Transfusion Reactions

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Canadian Blood Services

Laboratory Medicine & Pathobiology
UNIVERSITY OF TORONTO

TRANSFUSION MEDICINE 101
CAMP WITH THE BANK

Disclosures

- support from Canadian Blood Services for transfusion reaction research
- Hemovigilance Committee memberships (TTISS, ISBT)

Why Is This Important?

Blood transfusion is the most commonly performed procedure in healthcare

Roubinian et al. BMC Health Serv Res 2014.

Reactions occur in 1-10% of any given transfusion encounter

Kaufman et al. Transfusion 2015.
Hendrickson et al. Transfusion 2016.

Applied Practice / Attitudes

- ***Recognition matters:*** I will consider transfusion reactions on my differential diagnosis if relevant disturbances occur after product exposure

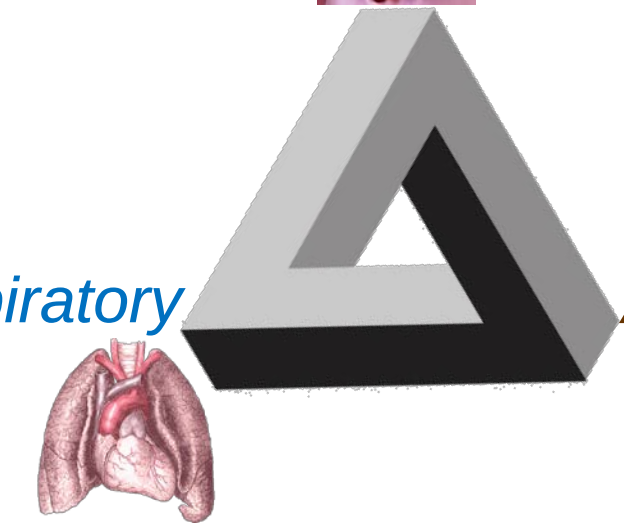
- ***Reporting matters:*** I will report these suspicions to my blood bank, as I appreciate the impact that feedback has on informing risks, and identifying (& neutralizing) dangers

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

Objectives: Focus: <u>Acute</u> Reactions (<24h)

Hemovigilance Overview:
Frequencies & “Entity-Positions”

Febrile



Cardiorespiratory

Allergic

Learn / organize by the Archetypes:

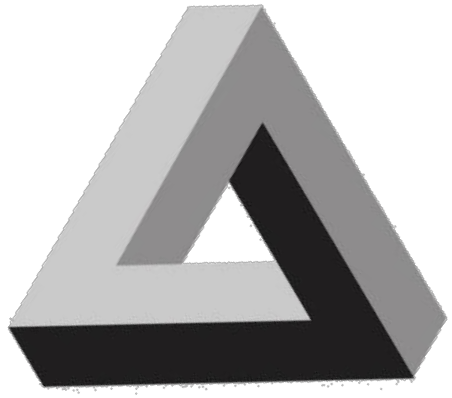
1. most common minor events

2. most important causes of transfusion-related mortality and severe morbidity

Learning Objective 1:

Hemovigilance Overview: Frequencies & Entity Positions

Deferred: the “Delayed” Entities



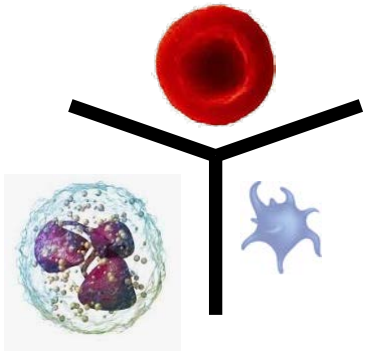
Delayed Serologic to Hemolytic Transfusion Reactions → HyperHemolysis Syndrome

(DSTR)

(DHTR)

(HHS)

Transfusion-Associated Graft Vs Host Disease (TA-GVHD)

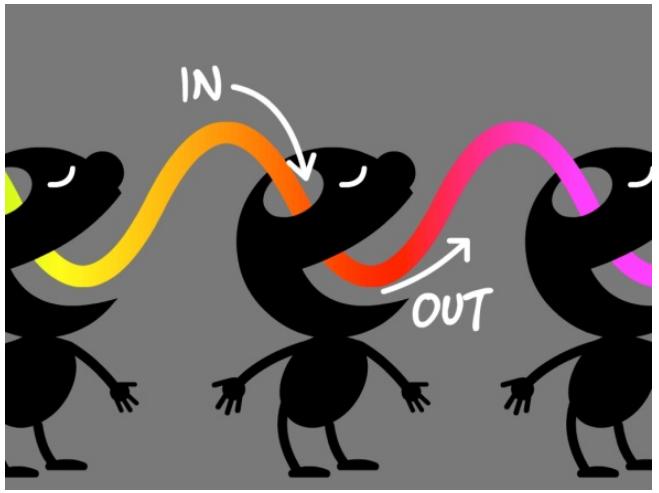


Platelet Transfusion Refractoriness →

Post Transfusion Purpura (PTP)

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 effects] and
  - transfusion-related errors [incidents/ “events”]

- TO WHOM are these reports meant to be directed?:
  - the Hospital Transfusion Service (“blood bank”)
  - internal incident reporting systems

Reporting Rules to External Stakeholders

- **TRACKERS** – Public Health Agency of Canada (PHAC) via Transfusion Transmitted Injuries Surveillance Systems (TTISS) in provinces & territories

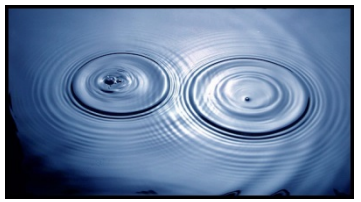
  Serious reactions, no matter whose fault

- **MAKERS** – Canadian Blood Services (CBS) or Derivative Manufacturers

  Serious reactions, with product or donor possibly to blame (quarantine/recall ramifications)

- **REGULATORS** – Health Canada Blood Regulations

  error/accident (E/A) to the Biological Product Compliance Program (BPCP)



  adverse reaction (A/R) to the Canada Vigilance Program (CVP):
  Health Products Surveillance and Epidemiology Bureau (HPSEB)
  Marketed Health Products Directorate (MHPD)

  Reactions owing to one's own intrusions on product

“Frequencies” By Severity

ISTARE - International Surveillance of Transfusion-Associated Reactions and Events

25 countries

2006 – 2012

133 million components

AFFSSaPS - France
Biovigilance Network - US
SHOT - UK
TTISS - Canada
TRIP- Netherlands

Politis. et al. Vox Sang. 2016

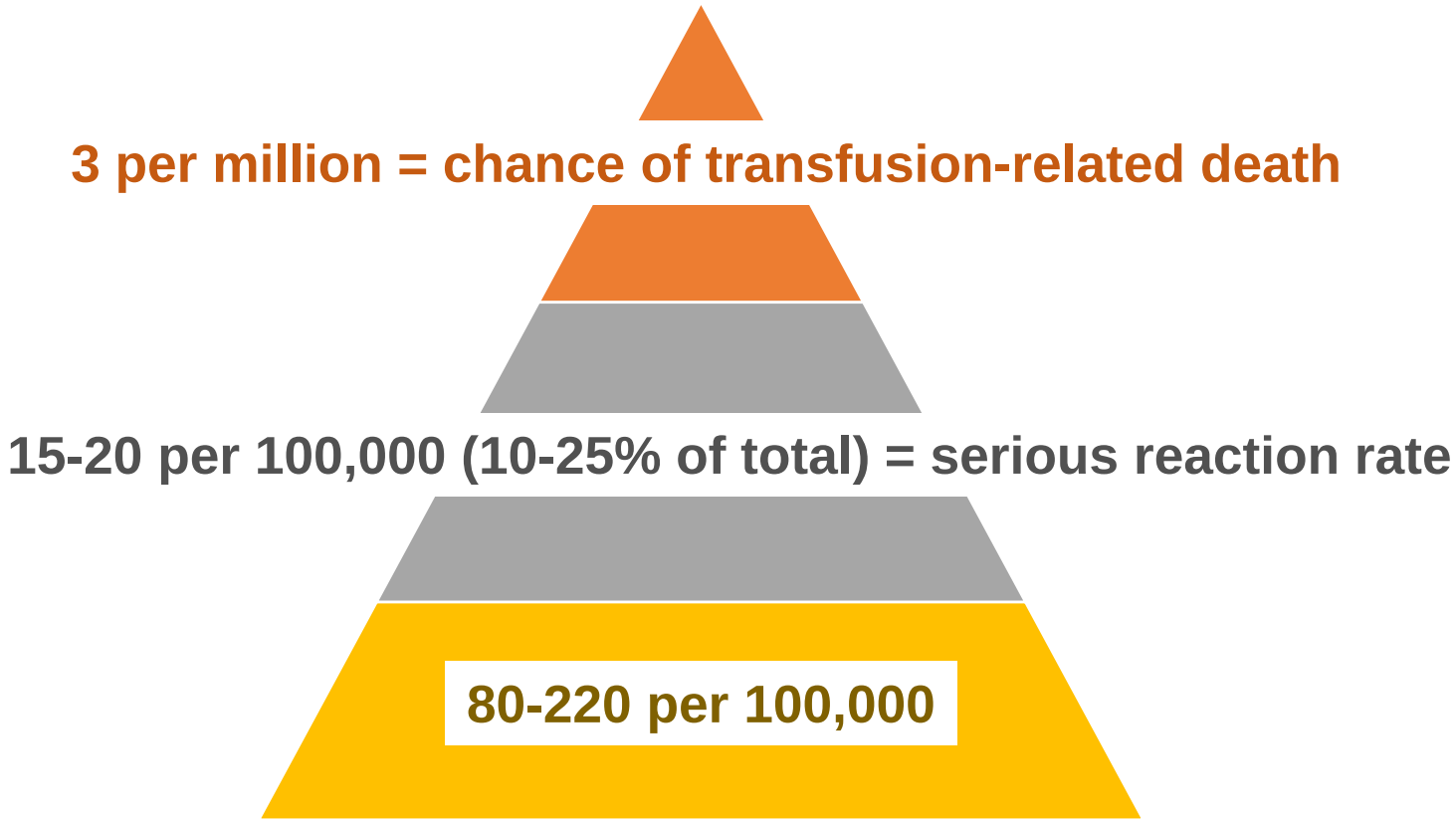
NHSN - National Healthcare Safety Network Hemovigilance Module of the CDC

