ORBCoN
Ontario Regional Blood Coordinating Network

bloody easy

Hamilton Health Sciences

Acute Hypotensive Reactions

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Transfusion Medicine Boot Camp for Nurses
November 27, 2024

Disclosure

Patient case information presented is fictitious, fabricated to enhance this learning opportunity.

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Learning Objectives

1. To review a case scenario suspicious for acute hypotensive reactions

2. To provide an overview of acute hypotensive reactions and their differentials

3. To outline new data from TTISS-ON and the literature on acute hypotensive reactions

John’s story

- John, 66 years old, Metastatic prostate cancer, dyslipidemia, hypertension, obesity and colon polyps.
- Admitted to 6 West at Hamilton General Hospital post surgery.
- **Medications:** Ramipril, Atorvastatin
- **Blood Group:** A+
- **Antibody Screen:** Negative
- **Transfusion**: Yes < 3 mo.
- I unit **Red Cell Concentrate (RCC)** transfusion started @12:00

Vital Signs

Vital Signs	Temperature (^{0}C)	BP (mmHg)	Pulse (per minute)	Respirations (per minute)	Oxygen Saturation (%)
Pre-Transfusion	36.9	122/68	76	18	95
Post-Transfusion	37.1	82/52	92	20	95

Clinical Observation

- Nausea/vomiting
- Facial flushing

Measures Taken

- Transfusion Stopped
- Chest X-ray: normal/unchanged from previous
- Blood work: Hemoglobin: **68**
  - was 78 Pre-Transfusion
- Patient Blood culture: pending
- Urinalysis: Negative

Poll Question

Pre-Transfusion knowledge

Possible Etiology?

a) Bacterial contamination
b) Acute hemolytic transfusion reaction
c) Anaphylactic reaction
d) TRALI
e) Hypotensive reaction

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Hypotensive Reaction?

- Before confirming, let's rule out other explanations for hypotensive reaction

Bacterial Contamination?

- ☒ Dyspnea
- ☑ Hypotension
- ☒ Fever

Vital Signs	Temperature (^{0}C)	BP (mmHg)	Pulse (per minute)	Respirations (per minute)	Oxygen Saturation (%)
Pre-Transfusion	36.9	122/68	76	18	95
Post-Transfusion	37.1	82/52	92	20	95

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Acute Hemolytic?

- ☒ Dyspnea
- ☒ Hemoglobinuria
- ☑ Hypotension
- ☒ Fever

Vital Signs	Temperature (^{0}C)	BP (mmHg)	Pulse (per minute)	Respirations (per minute)	Oxygen Saturation (%)
Pre-Transfusion	36.9	122/68	76	18	95
Post-Transfusion	37.1	82/52	92	20	95

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Anaphylaxis?

- ☒ Dyspnea
- ☑ Hypotension
- ☒ Urticaria
- ☒ Airway or Facial Edema

Vital Signs	Temperature (^{0}C)	BP (mmHg)	Pulse (per minute)	Respirations (per minute)	Oxygen Saturation (%)
Pre-Transfusion	36.9	122/68	76	18	95
Post-Transfusion	37.1	82/52	92	20	95

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TRALI?

- ☒ ACUTE Dyspnea
- ☑ Hypotension
- ☒ Urticaria
- ☒ Tachycardia
- ☒ Fever

Vital Signs	Temperature (^{0}C)	BP (mmHg)	Pulse (per minute)	Respirations (per minute)	Oxygen Saturation (%)
Pre-Transfusion	36.9	122/68	76	18	95
Post-Transfusion	37.1	82/52	92	20	95

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HYPOTENSIVE?

- ☑ Facial Flushing
- ☑ Hypotension

Vital Signs	Temperature (^{0}C)	BP (mmHg)	Pulse (per minute)	Respirations (per minute)	Oxygen Saturation (%)
Pre-Transfusion	36.9	122/68	76	18	95
Post-Transfusion	37.1	82/52	92	20	95

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Hypotensive Reaction

SBP (Systolic Blood Pressure) 80 mmHg or lower

AND

From pre-transfusion SBP: 30 mmHg or greater absolute decrease

or

15 to 25 % or greater relative decrease

or

intervention required to maintain SBP

- During the transfusion or within 4 hours of its completion without any other explanation for hypotension such as bacterial contamination, bleeding, or severe allergic reaction.

