

DAY 2 > TRANSFUSION REACTIONS & SICKLE CELL DISEASE



Transfusion Reactions

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M TORONTO Canada

Disclosure

- Relevant relationships with commercial entities:
 - None
- Potential for conflicts within this presentation:
 - Funding from Canadian Blood Services in transfusion reaction research
 - Hemovigilance committee memberships (TTISS, AABB, ISBT)
- Steps taken to review and mitigate potential bias:
 - Peer-reviewed content
 - Non-proprietary titles
 - Declaration of use-context (EBM vs off-label)





Blood transfusion is the most commonly performed hospital procedure, occurring in >10% of hospital stays.



Roubinian et al. BMC Health Serv Res. 2014; 14:213

https://healthtalk.unchealthcare.org/transfusion/



Kaufman et al. <u>Transfusion</u>. **2015**; 55: 144-53. Hendrickson et al. <u>Transfusion</u> **2016**; 56:2587-2596.



Jenkins et al. Jt Comm J Qual Patient Saf 2017; 43: 389-95

"... safety will never be an absolute;



it is only as good

as the human beings on the frontline



and the guidance

under which the system is regulated"



Dubin & Francis. Transfusion. 2013; 53(10 Pt 2): 2359-2364.

Objectives – Hemovigilance Philosophies

• **Recognition matters:** I will consider <u>transfusion reactions on my</u> <u>differential diagnosis</u> if relevant disturbances occur after product exposure

Reporting matters: I will report these suspicions to my blood bank, as I appreciate the impact that feedback has on <u>informing risks</u>, and <u>identifying (& neutralizing) dangers</u>

Collaboration matters: As a witness, I will share my observations & impressions







ACUTE



Within 24h

DELAYED



>24h **Days Weeks** Months later

Objectives – Entities to Know

 Describe presentation, frequency, and management of the <u>3 most</u> commonly encountered but minor adverse transfusion events

State the <u>3 most important causes of transfusion-related mortality and</u> <u>severe morbidity, ie- potentially life-threatening **aCute** transfusion <u>reactions</u> and how we mitigate the risks for these events</u>







surface-stuff: skin (rash)

DELAYED: (Deferred)



Delayed Hemolytic Transfusion Reactions (DHTR) → HyperHemolysis Syndrome (HHS)

<u>Transfusion-</u> <u>Associated Graft Vs</u> <u>Host Disease</u> (TA-GVHD) Platelet Transfusion Refractoriness → Post Transfusion Purpura (PTP)

+ other hazards,

from common (iron overload) to

uncommon (non-acute/non-bacterial infections)

How Can We Inform Patients of the Risks of Transfusion?



- By the extent to which we participate in **HEMOVIGILANCE**
- WHAT should be reported? :
 - all transfusion reactions [adverse events] and transfusion-related errors [incidents]
- TO WHOM are these reports meant to be directed?:
 - the Hospital Transfusion Service ("blood bank")
 - for internal committees
 - for external stakeholders

Reporting Rules: External Stakeholders



TRACKERS – Public Health Agency of Canada (PHAC) via Transfusion Transmitted Injuries Surveillance System (TTISS)

MAKERS – Canadian Blood Services (CBS) or Derivative Manufacturers

REGULATORS – Canada Vigilance Program

ISTARE - International Surveillance of Transfusion-Associated Reactions and Events 25 countries 2006 - 2012133 million components **AFESSaPS - France Biovigilance Network - US** SHOT - UK TTISS - Canada **TRIP-** Netherlands Politis et al. Vox Sang. 2016; 111(4):409-417. NHSN - National

Healthcare Safety Network Hemovigilance Module of the CDC USA 2013 – 2015 8 million components

Kracalik et al. <u>Transfusion</u> **2021**; 61: 1424-34.

"Frequencies"

3 per million = chance of transfusion-related death

15-20 per 100,000 (10-25% of total) = serious reaction rate

80-220 per 100,000

Qualifying the Event: Provisional Adjectives

- SEVERITY
 - Grade 1 (non-severe)
 - Mild
 - Moderate
 - Grade 2 (severe)
 - Grade 3 (life-threatening)
 - Grade 4 (death)



- IMPUTABILITY, CERTAINTY
 - Definite (certain)
 - Probable (likely)
 - Possible
 - Unlikely (doubtful)
 - Excluded



Aggregate Transfusion Transmitted Viral Infection (TTVI) hazards: < 1/10⁵





Aggregate non-TTVI hazards: >1/10⁵



Justice Horace Krever

Andrzejewski Jr et al. Int J Clin Transfus Med. 2014; 2: 45-57.