USA

2013 – 2015

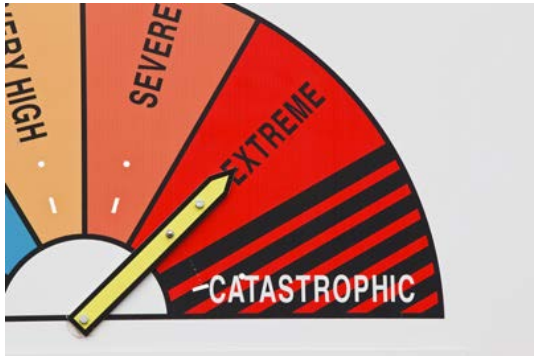
8 million components

Kracalik. et al. Transfusion 2021



“Qualifying” the Diagnosis in 2 Dimensions

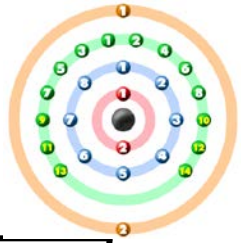
- SEVERITY
  - Grade 1 (non-severe)
    - Mild
    - Moderate
  - Grade 2 (severe)
  - Grade 3 (life-threatening)
  - Grade 4 (death)



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

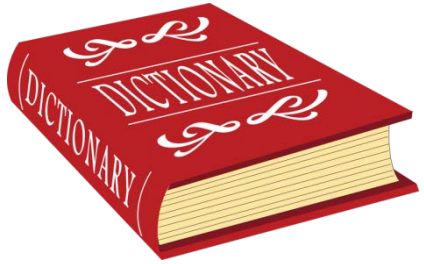
Minimum Disclosure Framework

in Layman's Terms & Logscale Frequencies



logscale		
1 2	**Common, minor events** ($1 / 10^1$-10^2)	non-serious **fever** non-serious **hives** make **antibodies** to donor antigens (RBC, HLA)
3 4 5	**Serious, potentially fatal events** ($1 / 10^3$-10^5)	**breathing trouble**: –volume-driven fluid excess –immune injury-driven fluid leaks –anaphylaxis / severe bronchospasm **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)



logscale 1 2 3 4 5 6

FNHTR	non-serious **fever**
ATR	non-serious **hives**
STR	make **antibodies** to donor antigens (RBC, HLA)
TAD TACO	**breathing trouble**: –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 / bag / test result)
TTVI	viral contamination of unit (**hepatitis, HIV**)
Emerging infections	**new** or **rare** (not tested-for) **bugs**
TA-GVHD, PTP	fatal immune “take-over” by product

Decoder Slide

logscale 1 2 3 4 5 6

FNHTR	febrile non-hemolytic transfusion reaction
ATR	allergic transfusion reaction (minor)
STR	serologic transfusion reaction (RBC DSTR, HLA PRA)
TAD	transfusion associated dyspnea(s)
TACO	–transfusion associated circulatory overload
TRALI	–transfusion-related acute lung injury
Anaphylaxis	–anaphylaxis / severe 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 infections	pathogens without interdiction tests
TA-GVHD, PTP, HHS	transfusion-associated graft-vs-host disease / post-transfusion purpura / hyperhemolysis syndrome

Reaction Odds by Item…

plasma

frozen

platelets

room temperature

RBCs

refrigerated

all plasma,
no cells

+(+) plasma
2.5 to 3▪10 ^{11} cells (PCV <1%)

→0 (<20mL) plasma
5▪10 ^{12} cells (PCV 65%)

→0

+++ BaCon risk ++

+++ allergic reaction risk +++ premedication +(+)

(+) +++ FNHTR risk ++(+)

++ + TACO risk diuresis +++

++ TRALI risk +++ +(+)

+++ TA-GVHD risk irradiation +(+)

Pathogenesis Sorting

qualitative insults

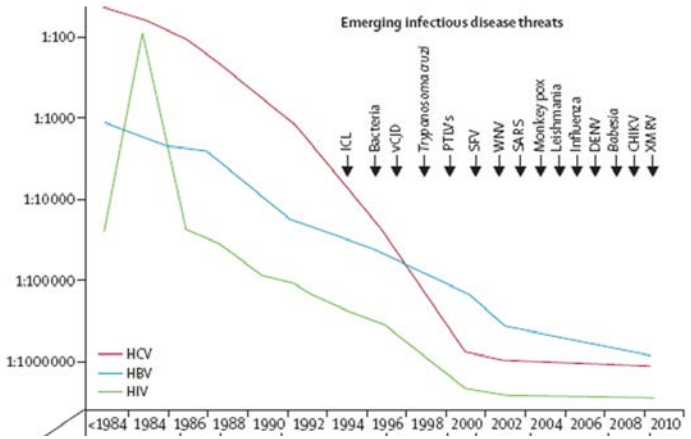
immune complex

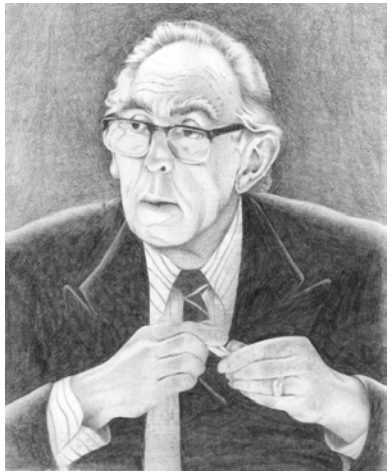
volume/ overload

infectious hazards

non-infectious hazards

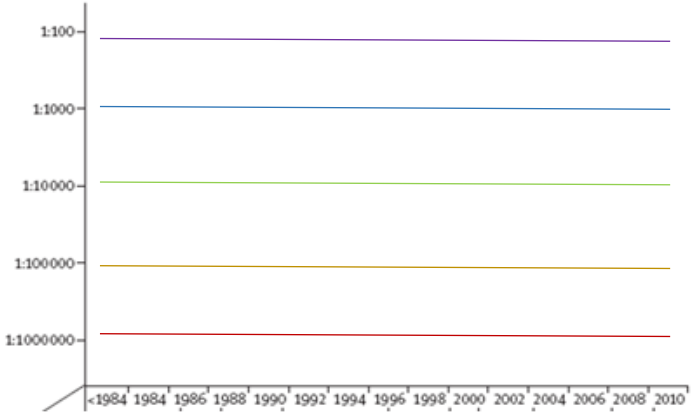
Aggregate TTVI risk:
< $1/10^5$





Justice Horace Krever
Inquiry Report: 1997

Aggregate non-infectious risks:
>$1/10^5$



Andrzejewski Jr. et al. *Improving patient safety in TM: contemporary challenges & roles for bedside and laboratory biovigilance in addressing them.* Int J Clin Transfus Med. 2014.

Goel et al. *Noninfectious transfusion-associated adverse events and their mitigation strategies.* Blood 2019.

Benefits of Pathogen Reduction

plasma

frozen

Octapharma:
Octaplas
solvent-detergent-treated plasma

platelets

room temperature

amotosalen-UVA

*PR: Cerus **Intercept***
PAS-E: Macopharma
pooled platelet psoralen-treated
apheresis platelet psoralen-treated

RBCs

refrigerated

all plasma,
no cells

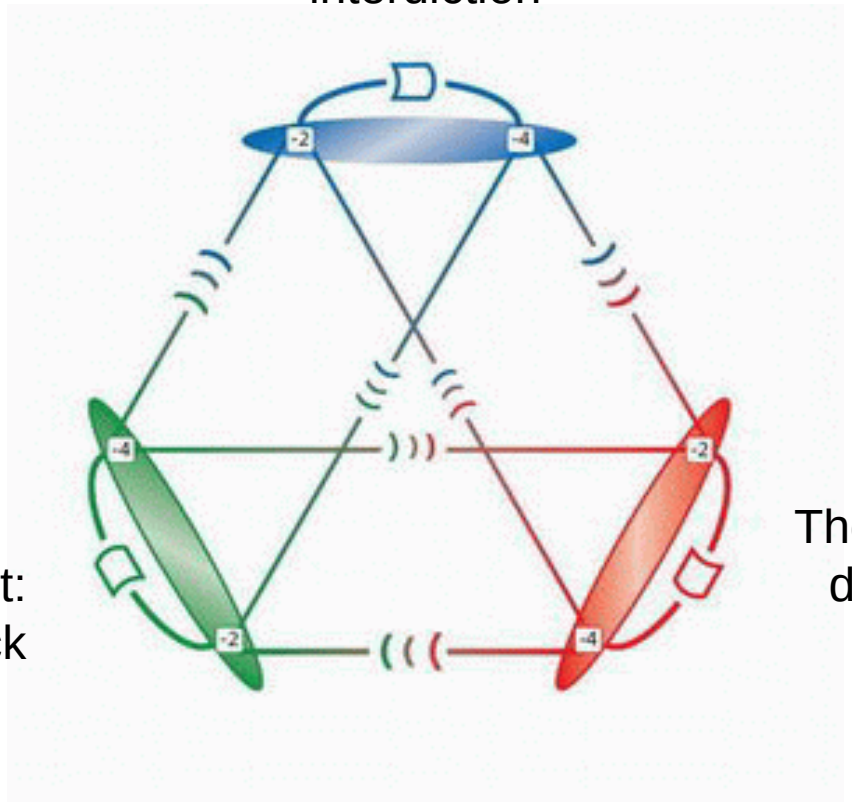
+ plasma
2.5 to 3▪10 ^{11} cells (PCV <1%)