Bradykinin Mediated Hypotension

- Bradykinin is believed to have a major role in producing hypotension.
- Patients taking ACE {angiotensin converting enzyme} inhibitor medication - decreased bradykinin degradation related to increased angiotensin converting enzyme.
- Also, some individuals have genetic polymorphism leading to decreased bradykinin degradation.

Bradykinin

- Bradykinin is vasoactive peptide that binds to receptors on the endothelium and causes hypotension.
- It's primarily metabolized by the Angiotensin Converting Enzymes (ACE) which may be used to manage HTN, by activation of B2 receptors, which lead to Nitric Oxide (NO) and PGI2 production
- Bradykinin is produced after FXII is activated due to contact with negatively charged surfaces (e.g. tubing systems, dialysis membrane or blood filters)

Poll Question

Post-Transfusion knowledge

Medications that would be an alert for very cautious monitoring during and post-transfusion?

a) Aspirin

b) Ramipril

c) Metoprolol

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Transfusion Reaction Patient care

- **DO NOT restart transfusion**
- Supportive care per physician's discretion: IV fluids
- If taking ACE {angiotensin converting enzyme} inhibitor medication, consider an alternative anti-hypertensive agent prior to additional transfusion
- Watch patient closely for the next one hour, developed fever, send blood with tubing to TM for blood culture

Poll Question

Type of Adverse Transfusion Reaction?

a) Bacterial contamination
b) Acute Hemolytic
c) Anaphylaxis
d) TRALI
e) Bradykinin Mediated Hypotension

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Poll Question

Relationship of Adverse Event to Transfusion?

a) Definite
b) Probable
c) Possible
d) Doubtful
e) Ruled Out

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Poll Question

Severity of Adverse Event?

a) Grade 1 (Non-Severe)
b) Grade 2 (Severe)
c) Grade 3 (Life-Threatening)
d) Not Determined

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Poll Question

Outcome of Adverse Event

a) Minor or No Sequelae
b) Major or Long-Term Sequelae
c) Death
d) Not Determined

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Back to John

- **Type of Adverse Transfusion Reaction:**

  Bradykinin Medicated Hypotension

- **Relationship of Adverse Event to Transfusion:**

  Possible

- **Severity of Adverse Event:**

  Grade 1 (Non-Severe)

- **Outcome of Adverse Event:**

  Minor or No Sequelae

TTISS Hypotensive Data (2019-2023)

Year	Count	Possible	Probable	Grade1 (Non-Severe)
2019	1		1	1
2020	0			
2021	3	3		3
2022	1	1		1
2023	1	1		1
TOTAL	6	5	1	6

- ~ 1-3% of total reported Transfusion Reactions
- All Non-Severe

LITERATURE on Hypotensive Reactions

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Hypotensive Reactions Generally Rare

Transfusion reactions: prevention, diagnosis, and treatment

Meghan Delaney, Silvano Wendel, Rachel S Bercovitz, Joan Cid, Claudia Cohn, Nancy M Dunbar, Torunn O Apelseth, Mark Popovsky, Simon J Stanworth, Alan Tinmouth, Leo Van De Watering, Jonathan H Waters, Mark Yazer, Alyssa Ziman, for the Biomedical Excellence for Safer Transfusion (BEST) Collaborative

Lancet 2016; 388: 2825–36

	Prevalence (per 100 000 units transfused)
Allergic transfusion reaction	112·2
Anaphylactic transfusion reaction	8
Acute haemolytic transfusion reaction	2·5–7·9
Delayed haemolytic transfusion reaction	40
Delayed serological transfusion reaction	48·9–75·7
Febrile non-haemolytic transfusion reaction	1000–3000
Hyperhaemolytic transfusion reaction	Unknown
Hypotensive transfusion reaction	1·8–9·0
Massive transfusion associated reactions (citrate, potassium, cold toxicity)	Unknown
Post-transfusion purpura	Unknown
Septic transfusion reaction	0·03–3·3 (product dependent)
Transfusion-associated circulatory overload	10·9
Transfusion-associated graft versus host disease	Extremely rare (near 0%) with irradiation or pathogen reduction methods
Transfusion-associated necrotising enterocolitis	Unknown
Transfusion-related acute lung injury	0·4–1·0 with mitigation (varies by component and post-implementation of risk mitigation strategies)

Table 1: **Rates of transfusion reactions**

Incidence and characteristics of hypotensive transfusion reaction: 10-year experience in a single center

Transfusion. 2022;62:2245–2253.