Goel et al. <u>Blood</u> 2019; 133: 1831-9

Minimum Disclosure Framework

in Lavman's Terms & Loascale Frequencies



logs	in Layman's Terms & Logscale Frequencies			
scale 1 2	Common, minor events (1 / 10 ¹ -10 ²)	non-serious fever non-serious hives make antibodies to donor antigens (RBC, HLA)		
	Serious, potentially fatal	<u>breathing trouble</u> : –volume-driven fluid excess		
3 4	events (1 / 10 ³ -10 ⁵)	 –immune injury-driven fluid leaks –anaphylaxis / severe bronchospasm 		
Л		bacterial contamination of unit botched process (wrong sample or bag)		
6	Extremely rare events (1 / 10 ⁶ or less)	viral contamination of unit (hepatitis, HIV) new or rare (not tested-for) bugs fatal immune "take-over" by product		

Your Acronymic Glossary (What to Learn)



FNHTR	-non-serious fever
ATR	-non-serious hives
STR	-trigger new antibodies to red cells
TAD	-breathing trouble:
ТАСО	-volume-driven fluid excess
TRALI	-immune injury-driven fluid leaks
Anaphylaxis	–anaphylaxis / severe bronchospasm
TAS ("BaCon")	-bacterial contamination of unit
AHTR / IBCT / WBIT	-botched process (wrong sample or bag)
ΤΤνι	-viral contamination of unit
Emerging infections	-new, unexpected bugs
TA-GVHD, PTP	-fatal immune "take-over" by product



Secret Decoder Slide

FNHTR	febrile non-hemolytic transfusion reaction
ATR	allergic transfusion reaction
STR	sensitization (serologic transfusion reaction)
TAD	transfusion-associated dyspnea
TACO	transfusion-associated circulatory overload
TRALI	transfusion related acute lung injury
Anaphylaxis	anaphylaxis (allergic bronchospasm)
TAS ("BaCon")	transfusion-associated sepsis/bacterial contamination
AHTR / IBCT / WBIT	acute hemolytic transfusion reaction/incorrect blood component transfused/wrong blood in tube
TTVI	transfusion transmitted viral infection
Emerging infection	new, unexpected bugs
TA-GVHD, PTP	transfusion-associated graft-vs-host disease, post-transfusion purpura

Our First Defense: Vital Signs: HR, BP, T, RR, SpO2

- time 0: vital signs
- 1st 15 minutes: SLOW infusion (50cc/h)
- at 15 minutes: v

vital signs re-check

 end: must be within 4 h; re-check vital signs

reaction: vital signs

deadliest outcomes show up fast... & dose-dependent







Febrile



Adapted from Ontario's Transfusion Transmitted Injuries Surveillance System (TTISS) Transfusion Reaction Chart <u>https://ttiss.mcmaster.ca/wp-content/uploads/2017/08/Transfusion-Reaction-Chart-V_2.2-Pocket-and-Poster.pdf</u>

When Is It A Fever (Pyrexia) ?



T > 38^oC AND ↑ by Δ1^oC



OR

• the cytokine-provoked equivalent of chills or rigors







Cohen R et al. Transfusion. 2017; 57(7):1674-1683.

The "High Risk" Fever: *PacOn Pad Match*

Shih et al. <u>Transfusion</u> 2019; 59: 2292-300.

blood group antigen systems

(ABO, Rh, ...) containing structures that are naturally "polymorphic"

http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/

Möller et al. <u>Blood Advances</u>, **2016**; 1(3):240-249. **ERYTHF**

ERYTHROGENE

Acute Hemolytic Transfusion Reaction (AHTR)

- immune
 - active/major (recipient antibodies)
 - passive/minor (donor antibodies)

non-immune

- devices damaging RBCs: heat or pressure infusers
- biochemical:
 - potentiators of pre-existing hemolytic condition
 - C3/C4: PNH, CAS
 - donor RBC hemolysis
 - G6PD deficiency

IBCT –

Incorrect Blood Component Transfused

Acute (or Delayed) Hemolytic Transfusion Reaction

- active AHTR = MAJOR INCOMPATIBILITY
 - recipient makes antibodies that destroy foreign RBC
- eg. RBC incompatible for (ABO or non-ABOblood) antigens

Acute (or Delayed) Hemolytic Transfusion Reaction

- passive AHTR =
 MINOR INCOMPATIBILITY
 - product contains antibodies that destroy host RBC

eg. ABO antibodies ("isohemagglutinins") targeting recipient

Panch et al. <u>N Engl J Med</u> **2019**; 381: 150-62 Janatpour et al. <u>Am J Clin Pathol</u> **2008**; 129: 276-81.