→0 (<20mL) plasma
5▪10 ^{12} cells (PCV 65%)

→0		→0	**BaCon risk**	++
+	*allergic reaction risk*	+		+(+)
→0		+	*FNHTR risk*	++(+)
+		+	*TACO risk*	+++
→0	*TRALI risk*	+	diuresis, irradiation	+(+)
		→0	**TA-GVHD risk**	+(+)

Why Else Reporting is Important: Others… & the 3 Dimensions of Time

The present: interdiction



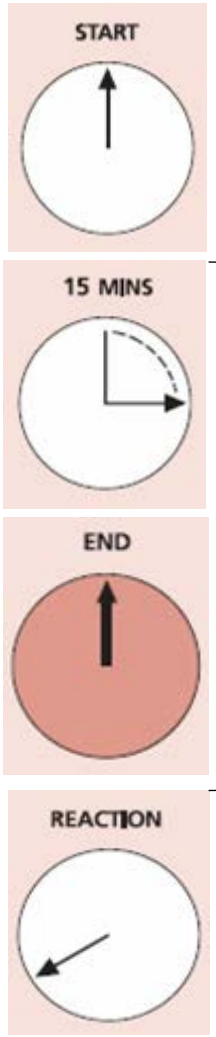
The past: lookback/traceback

The future: deferral

Aggregate signals

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

- time 0: vital signs
- 1st 15 minutes: SLOW infusion (50cc/h)
- **at 15 minutes:** vital signs re-check
- end: must be within 4 h; re-check vital signs
- reaction: vital signs



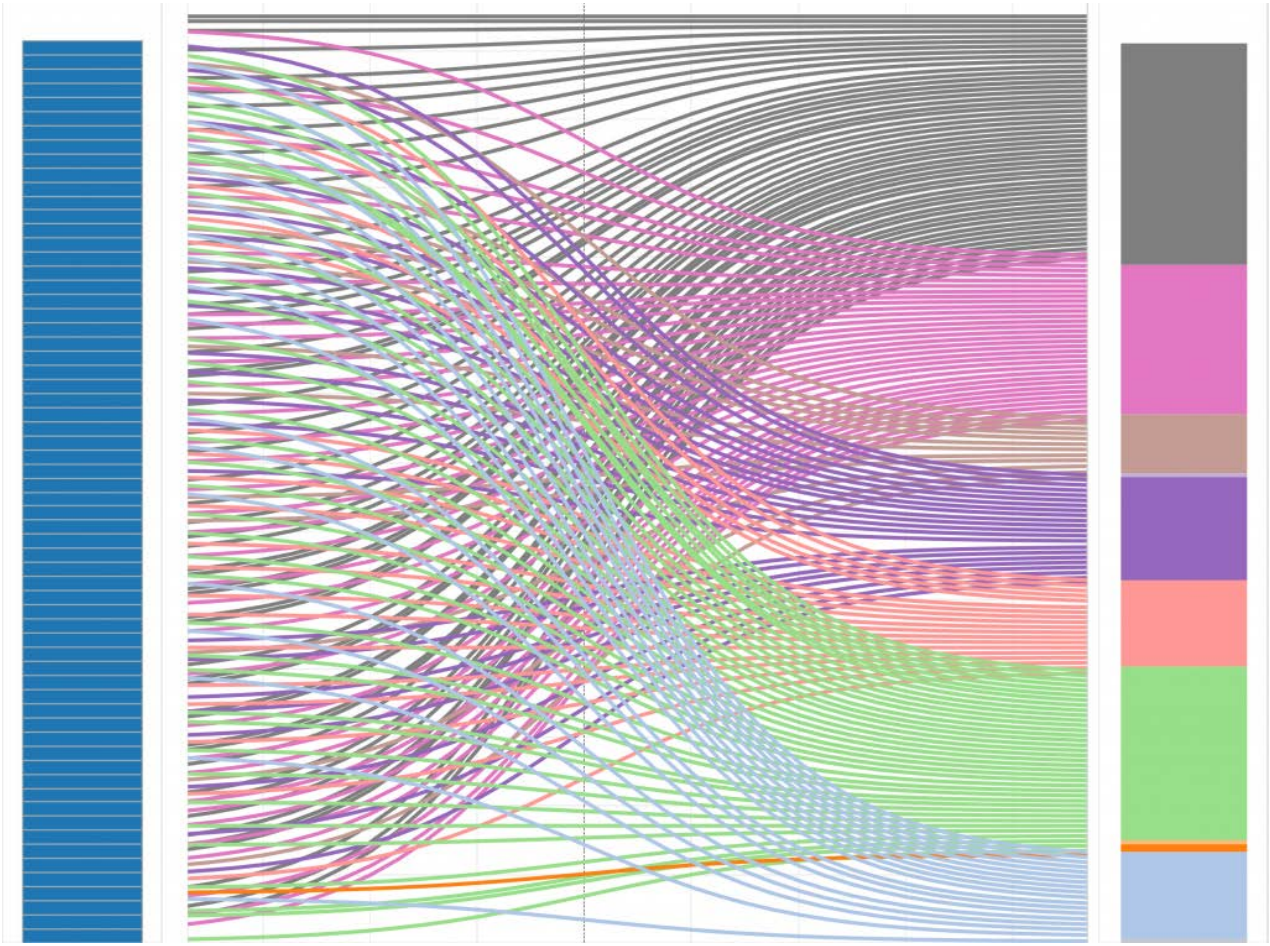
Not good when these are one and the same

deadliest outcomes show up fast… & with dose-dependence

Reporting

The individual experience (*presentation archetypes*):

YOU = bedside detectors / 1st reporters



The technical entity (final diagnosis):