Blood components	No. of issued component	No. of cases	Incidence[a]
RBC	451,817	21	0.46
pRBC	211,671	12	0.57
Poststorage filtered RBC	8,899	0	0
Prestorage filtered RBC	231,247	9	0.39
Platelet	219,426	14	0.64
RDP[b]	29,887	1	0.33
Poststorage filtered RDP[b]	66,692	5	0.75
SDP	122,847	8	0.65
FFP[c]	70,712	2	0.28
Total	741,955	37	0.50

Abbreviations: RBC, red blood cell; pRBC, packed red blood cell; RDP, random donor platelet; SDP, single-donor apheresis platelets, FFP, fresh frozen plasma.

[a]Incidence is presented as number of cases per 10,000 units transfused.

Bradykinin Is Likely A Key Factor…

- Initially was associated with plasma protein fraction (PPF; predecessor for albumin) and linked to FXII in the 1970s.
- Open label study done in 1982 comparing PPF to albumin as colloid replacement in open heart surgery → higher incidence of hypotension in PPF, correlated with FXII and bradykinin
  - Eventually led to albumin being the colloid of choice
- Recognized again in 1993 where the AABB reported 25 cases of acute hypotension with platelet products
  - Question of interactions with medications and platelet filters?

American Journal of Therapeutics 19, e90–e94 (2012)

Committee Report

Hypotensive reactions: a previously uncharacterized complication of platelet transfusion?

TRANSFUSION 1996;36:904–909.

H.A. HUME, M.A. POPOVSKY, K. BENSON, A.B. GLASSMAN, D. HINES, H.A. OBERMAN, P.T. PISCIOTTO, AND K.C. ANDERSON

Table 2. *Hypotensive PTRs (n = 17): component characteristics*

Characteristic	Number of transfusions
Type of platelet component	
Pooled random-donor	7
Apheresis, not HLA-matched	8
Apheresis, HLA-matched	2
ABO-identical transfusions	
Yes	13
No	4
Length of platelet storage	
≤3 days	5
4 days	5
5 days	6
Unknown	1
Gamma radiation	
Yes	8
No	9
WBC-reduction filtration	
Yes, before storage	2
Yes, at bedside	12
Yes, site and timing not indicated	1
No	2

Table 3. *Hypotensive PTRs (n = 17): clinical characteristics*

Characteristic	Number of transfusions
Time from start of transfusion to onset of reaction	
<15 minutes	7
15 minutes-1 hour	8
>1 hour	1
Unknown	1
Duration of reaction	
<6 hours	14
6-12 hours	1
>12 hours	2

Letters to the Editor

Bradykinin generation during filtration of platelet concentrates with a white cell-reduction filter

TSUNEO A. TAKAHASHI, DSC
HIDEKI ABE, MPHARM
MARI HOSODA, BSC
KUNIHIKO NAKAI, PHD
SADAYOSHI SEKIGUCHI, MD, PHD
Japanese Red Cross
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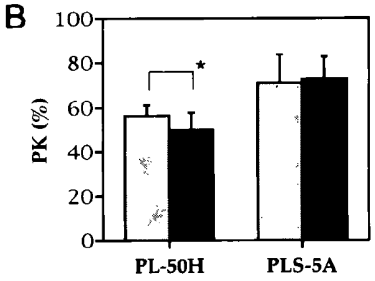
Yamanote 2-2, Nishi-ku
Sapporo, 063 Japan

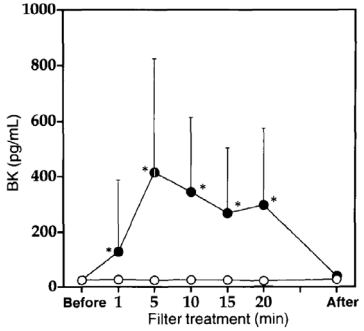
Activation of the contact system by filtration of platelet concentrates with a negatively charged white cell-removal filter and measurement of venous blood bradykinin level in patients who received filtered platelets

M. Shiba, K. Tadokoro, M. Sawanobori, K. Nakajima, K. Suzuki, and T. Juji

From the Department of Research, the Japanese Red Cross Central Blood Center, and the Department of Internal Medicine, the Japanese Red Cross Medical Center, Tokyo, Japan.