Why/How Does The Mistake of Hanging ABO-Incompatible Blood Happen?

1 in 14,000 chance for incorrect blood component transfused (IBCT)

1 in 3000 samples labelled with another patient's name! (Wrong Blood In Tube [WBIT])

- 1. Errors in specimen collection (15%)
- 2. Errors in blood administration (majority)

hanging in haste without Positive Patient Identification (PPId)

Human Errors Perspective – Sample Rules and Calls for Higher Technology

- risk of ABO-incompatible transfusion: 1/40,000 > aggregate risk of all TTVI (1/50,000)
- if sample labeled incorrectly: 1:28 chance of WBIT
- machine-readable systems 个 safety by >5-fold beyond manual/human processes

Is There Hemolysis?

- without attributable bleeding, reticulocytosis / polychromasia / ↑ MCV (or a *non-elevated* reticulocyte count) maps to negative (*exaggerated*) balance
- visible or measured elevation of pfHb
- breakdown markers
 - 一个 bilirubin (unconjugated-predominant), AST
- 90% Sn ← ↑ LDH (& AST > ALT) + haptoglobin
- Conversely, N LDH (<220 U/L) & N hapto (>0.25g/L): 92% Sn to rule Out.
- hemoglobinuria/hemosiderinuria ± pigment nephropathy

Elliott et al. Transfusion 2003; 43: 297.

If So, Is It Immune Incompatibility-Related?

- C3/C4 consumption?
- ferritin surge?

Time

TRANSFUSION SAFETY

Committed to share patient's alloantibody history Blood bank software vendor SCC Soft Computer[®] sunquest. A WellSky **HAEMONETICS**[®] Serner[®] MEDITECH

Encourage your vendor to join the Alloantibody Exchange.

https://www.change.org/AlloantibodyInformationSharing2ImproveTransfusionSafetyForAllEverywhere

Bacterial Contamination (BaCon) / Transfusion-Associated Sepsis (TAS)

Walker et al.: Transfusion 2020; 60: 2029-37.

Culture / Investigation Pathway

PRE	PC	CONCLUSIONS	
PATI	ENT	PRODUCT	
+	+	0/ND	Pre-existing sepsis
0/ND	+	+	Definite BaCon
0/ND	0/ND	+	Probable BaCon
0/ND	+	0/ND	Possible BaCon
+/0/ND	0/ND	0/ND	Doubtful BaCon

Review of Donation/Donor Information

Febrile Non-Hemolytic Transfusion Reaction (FNHTR): Diagnosis of Exclusion

• common: **1/20** platelet transfusions, **1/300** RBC transfusions

- <u>recipient</u> has anti-leukocyte antibodies (because of previous exposure to blood)
 - WBC in product complexed on transfusion

- product has "pyrogens"
 - cytokines / inflammatory mediators accumulate,

inducing fever on transfusion

Blood Product Given \rightarrow Respiratory Distress

Most "important" of all transfusion hazards

High case morbidity & mortality rates, at high frequency

Accounting for 60% of transfusion-related deaths

cardiogenic

transfusion-associated circulatory overload (TACO)

non-cardiogenic

transfusion-related acute lung injury (TRALI)

allergic reaction (bronchospasm)

bacterial contamination or incompatibility reaction (off-target)

underlying disease process

transfusion-associated dyspnea (TAD)

REPORT DISTRESS EVENTS WITHIN 6-12H OF PRODUCT

1 Volume Status as the Discriminant (exam)

2 Structure: Infiltrates?

transfusionassociated circulatory overload (TACO)

transfusion-related acute lung injury (TRALI)

Shared: 2-hit model

Fluid driver:hydrostaticpermeability/leakImmunology:-+Agent:dangerous doctordangerous donorBiomarker:cardiac stressleukoagglutinins

Vlaar & Juffermans. Lancet 2013; 382:984-94.

Ware & Matthay. <u>N Engl J Med</u> **2005**; 353:2788-96.