FACULTY = laboratory consultants / end-reporters

“React-Response” – Parametric & Pragmatic Guidance

Febrile

Allergic

Dyspneic

Shock

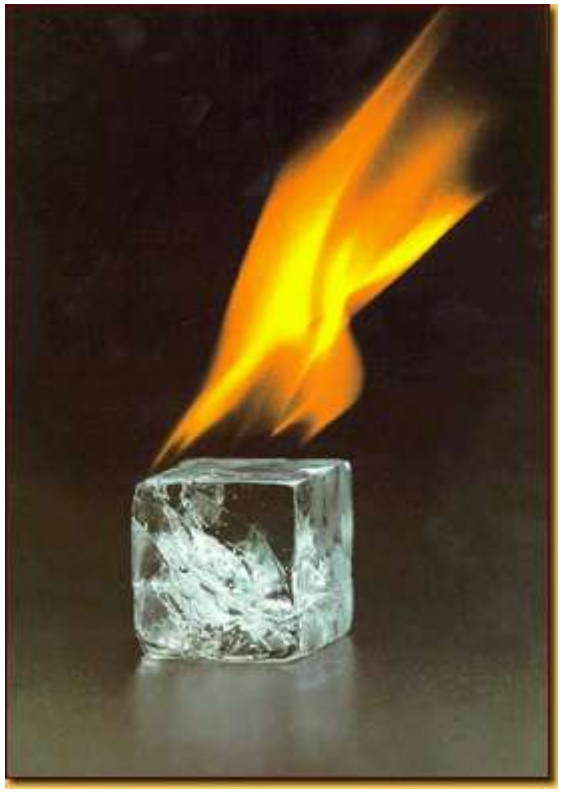
SIGNS & SYMPTOMS		TIMING	POSSIBLE ETIOLOGY	RECOMMENDED INVESTIGATIONS	SUGGESTED TREATMENT AND ACTIONS
FEVER: Temperature of at least 38° C and an increase of at least 1° C from pre-transfusion **and/or** Shaking Chills/Rigors NOTE: Isolated symptom subjective chills, may consider as Low Risk	**Low Risk:** 38° C to 38.9° C but **NO** other symptoms	During or up to 4 hours post transfusion.	Febrile non-hemolytic transfusion reaction	No testing required	• Antipyretic • With physician order and if blood still viable, may resume transfusion with close patient assessment • If recurrent reactions, possible trial of antipyretic premedication
	High Risk: a) at least 38° C but with other symptoms or b) 39° C or greater or c) Shaking Chills/ Rigors	Often within first 15 minutes. During or up to 4 hours post transfusion.	Febrile non-hemolytic transfusion reaction Bacterial contamination Acute hemolytic transfusion reaction	• TML: Group & Screen, DAT • TML: Blood component culture • Patient blood culture (from a different peripheral site) • Urinalysis (first void post-reaction) • Hemolysis work-up: CBC, bilirubin, LDH, AST, haptoglobin, reticulocyte count, blood film • If indicated, assess for - AKI {Acute Kidney Injury} (electrolytes, creatinine) - DIC {Disseminated Intravascular Coagulation} (INR, PTT, fibrinogen, D-dimer)	**DO NOT restart transfusion** • Return blood to TML for clerical check & culture • Broad spectrum IV antibiotics; DO NOT wait for culture results • Aggressive hydration; maintain good urine output • Supportive care per physician’s discretion: IV fluid, vasopressors, oxygen, respiratory support • Monitor for hypotension, renal dysfunction, DIC {Disseminated Intravascular Coagulation} • If severe rigors, consider meperidine (if no patient contraindications) • **Serious reaction, call TML immediately**
URTICARIA (Hives) Rash or Itching	Less than 2/3 body surface but **NO** other symptoms	During or up to 4 hours post transfusion.	Minor allergic	No testing required	• Antihistamine • With physician order and if blood still viable, may resume transfusion with close patient assessment • If recurrent/severe reactions, possible trial of antihistamine premedication
	2/3 body surface or more but **NO** other symptoms	Often early in transfusion. During or up to 4 hours post transfusion.	Minor allergic (Extensive)	No testing required	**DO NOT restart transfusion** • Antihistamine; may require steroid if symptoms slow to resolve • If recurrent/severe reactions, possible trial of antihistamine /steroid premedication • If continued reactions with premedication, possible trial of washed/plasma depleted components
	With other symptoms, i.e., Airway or Facial Edema, DYSPNEA, HYPOTENSION	Often early in transfusion. During or up to 4 hours post transfusion.	Anaphylactoid reaction /Anaphylaxis	• If also DYSPNEA: chest X-ray, • If also hypoxia: blood gases • Suggest consult Transfusion Medicine physician: explore if indication for - TML: Group & Screen, DAT - Haptoglobin - IgA level (if pre-transfusion sample available) - Anti-IgA testing (performed via Canadian Blood Services, TML will assist in sending samples)	**DO NOT restart transfusion** • **Epinephrine;** consider steroid, antihistamine • Return blood to TML for clerical check • Supportive care per physician’s discretion: oxygen, respiratory support, vasopressors • Pending outcome of investigations, washed/plasma depleted components • **Serious reaction, call TML immediately**
DYSPNEA or SpO_2 (oxygen saturation) of 90 % or less and a decrease of at least 5 % from pre-transfusion or intervention required to maintain SpO_2 (oxygen saturation)	With **Hypertension,** tachycardia, +/- FEVER	During or up to **12 hours** post transfusion	TACO* (Transfusion Associated Circulatory Overload)	• TML: Group & Screen, DAT • Consider chest x-ray: Findings - pulmonary edema, Kerley B lines, peri bronchial cuffing, may be pleural fluid • Cardiac biomarkers (as available)	**DO NOT restart transfusion** • Oxygen, high fowler’s position, diuretics (document fluid balance) • **Future transfusion:** Slow transfusion rate Pre-transfusion diuretics ** Consider TML to divide unit (as available)
	ACUTE DYSPNEA With **HYPOTENSION,** tachycardia, +/- FEVER	During or up to **6 hours** post transfusion	TRALI (Transfusion Related Acute Lung Injury)	• TML: Group & Screen, DAT • Chest x-ray: Findings – bilateral interstitial /alveolar infiltrates without elevated pulmonary pressures • If also hypoxia: blood gases • Canadian Blood Services requires follow up information & patient blood tests, contact TML, will assist in sending samples	**DO NOT restart transfusion** • Supportive care per physician’s discretion: oxygen, respiratory support, vasopressors (benefit uncertain for diuretics {document fluid balance}, steroids, and bronchodilators) • **Serious reaction, call TML immediately**
	With FEVER +/- HYPOTENSION	Possible Etiology: Bacterial contamination, Acute hemolytic transfusion reaction **Consider/Follow FEVER, High Risk:** Timing, Recommended Investigations, Suggested Treatment and Actions			
	With URTICARIA, Airway or Facial Edema, HYPOTENSION	Possible Etiology: Anaphylactoid Reaction / Anaphylaxis **Consider/Follow URTICARIA, With other symptoms:** Timing, Recommended Investigations, Suggested Treatment and Actions			
	Mild respiratory symptoms that do not align with TACO or TRALI	During or up to **24 hours** post transfusion	TAD (Transfusion Associated Dyspnea)	• Consider chest x-ray: Findings - normal/unchanged, no pulmonary edema, No bilateral interstitial/alveolar infiltrates	**DO NOT restart transfusion** • Supportive care per physician’s discretion: oxygen, respiratory support
HYPOTENSION 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	Alone or with facial flushing	During or up to 4 hours post transfusion	***Bradykinin mediated hypotension	No testing required	**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
	With FEVER, +/- DYSPNEA	Possible Etiology: Bacterial contamination, Acute hemolytic transfusion reaction **Consider/Follow FEVER, High Risk:** Timing, Recommended Investigations, Suggested Treatment and Actions			
	With URTICARIA, Airway or Facial Edema, DYSPNEA	Possible Etiology: Anaphylactoid Reaction / Anaphylaxis **Consider/Follow URTICARIA, With other symptoms:** Timing, Recommended Investigations, Suggested Treatment and Actions			
	With ACUTE DYSPNEA, tachycardia +/- FEVER	Possible Etiology: TRALI **Consider/Follow ACUTE DYSPNEA:** Timing, Recommended Investigations, Suggested Treatment and Actions			

https://ttiss.mcmaster.ca/wp-content/uploads/2020/10/TTISS-2020-10-08-Symptom-Transfusion-Reaction-Chart.pdf

Learning objective 2:

Febrile Archetypes

When Is It a Fever (Pyrexia)?



- T > 38ºC AND ↑ by Δ1ºC

OR

- the cytokine-provoked equivalent of chills or rigors

Fever's Differential Diagnosis

fever = 1st presenting feature (usually)

danger gradient

HIGH RISK FEVER

acute hemolytic transfusion reaction (AHTR)

bacterial contamination (BaCon)/
transfusion-associated sepsis (TAS)

fever due to underlying disease

LOW RISK FEVER

febrile non-hemolytic transfusion reaction (FNHTR)

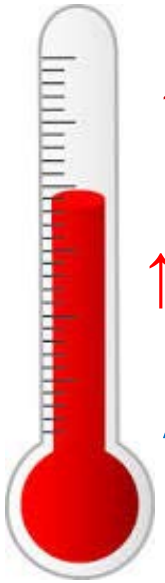
frequency gradient

& test

avoid
waste

Cohen et al. *Feeling the Burn: The Significant Burden of Febrile Non-Hemolytic Transfusion Reactions.* Transfusion 2017.

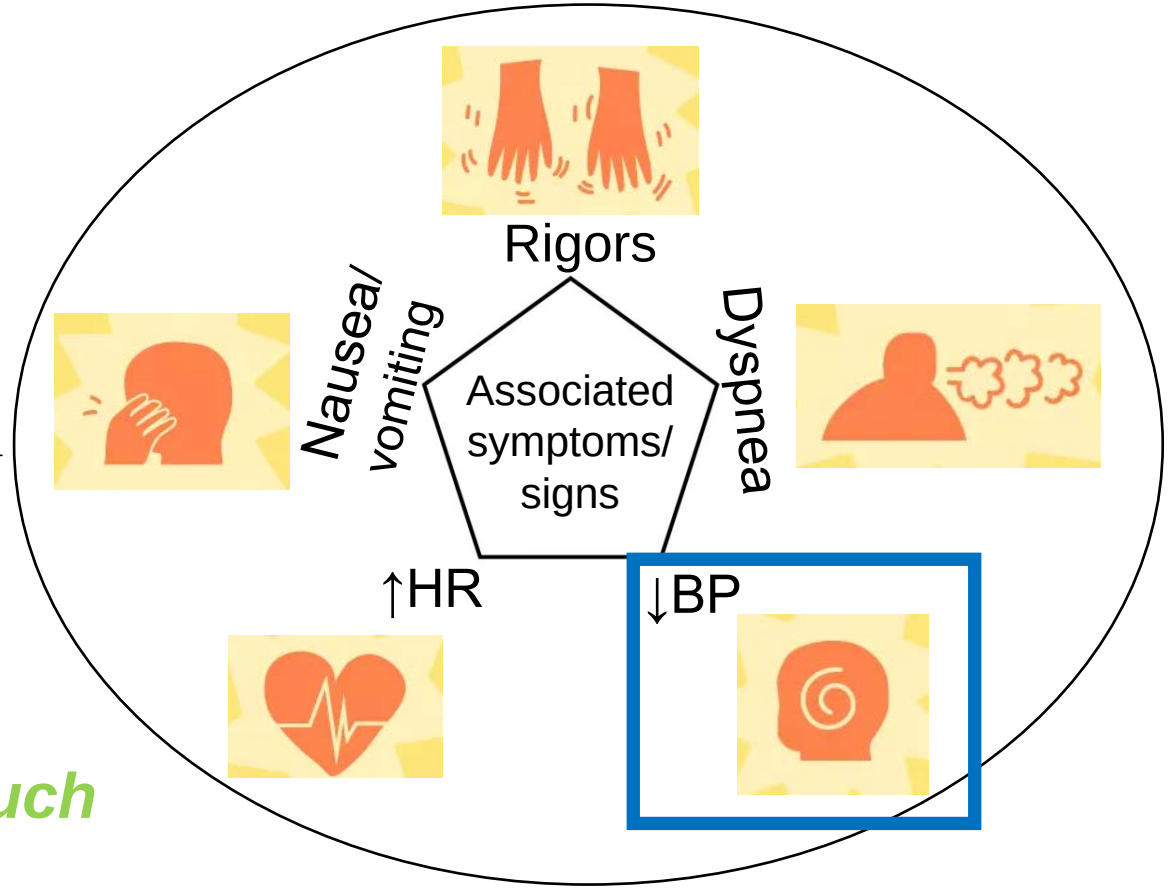
The “High Risk” Fever:
?BaCon ?Bad Match



↑Δ1°C to ≥39°C

↑Δ1°C to ≥38°C + any…

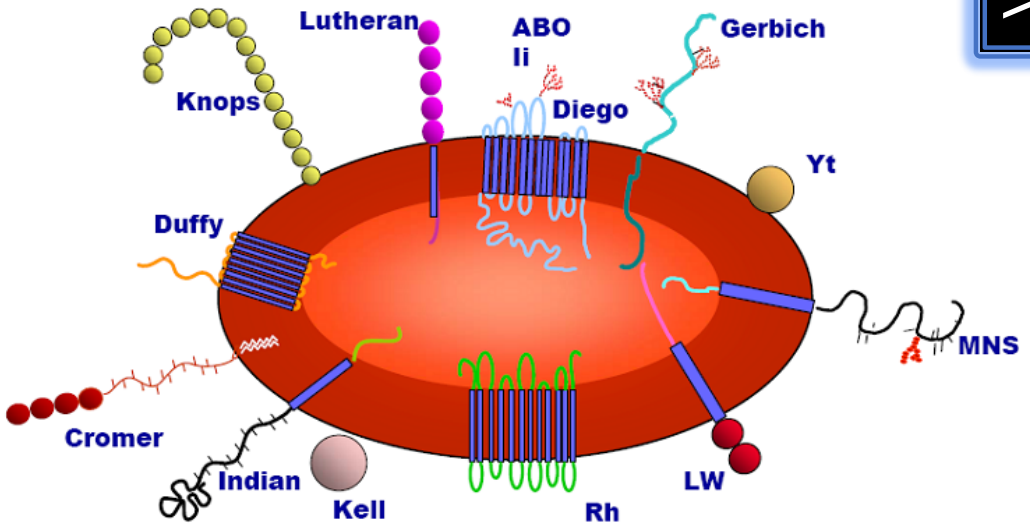
Antipyretic + any…



Early checkpoint changes as such

Shih et al. *The BEST criteria improve sensitivity for detecting positive cultures in residual blood components cultured in suspected septic transfusion reactions.* Transfusion 2019.