Negatively charged filter



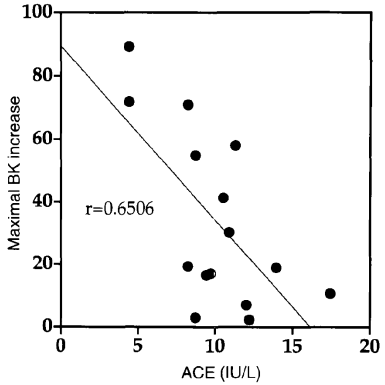
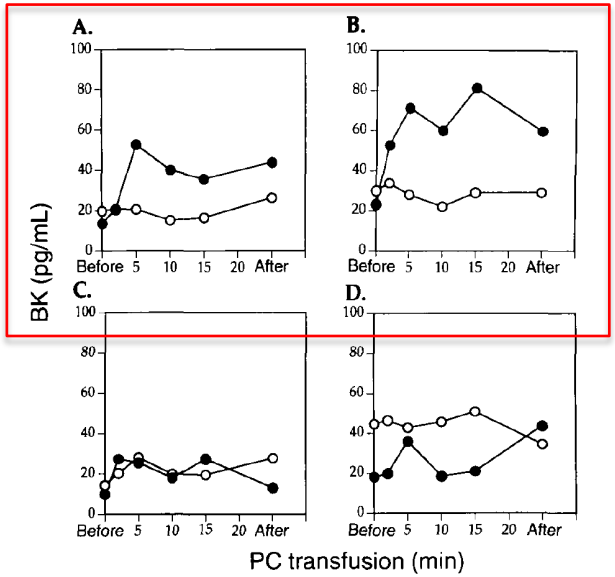


Fig. 4. Effects of ACE activity in PCs on generation of BK by negatively charged WBC-reduction filtration (n = 15).



Atypical reactions associated with use of angiotensin-converting enzyme inhibitors and apheresis

H.G. Owen and M.E. Brecher

TRANSFUSION 1994;34:891–894.

- 299 consecutive patients receiving therapeutic plasma exchange with albumin
- 14 patients with ACE-I all had hypotensive reactions
- 20 of 285 (7%) not receiving ACE-I had hypotensive reactions

Table 1. *Severity of reactions when ACE inhibitors were given or withheld within 24 hours of TPE or were not prescribed*

Drug	Number of patients	ACE given: Reactions			ACE withheld: Reactions		
		Slight	Moderate	Severe	Slight	Moderate	Severe
Enalapril	8	8	5	10	5	1	2
Captopril	6	8	4	2	0	0	0
Lisinopril	1*	1	1	0	0	0	0
Benazepril	1*	1	1	0	1	0	0
Total		18	11	12	6	1	2

* These patients also received enalapril.