Transfusion Associated Circulatory Overload (TACO):

≥ 1 REQUIRED:

OCCURRING WITHIN ≤ **12H** AFTER TRANSFUSION

- \downarrow spO₂ % without other causes
- bronchospasm/wheezing

L heart findings without other

frothing/pink sputum

Pulmonary Edema

Radiography:

new/worsening changes, eg-

- effusions
- widened vascular pedicle
- lobar vessel enlargement
- peribronchial cuffing
- Kerley lines
- alveolar edema
- cardiac silhouette enlargement

AND: 1 OR MORE OF:

AND/

OR

Cardiovascular system changes not from underlying condition

- tachycardia
- \uparrow BP, PP (or \downarrow if cardiogenic shock)
- JVP distension/↑ CVP/↑ cardiac silhouette
- peripheral edema

Physical

causes, eq-

crackles

cough

53

orthopnea

+ fluid balance or weight gain
 diuretic or dialytic response

for a MINIMUM OF **3** CRITERIA

ISBT Working Party on Haemovigilance, IHN, & aaBB: TACO Definition 2018 <u>https://www.isbtweb.org/fileadmin/user_upload/TACO_2018_definition_March_2019.pdf</u> Wiersum-Osselton et al. <u>The LANCET Haematology</u> **2019**; 6(7): e350-e358.

TACO Landscape

Common – 1-10% of encounters

Hendrickson JE et al, <u>Transfusion</u> 2016; 56: 2587

• Assumed to be **reversible with diuretics**

Roubinian N & Murphy EL, IJCTM 2015; 17

• Rising in rank as **commonest** reaction entity among **transfusion-related deaths**

TTISS (Ontario) 2014-2018: 13/35	(37%) 37%
SHOT (UK)	2010-2020: 104/21	2 (49%) (95% CI:
FDA (USA)	2014-2019: 72/262	(27%) 33-41%)

• Often serious (1/5 to ICU) ...

LOS effects...

CFR: **1-10%**

Lieberman L et al, Transfus Med Rev 2013; 206 Roubinian NH et al, Crit Care Med 2018; 577 Murphy EL et al, Am J Med 2013; e29

TACO: Accreditation Standards <u>Expect</u> Lab-to-Bedside Prevention Efforts

New aaBB Standard 5.19.7 Transfusion-Associated Circulatory Overload (TACO) (30th edition, 2016): *"The BB/TS shall have a policy for responding to requests for products for patients identified by the ordering physician or other authorized health professional as being at increased risk for TACO."*

TACO: Risk Factors (Finding Who Needs Mitigation)

<u>cardiorespiratory</u> dysfunction

- MI, CHF, diuretics, abnormal cardiac studies
- tachypnea [RR>20], ambient air hypoxia [SpO2
 <92%], JVP >3cm ASA, bilateral chest rales, extra heart sounds [S3, S4]
- <u>renal</u> dysfunction
- <u>age</u>
 - youngest
 - oldest (>60-70 years)
- **positive** fluid balance
 - weights, ins/outs, physical signs
- Li et al. <u>Transfusion</u> **2011**; 51:338-43.
- Lieberman et al. Transfus Med Rev 2013; 27:206-12.
- Andrzejewski Jr et al. <u>Transfusion</u> **2013**; 53:3037-47.
- Alam et al. <u>Transfus Med Rev</u> 2013; 27:105-12.
- Clifford et al. <u>Anesthesiology</u> 2015; 122:21-8.
- Roubinian et al. <u>Crit Care Med</u> **2018**; 46:577-85.

- small receiver: low body weight
- anemic hyperdynamism
- heavy-handed giver:
 - unwritten orders (verbal)
 - unassessed patient
 - big order
 - too fast
 - preceding crystalloids: "STACO"

TACO: How to Change the Order to Mitigate Risk

- lower the trigger
- cancel
 - alternatives?
- reduce order size/volume
 - 1 instead of 2u RBC
 - concentrates instead of components
- slow the infusion rate
- (advance) volume decanting
 - diuretics, more UF on dialysis

New aaBB Standard 5.19.7 Transfusion-Associated Circulatory Overload (TACO) (30th edition, 2016): *"The BB/TS shall have a policy for responding to requests for products for patients identified by the ordering physician or other authorized health professional as being at increased risk for TACO."*

?Transfusion Related Acute Lung Injury (TRALI)

Wong et al. <u>Transfusion</u> **2017**; 57:2076.

Transfusion Related Acute Lung Injury (TRALI):

Bilateral Infiltrates

CXR, CT, US

Acute Onset Hypoxemia

- paO2/FiO2 ≤ 300
 - spO2 <90% on room air

OXYGEN

• Other clinical evidence

Left Atrial Hypertension: absent, or (if present), not the main contributor to hypoxemia

Echo, PCWP

Onset during or within <u>6h</u> of transfusion (Pulmonary edema/ LAH studies captured within 24h)

C.