As of 2023: 45 blood group antigen systems



>200000 RBC blood group genetic alleles

>1000 RBC blood group coding region variants

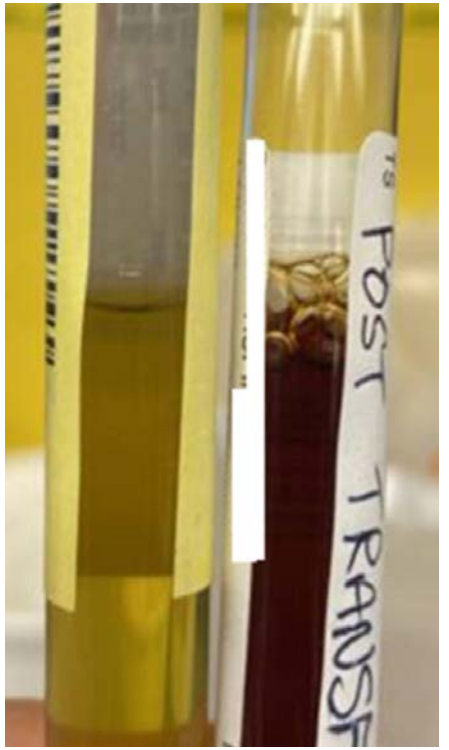
>400 RBC antigens (known to provoke antibodies)

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

Acute Hemolytic Transfusion Reaction (AHTR)

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

- **non-immune**
  - mechanical: 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 (AHTR, DHTR)

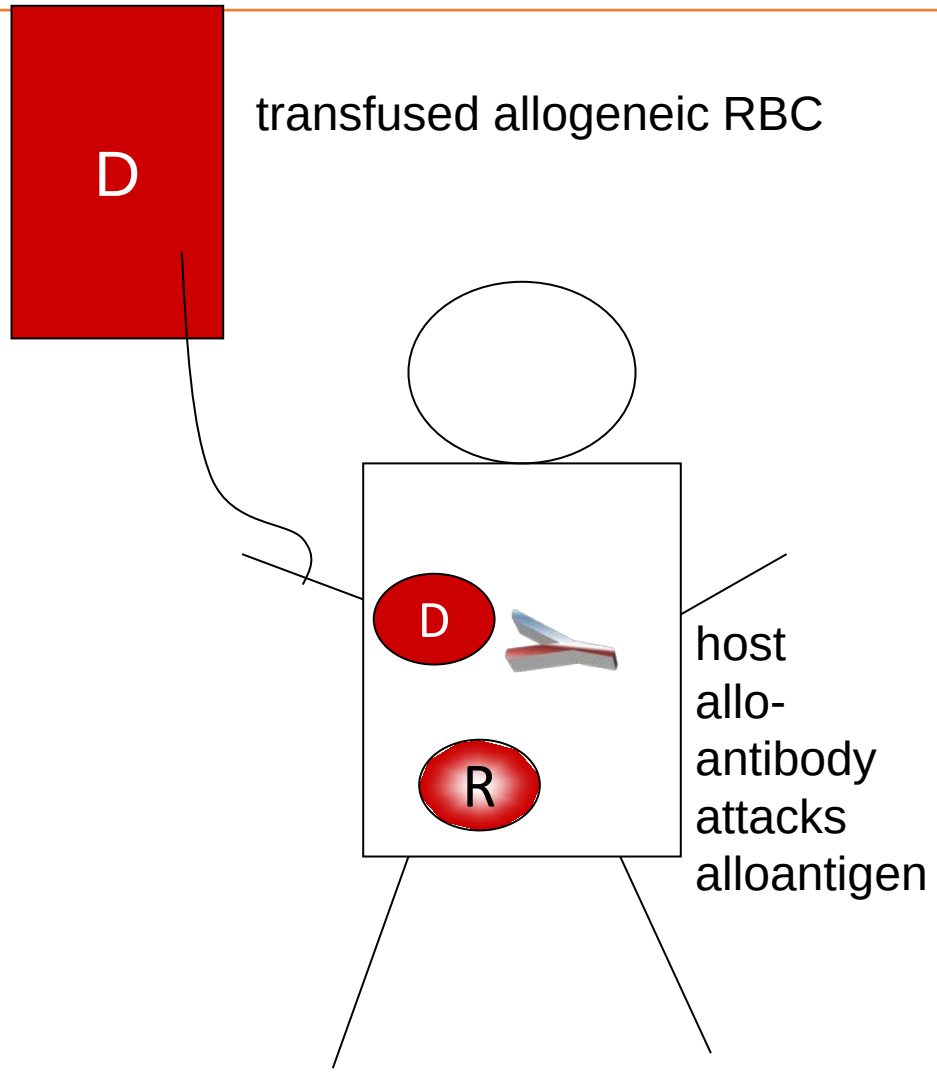
- **active** AHTR =

a *MAJOR* INCOMPATIBILITY

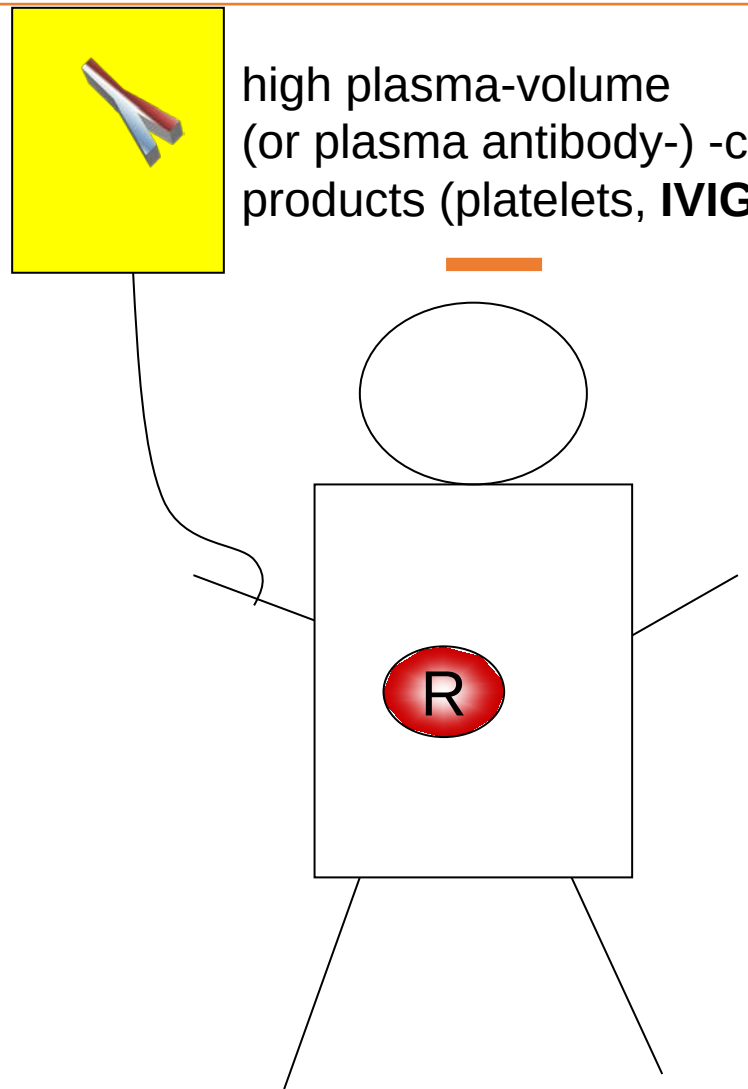
recipient immune system has/makes antibodies against foreign RBC

eg. RBC incompatible for

(ABO *or non-ABO*- blood) antigens



Acute (or Delayed) Hemolytic Transfusion Reaction (AHTR, DHTR)