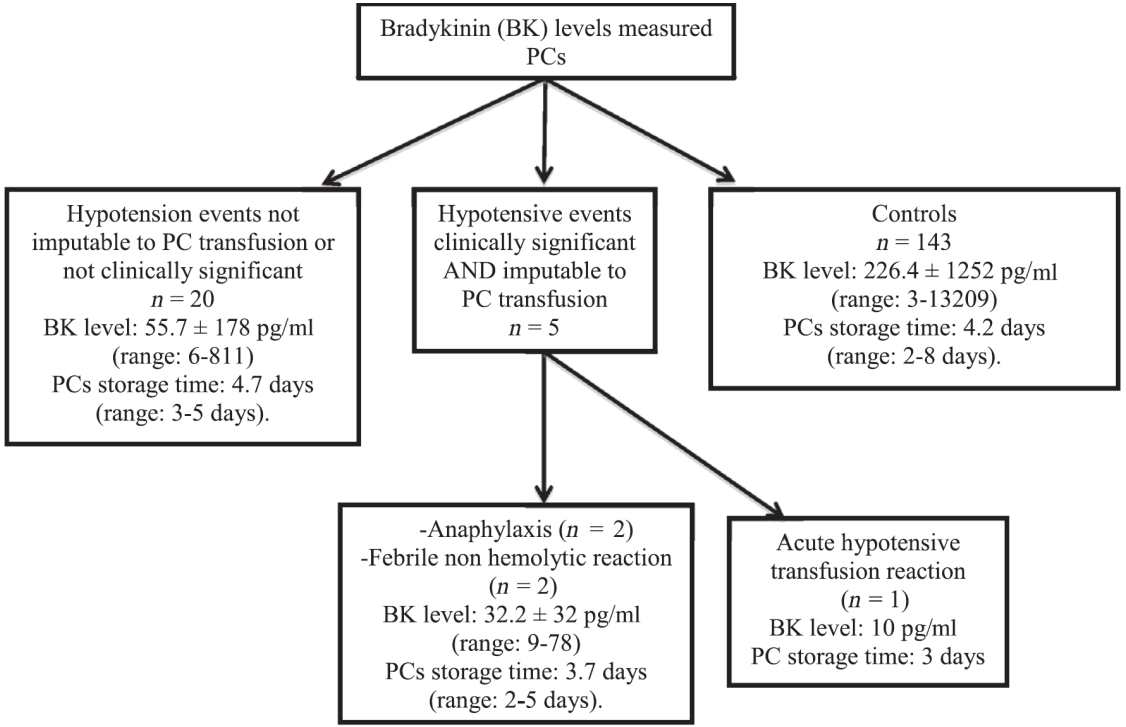
But Not The Only Factor

Vox Sanguinis (2016) **110**, 150–158
ORIGINAL PAPER

DOI: 10.1111/vox.12329

Incidence of hypotension and acute hypotensive transfusion reactions following platelet concentrate transfusions

G. Du Pont-Thibodeau,[1] N. Robitaille,[2] F. Gauvin,[1] L. Thibault,[3] G.-É. Rivard,[2] J. Lacroix[1] & M. Tucci[1]
[1]Division of Pediatric Critical Care Medicine, Department of Pediatrics, Sainte-Justine Hospital and Université de Montréal, Montreal, QC, Canada
[2]Division of Hematology-Oncology, Department of Pediatrics, Sainte-Justine Hospital and Université de Montréal, Montreal, QC, Canada
[3]Research and development, Héma-Québec, Québec city, QC, Canada



Risk Factors Are Not Always Clear

Hypotensive transfusion reactions in the era of prestorage leukoreduction

Monica B. Pagano,[1] Paul M. Ness,[2] Olga S. Chajewski,[3] Karen E. King,[2] Yanyun Wu,[4] and Aaron A.R. Tobian[2]

- Two centre study with pre-storage leukoreduction from 2011-2012 found 35 patients
  - About half were on extracorporeal circuits but only 4 patients on ACE-I
  - Largely associated with platelets

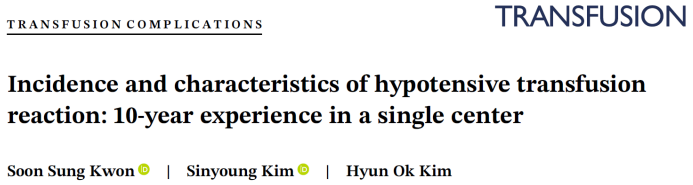
Clinical Pattern in Hypotensive Transfusion Reactions

Ryan A. Metcalf, MD,* Sara Bakhtary, MD,† Lawrence Tim Goodnough, MD,‡ and Jennifer Andrews, MD, MSc§

- Single centre study with pre-storage leukoreduction from 2014-2015 found 10 patients:
  - All 10 patients were on ACE-I and 9 were on extracorporeal circuits
  - Mix of blood components

Recurrence of Reactions After Restart

- In their 10 patients, all patients had their blood pressure improve upon cessation of the transfusion
- Five patients had recurrent hypotension upon restarting the transfusion



- In 23/35 patients, transfusions were sustained with supportive management
- In 14 cases where transfusion stopped, 7 cases had transfusion resume without severe complications

Classic Acute Hypotensive Reaction Versus Variations In Literature

- **Classically:**
  - Associated with ACE-I
  - Associated with negatively charged surfaces: cardiopulmonary bypass, apheresis
  - Associated with platelet transfusions
  - Can never be restarted

- **Sometimes:**
  - May not always happen with ACE-I and risk can still occur with discontinuation
  - Can happen in all clinical scenarios
  - Can be associated with other blood components and products
  - Consideration of restarting if there is no alternative blood component