No alternative ARDS risk factors

Direct Lung Injury:

- aspiration
- pneumonia
- toxic inhalation
- lung contusion
- vasculitis
- near drowning

Indirect Lung Injury

- non-pulmonary sepsis
- multiple trauma
- burn injury
- acute pancreatitis
- non-cardiogenic shock
- cardiopulmonary bypass
- drug overdose

* Neither leukoagglutinating (HLA or HNA) antibodies in donors (nor confirmation of cognate antigens in recipient) are required

TRALI: How It Happens: 2nd Hit[s] (in a 1st-Hit Host)

- <u>donor</u> had incidental anti-leukocyte antibodies (ALA) collected into product
 - ALA (HLA [II>I], HNA) delivered IV
 - ALA account(ed) for most cases

cognate Ag binding → activation (TRAIL)*

Product factors

...

Resting

Primed

Host (EC/WBC) state

Activated

- products release biologically active lipids
 - biologically active lipids, lysoPC, microparticles
 - cytokines, chemokines (HMGB1, solCD40L)
 - NETs, mtDNA

donor cells release harmful humours

Sachs. <u>Curr Opin Hematol</u> **2011**; 18: 436-42. Kopko et al. <u>Transfusion</u> **2019**; 59: 1147-51.

Mitigating Femme Fatale Effect: Fewer TRALI Cases Expected (Seen) Now

- commonest way for (healthy) donors to (RBC/WBC)sensitize is PREGNANCY
- production methods account for this potentially harmful "immune knowledge"

OR ~0.5

EVER-PAROUS WHOLE BLOOD (irrespective of gravidity): plasma diverted for "recovery"/fractionation (pooling = dilution)

buffy coat platelets now pooled in male plasma

red cells still used for direct component therapy

apheresis plasma or platelets: MEN or NULLIPARAS

- Muller et al. <u>Transfusion</u>. **2015**; 55(1):164-75.
- Schmickl et al. <u>Crit Care Med</u>. **2015**; 43(1):205-25.

Culpability/Certainty Spectrum:

& worsening in the last 12h

TARDS

TRALI Epidemiology

Vossoughi et al. <u>Transfusion</u> **2019**; 59: 2567-74

 Transfusionattributable
 TTISS (Ontario) 2014-2018: 9/35 (26%) SHOT (UK) 2010-2020: 7/212 (3%)
 FDA (USA) 2014-2019: 59/225 (26%)
 13-19%)

• IHM: up to 50%

• CFR: 5-25%

Why is dyspneic/hypoxic reaction reporting so important?

- A. Billings bring revenue
- B. Quality signal on dangerous doctors/facilities
- C. Reporting improves real-time care
- D. Co-component quarantine, donor investigation (deferral)
- E. Enables legal actions

Allergic Reactions

surface-stuff: skin (rash)

The Allergic Spectrum

- cutaneous eruption (= urticaria, pruritis, erythema, flushing)
- angioedema (=subcutaneous rather than cutaneous)
- respiratory:

danger gradient

- bronchospasm
 - wheezing, stridor, hoarseness, dyspnea, hypoxia, feeling of asphyxia/doom
- gastrointestinal instability:
 - nausea/vomiting/abdominal cramping/diarrhea
- cardiovascular instability:
 - hypotension, chest pain, tachycardia
- anaphylactoid / anaphylactic reaction ± death

frequency gradient

1% incidence 90% of ATR cases

fatal anaphylaxis: 1 in 2-10 million

Why Allergic Reactions Happen

CLASSIC ALLERGIC IgE

 Recipient IgE to incoming donor allergens

- eg. drug & food allergens transfused to patient
- Donor IgE to recipient allergens
 - eg. donor's peanut allergy passed into recipient

RECIPIENT HAS MISSING OR VARIANT PROTEIN AND REACTS TO WILD-TYPE PROTEIN

<5% of cases

- eg IgA, haptoglobin,
 complement, albumin,
 α1anti-trypsin, transferrin
- anti-protein IgG develops

Hypotension

acute hemolytic transfusion reaction (AHTR)

bacterial contamination (BaCon)

severe allergic transfusion reaction / anaphylaxis

bradykinin shock?

Testing Approach

- We investigate with the following panels for:
 - Febriles: <u>hemolysis</u>, microbiology
 - Dyspneics: hemolysis, microbiology, CBS (donor ALA)
 - Hypotensives: <u>hemolysis</u>, microbiology
 - Anaphylactics: <u>hemolysis</u>, ?lgA/anti-lgA lgG

(?other protein deficiencies)

Blood bank sample: BIAS = exploration for immune hemolytic incompatibility

Major Take-Home Messages

• most common (acute) killers: <u>TRALI & TACO</u>, AHTR-IBCT, TAS

- you report to us, & we report within and to outside channels
- the only measure that has the power to mitigate EVERY single transfusion reaction type, is AVOIDANCE of the order itself...

Happy Transfusion Endings...