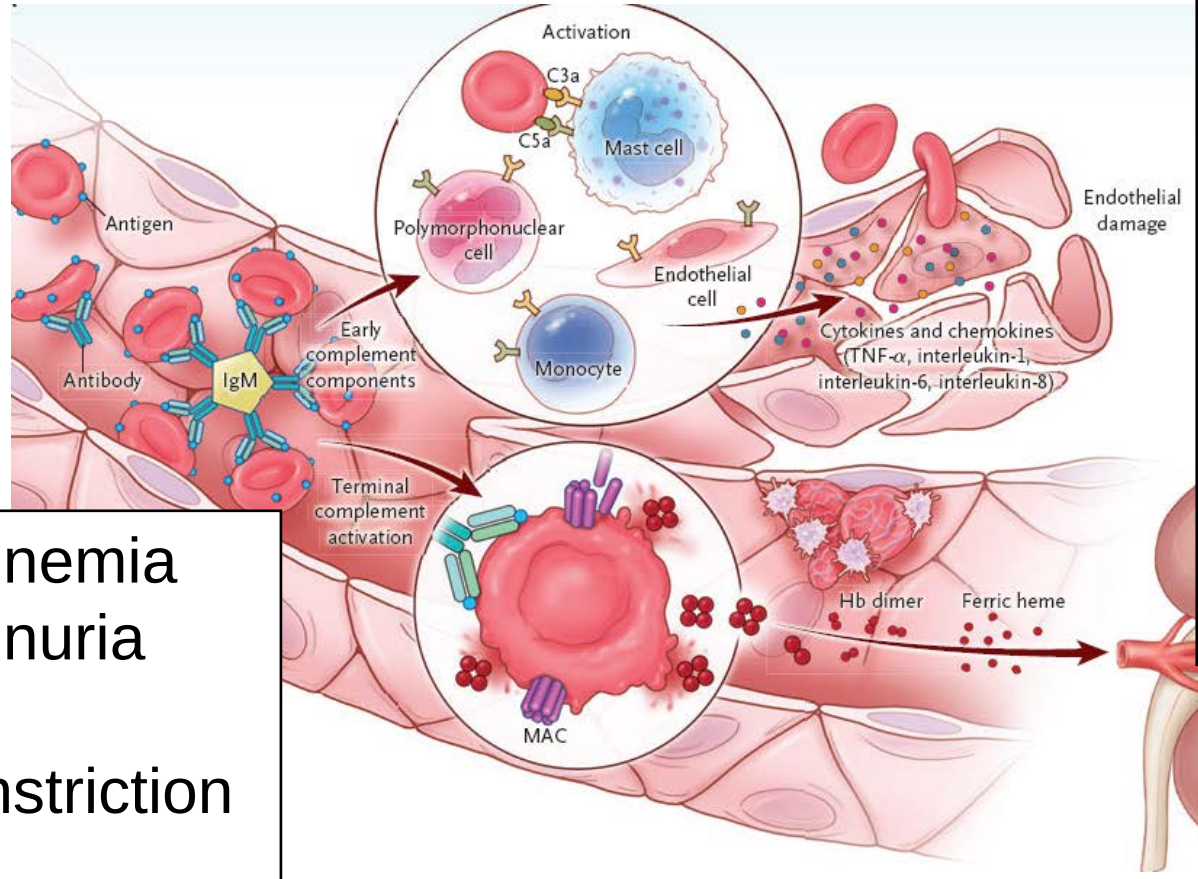
- **passive** AHTR =

a *MINOR* INCOMPATIBILITY

product contains anti-host RBC antibodies

eg. ABO antibodies ("isohemagglutinins") in product can target recipient

(Acute) Hemolytic Transfusion Reaction



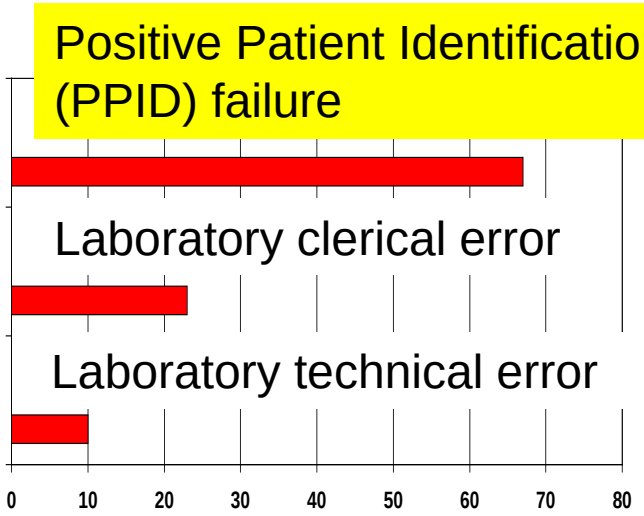
Hemoglobinemia
Hemoglobinuria
AKI:
- Vasoconstriction
- ATN

Shock
Fever
DIC
Doom
Flank Pain
Dyspnea
- Capillary permeability
- NO scavenging

Panch et al. NEJM 2019.
Jantapour et al. Am J Clin Path 2008.

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

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



~1/10^3 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)

% of Major ABO Incompatible Transfusion Errors

Linden et al. Transfusion 1992.

Human Errors Perspective – Sample Rules and Calls for Higher Technology

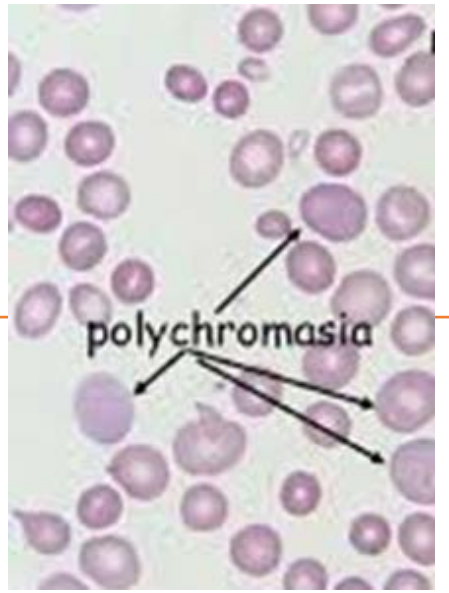
- risk of ABO-incompatible transfusion: 1/40,000 > aggregate risk of all TTVI (1/50,000)

- if sample labeled incorrectly: 1:28 chance of WBIT

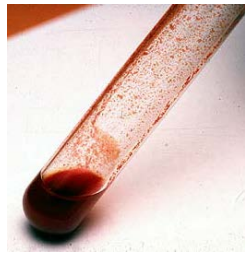
- machine-readable systems ↑ safety 5-fold > manual/human processes

Forest et al. *The Impact of an Electronic Ordering System on Blood Bank Specimen Rejection Rates.* Am J Clin Pathol 2017.
Kaufman et al. *Electronic patient identification for sample labeling reduces wrong blood in tube errors.* Transfusion 2019.

Is There Hemolysis?



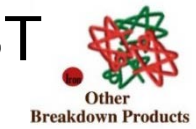
- without attributable bleeding,
  reticulocytosis / polychromasia / ↑ MCV
  (or a *non-elevated* reticulocyte count)
  maps to negative (*exaggerated*) balance



- visible or measured elevation of pfHb

- breakdown markers
  - ↑ bilirubin (unconjugated-predominant), AST
  - ↑ **LDH** (& AST > ALT)
  - ↓ **haptoglobin**

90% Sn



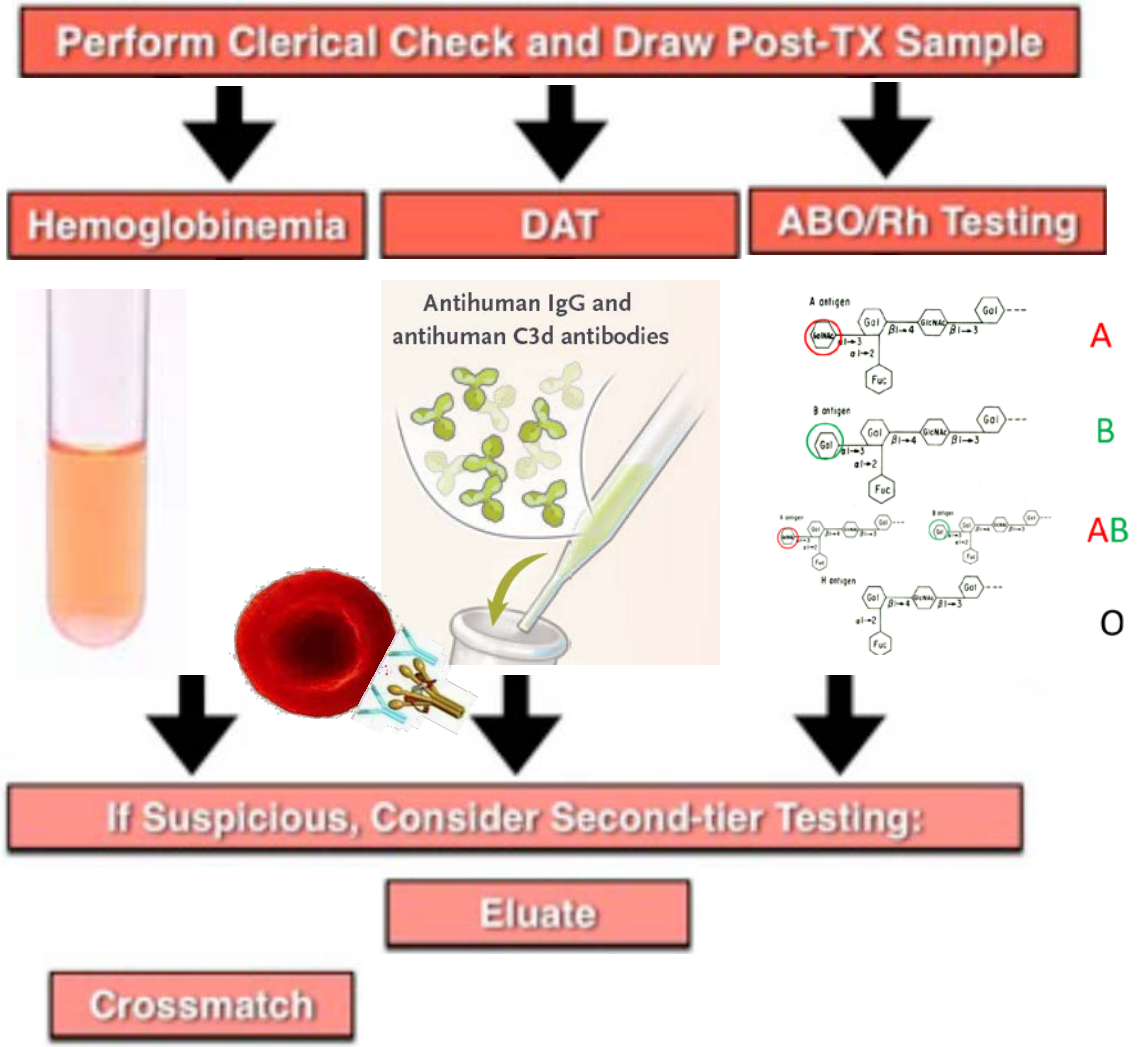
Conversely,
N LDH (<220 U/L) &
N hapto (>0.25g/L): 92% Sn to rule Out.

