Transfusion Reaction Annual Data Reports and Case Studies	Dr. Kate Chipperfield MD FRCPC Regional Medical Leader, Blood Transfusion Medicine, VCH

Next Steps

- **Visit LearningHub** - LearningHub Link
  https://edreg.cw.bc.ca/phsaedcalendar/Home.aspx
- **Note:**
  - Need LearningHub Username and Password
  - Confirm your email with LearningHub if not done
- **Complete:**
  - Participant Evaluation
  - Quiz (**Closes midnight November 4, 2011**)