Definitions of Hypotensive Reaction for Reporting

- Current Canadian definition (TTISS Manual – for revision)
  - ↓ SBP by ≥ 30 mmHg AND
  - SBP < 80 mmHg or shock (with no other explanation)
    - Usually occurring quickly, but can be within 4 hours of transfusion

- UK definition (SHOT hemovigilance program)
  - ↓ SBP by ≥ 30 mmHg within 1 hour AND SBP < 80 mmHg
  - Severe is defined as above including shock (acidemia or vital organ impairment)

US National Healthcare Safety Network Protocol

- All other adverse reactions presenting with hypotension are excluded AND hypotension within 1 hour of transfusion
  - Adults: ↓ SBP by ≥ 30 mmHg AND SBP < 80 mmHg
  - Pediatrics and neonates: ≥ 25% drop in SBP and any BP value respectively

- Specific imputability categories:
  - Definite: 1) Occurs less than 15 minutes after the start of the transfusion AND 2) Responds rapidly (i.e., within 10 minutes) to cessation of transfusion and supportive treatment AND 3) no other explanatory conditions
  - Probable: 1) Occurs between 15 minutes and 1 hour OR 2) Patient does not respond rapidly OR 3) there are other potential causes

Reporting Acute Hypotensive Reactions

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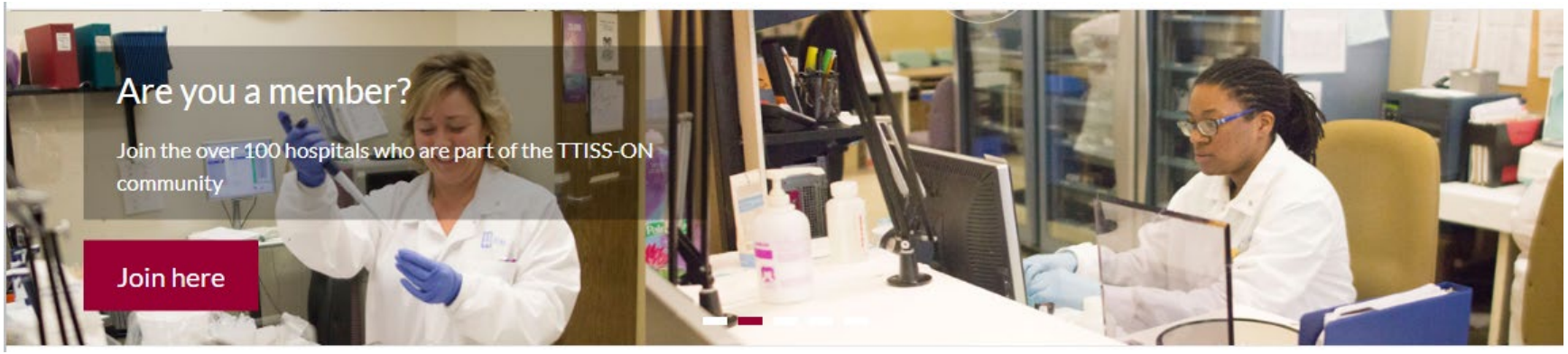
Ontario Transfusion Transmitted Injuries Surveillance System

Transforming transfusion one unit at a time...

https:/ttiss.mcmaster.ca



Michael G. DeGroote Centre for Transfusion Research

McMaster University

Transfusion Transmitted Injuries Surveillance System (TTISS)

- WHO defines hemovigilance as a system to "**facilitate monitoring and evaluation** of the blood system, including donor safety, blood product quality and safety, and **transfusion safety**"
  - Informs system changes – mitigation of TRALI, reducing wrong blood given, highlighting death from TACO
  - Canadian TTISS system → established in 2001 (recommendation from Krever Report)

- National initiative organized by PHAC (Health Canada – Canada Vigilance Program, Blood Suppliers, Manufacturers (blood products), and Canadian Hospitals (backbone of the system)

- Canadian hospitals **should identify and report all adverse transfusion events (ATEs)** to:
  - Blood components (red blood cells, plasma, platelets and cryoprecipitate)
  - Blood products (IVIG, factor concentrates etc.)