- hemoglobinuria/hemosiderinuria ± pigment nephropathy

Elliott et al. *Visualizing the Hemolytic Transfusion Reaction.* Transfusion 2003.

If So, Is It Immune Incompatibility-Related?

look at labels

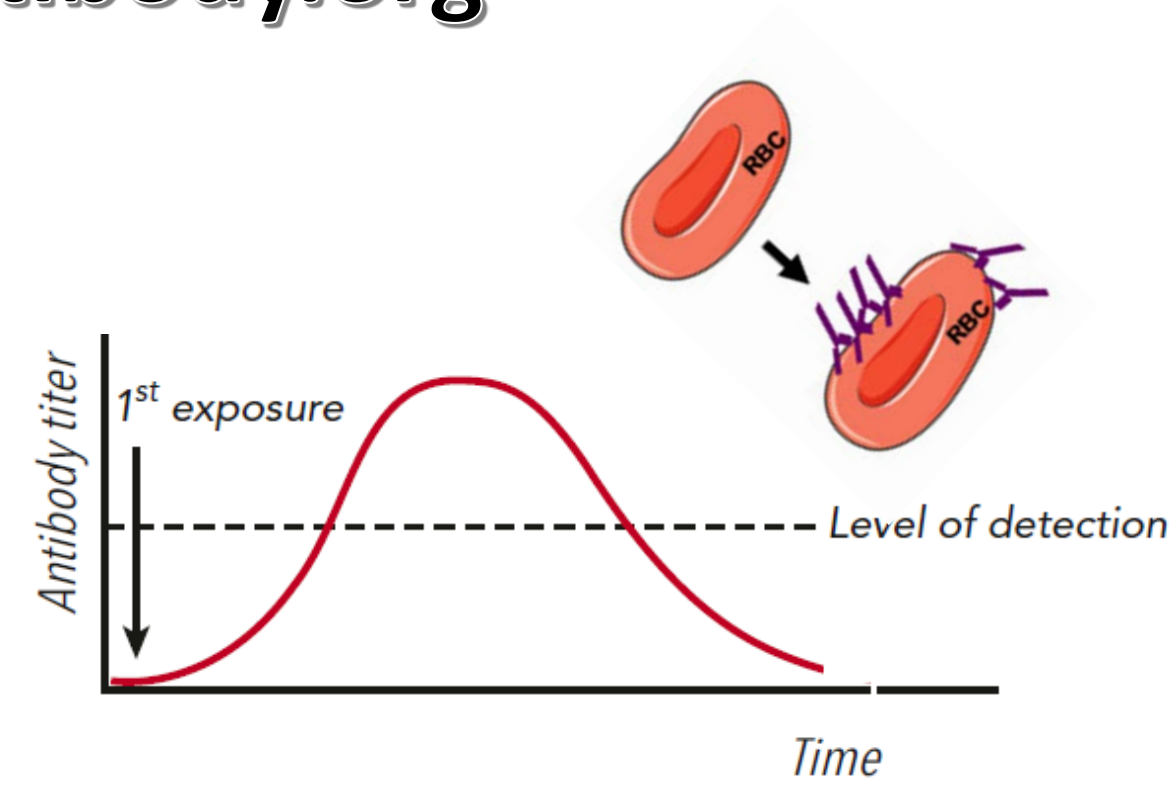


- DIC?
- C3/C4 ↓?
- ferritin ↑?
- HbEP clues?

Alloantibody Exchange

Saving lives by helping blood bank software vendors work together

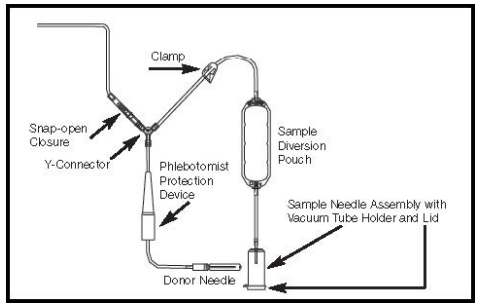
www.alloantibody.org



https://www.change.org/AlloantibodyInformationSharing2ImproveTransfusionSafetyForAllEverywhere

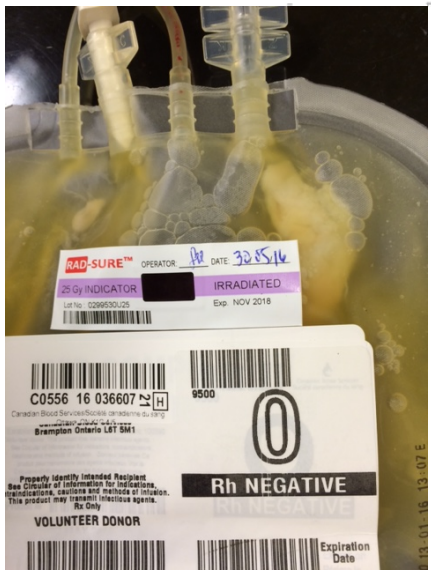
Bacterial Contamination (BaCon) / Transfusion-Associated Sepsis (TAS)

1. Diversion Pouch

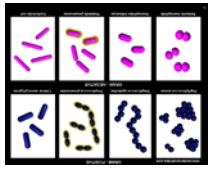


2. Pre-Release Incubation/ Culture System on All Platelets

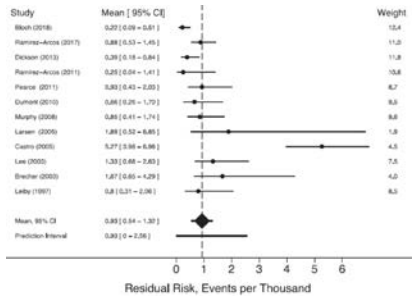
1 / 100,000



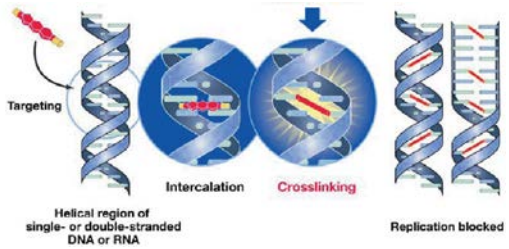
Residual Risk



GPC (skin)>
GNB (IV)



1 / 1000



→ 0

Culture / Investigation Pathway

PRE	POST		CONCLUSIONS
PATIENT		PRODUCT	
+	+	0 / not done	Pre-existing sepsis
0 / not done	+	+	Definitive!
0 / not done	0 / not done	+	Probable…
0 / not done	+	0 / not done	Possible?
+/ 0 / not done	0 / not done	0 / not done	Doubtful.

pathogen-reduced item:
low yield / unlikely: waive
(SDP, IVIG, PPPT/APPT)

untreated item:
higher yield: conduct C&S
(PP/AP, UAP-PAS, RBC, FP)

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

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

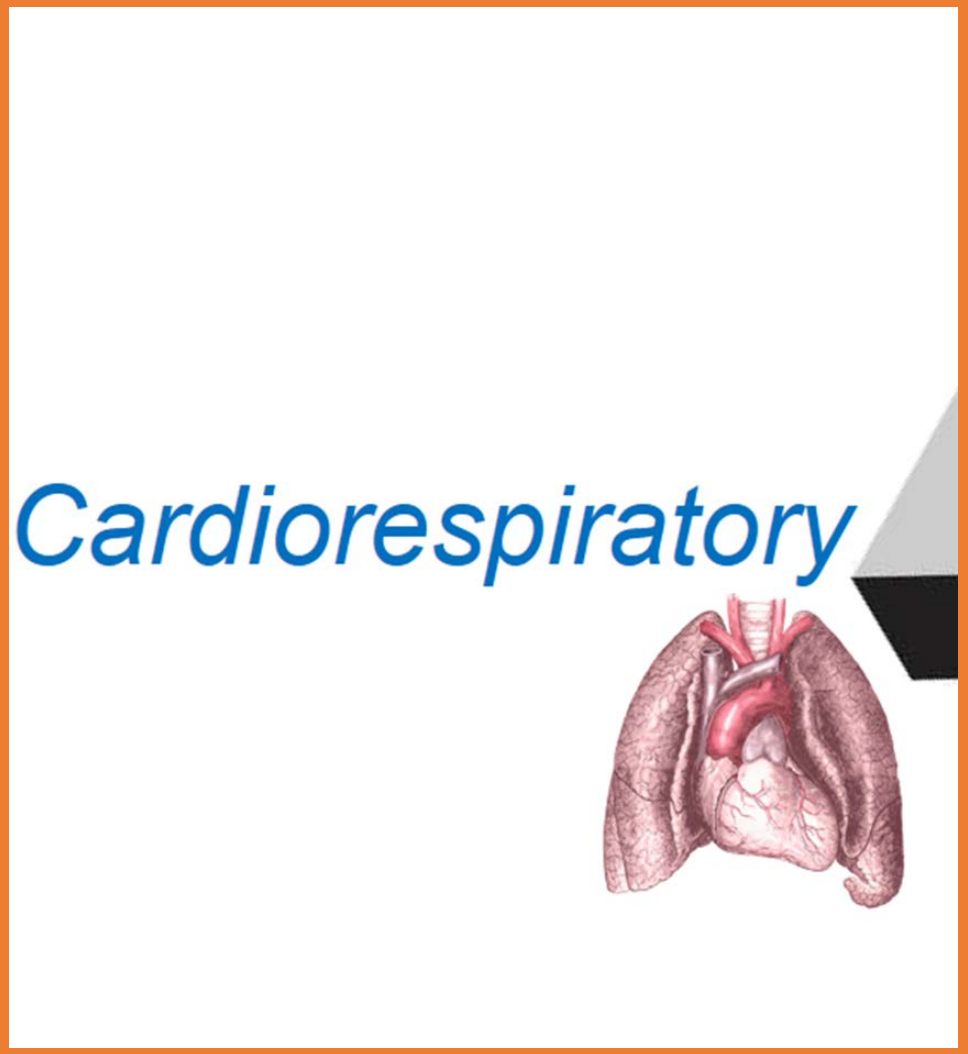
- **<u>recipient</u> has anti-leukocyte antibodies** (because of previous exposure to blood)
  - residual product leukocytes complexed on transfusion