The Canadian Hemovigilance System

The Canadian Hemovigilance System consists of two arms:

Health Canada- Canada Vigilance Program (Regulator) Mandatory

- Canadian Blood Product suppliers
  -Canadian Blood Services
  -Héma Québec
- Manufacturers of plasma derivatives

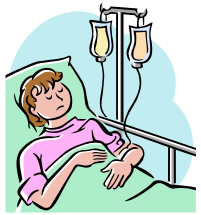
Purpose: Monitors Adverse Transfusion Events (ATEs) related to the blood supply to ensure the safety of the blood product

Public Health Agency of Canada (PHAC) contracted by Ministry of Health in Ontario (MOH) – Blood Contribution Program

- TransfusionTransmitted Injuries Surveillance System (TTISS)

Purpose: Monitors all moderate to severe ATE's for surveillance and risks (related or unrelated to the blood product)

Documenting Reactions



ATRs Identified and reported to Transfusion Medicine Lab (TML)

→

Investigation
- Type of Reaction
- Relation to transfusion
- Severity

→

Reported to 1 or more:
PHAC
Health Canada
Blood Supplier (CBS/HQ)

Reportable Reactions (R-ATRs)

Acute Hemolytic Reactions (AHR)
Aseptic Meningitis (ASPT)
Bacterial Infection (BACT)
Delayed Hemolytic (DHR)
Hypotensive Reactions (HYPT)
IVIG Headache (IVIG-HD)
Severe Anaphylactic or Anaphylactoid (SAAR)
Transfusion Associated Circulatory Overload (TACO)
Transfusion Associated Dyspnea (TAD)
Transfusion Related Acute Lung Injury (TRALI)
Other

Non-Reportable Reactions (NR-ATRs)

Febrile Non-Hemolytic Reactions (FNHR)
Minor allergic

Delayed Serological Reaction

Canadian Transfusion Adverse Event Reporting Form

Case ID: _____

CANADIAN TRANSFUSION ADVERSE EVENT REPORTING FORM

PAGE 1 OF 3

☐ INCIDENT (Complete sections 1,3,& 6 before & complete all sections during/after)
☐ ADVERSE REACTION (Complete all sections)

PRODUCT TRANSFUSED ☐ YES ☐ NO

FACILITY IDENTIFICATION

NAME OF FACILITY	HOSPITAL CODE	CITY	PROVINCE

1. RECIPIENT IDENTIFICATION

LAST NAME | FIRST NAME

HEALTH CARD NUMBER | HOSPITAL CARD NUMBER

Date of Birth: Day / Month / Year

Sex: ☐ Male ☐ Female ☐ Other ☐ Unknown

2. CLINICAL HISTORY

Blood Group: **ABO:** ☐ A ☐ B ☐ O ☐ AB **Rh:** ☐ Pos ☐ Neg

Pregnancies/Miscarriages ☐ Yes <3 mo. ☐ Yes >3 mo. ☐ No ☐ Unknown

Transfusions ☐ Yes <3 mo. ☐ Yes >3 mo. ☐ No ☐ Unknown

Immune-Compromised ☐ Yes ····· Describe: _____

Patient Diagnosis/Category: _____
Please see reverse for categories.

☐ Other Clinical History ····· Describe: _____

3. DATE, TIME AND PLACE OF INCIDENT / ADVERSE REACTION

	Day	Month	Year	Time (hh:mm)
Date and time **occurred**:				
Date and time **reported**:				

Place **occurred**: ☐ ICU ☐ ER ☐ MSW ☐ OB ☐ OR ☐ REC ☐ CHR ☐ OP
Please see reverse for definitions.

3a. Incident Information

☐ Patient Identification Incident ····· Specify: _____

☐ Product Related Incident ····· Specify: _____

3b. Premedication and Anesthesia

Premedication: ☐ Yes ····· ☐ No

Specify drug/dose/route:

Ontario's TTISS Online form

159 hospitals (All Hospitals Reporting) since 2018

- **TTISS-ON** have developed its own online database, flexible add users, sites can download their own reports.
- REDCap database to download/extract your own data for "internal hospital reports"
- Has an ONLINE "printable PDF Form" (TTISS) (CTAERF)/TTISS form from database

  If related to the blood quality print off PDF version of the online form and send to other Regulatory Agencies

Hamilton Health Sciences

www.hamiltonhealthsciences.ca

Acute Hypotensive Reactions

Dr. Andrew Shih, Nour Alhomsi