- **product has “pyrogens”**
  - cytokines / inflammatory mediators accumulate,

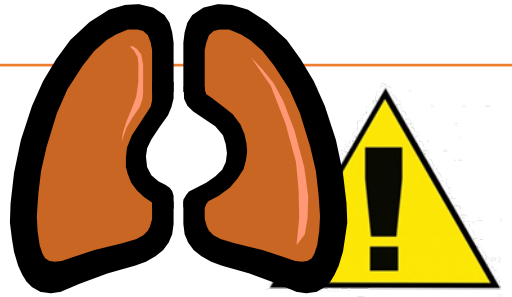
    inducing fever on transfusion

Learning objective 2:

Cardiorespiratory Archetypes



Blood Product Given → Respiratory Distress



Most "important" of all transfusion hazards

High case morbidity & mortality rates, at high frequency

at the individual level

at the population level

Accounting for 60% of transfusion-related deaths

Differential Diagnosis for Dyspnea Associated with a Transfusion

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)

STOP ASAP

REPORT
DISTRESS
EVENTS
WITHIN 6-12H
OF PRODUCT

Decipherment

1 **Volume Status** as the Discriminant

(physical examination)

2 Structure: Infiltrates?

(radiography)

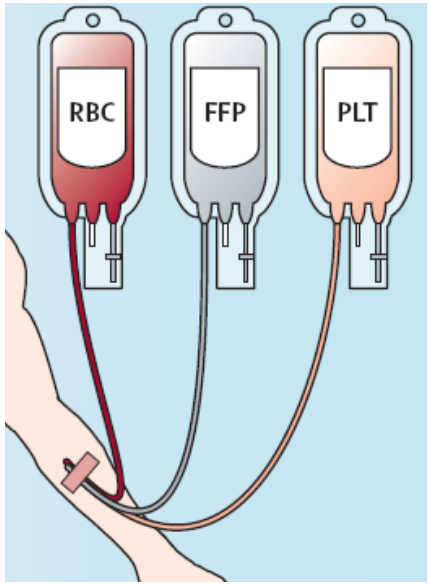
3 (De)Function: Hypoxia?

(oximetry/ABG)

Double Jeopardy: 2-Hit Models…

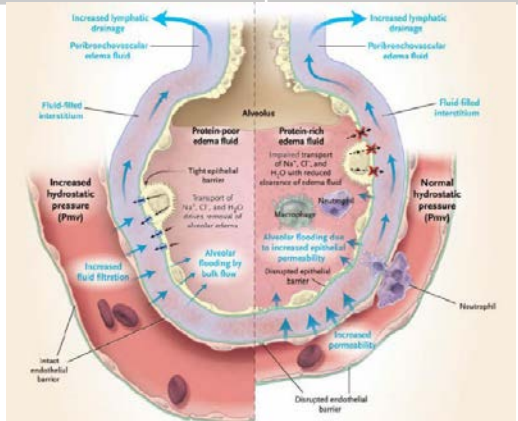
more congestive

more humoral



Vlaar & Juffermans.
Lancet 2013.

	transfusion-associated circulatory overload (TACO)	transfusion-related acute lung injury (TRALI)
Fluid mode:	**hydrostatic**	**permeability/leak**
Immunologic?	-	+
“Agent”	dangerous doctor	dangerous donor
Biomarker	cardiac stress	leukoagglutinins



Ware & Matthay.
NEJM 2005.

Transfusion Associated Circulatory Overload (TACO)

Wiersum-Osselton et al.
The Lancet Haem 2019.

≥ 1 REQUIRED:

OCCURRING WITHIN ≤ **12H** AFTER TRANSFUSION

Respiratory Distress

eg-

- *tachypnea, dyspnea, cyanosis*
- *↓spO_2 % without other causes*
- *bronchospasm/wheezing*

AND/ OR

Pulmonary Edema

Physical

L heart findings *without other causes, eg-*

- *crackles*
- *orthopnea*
- *cough*
- *S3*
- *frothing/pink sputum*

Radiography:

new/worsening changes, eg-

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

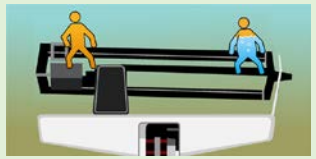
AND: 1 OR MORE OF:

Cardiovascular system changes

not from underlying condition

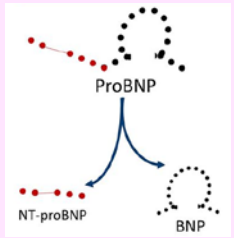
- *tachycardia*
- *↑BP, PP (or ↓ if cardiogenic shock)*
- *JVP distension/↑ CVP/↑cardiac silhouette*
- *peripheral edema*

Fluid overload



- *+ fluid balance or weight gain*
- *diuretic or dialytic response*

Natriuretic peptide (BNP)



↑ > ULN and 1.5x pre-transfusion value

for a MINIMUM OF **3** FINDINGS

Transfusion Associated Circulatory Overload (TACO)

- Common – **1-10%** of encounters

Hendrickson et al. Transfusion 2016.

- Sometimes **“hot”**

Parmar et al. Vox Sang. 2017.

- Assumed to be **reversible with diuretics**

Roubinian & Murphy. IJCTM 2015.

- Risen in rank as **commonest** reason for **transfusion-related death**

TTISS (Ontario)	2014-2018:	13/35 (37%)	**37%**
SHOT (UK)	2010-2020:	104/212 (49%)	(95% CI:
FDA (USA)	2014-2019:	72/262 (27%)	**33-41%**)

- Often serious (**1/5 to ICU**) …

LOS effects…

CFR: **1-10%**

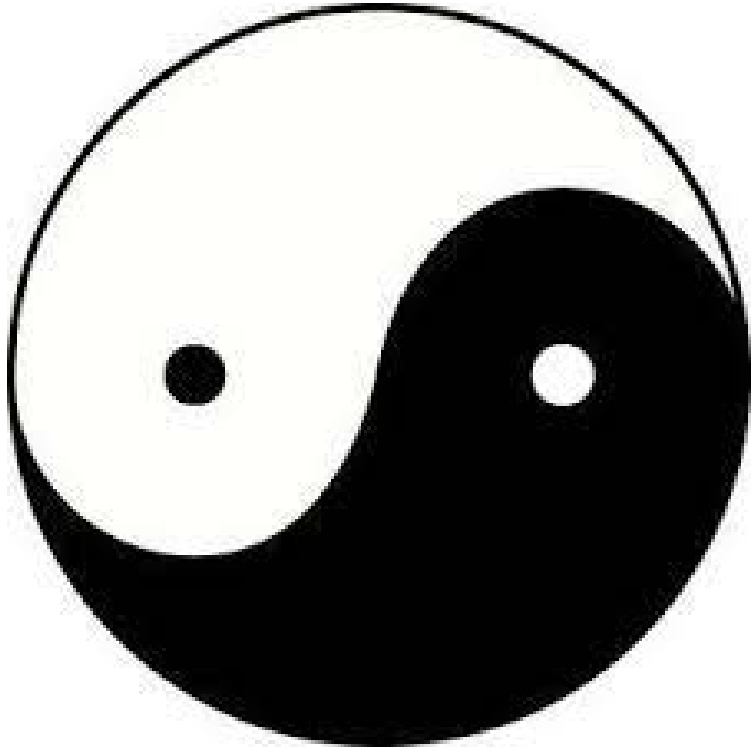
Lieberman et al. Transfus Med Rev 2013.

Roubinian et al. Crit Care Med 2018.

Murphy et al. Am J Med 2013.

TACO: Accreditation Standards Expect Lab-to-Bedside Prevention Measures

IDENTIFY WHO IS AT RISK



MODIFY THE ORDER

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)

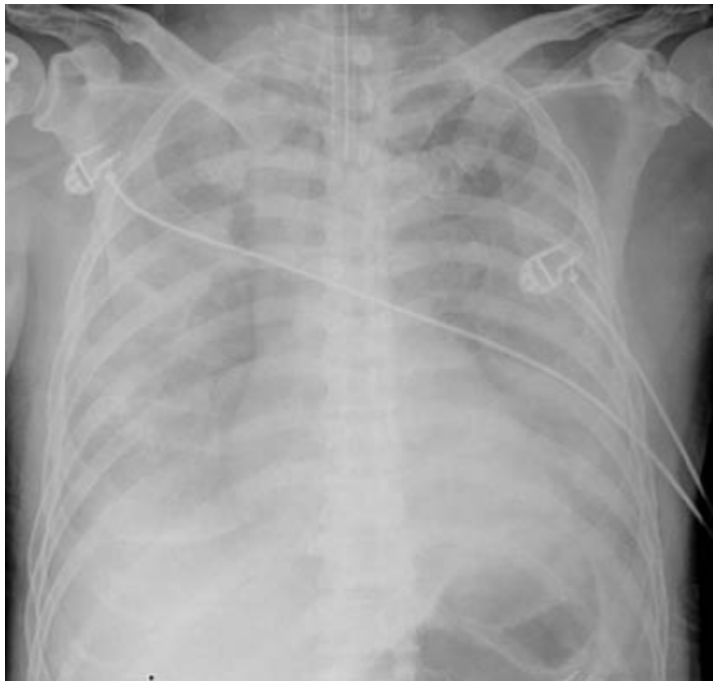
- **C**ardiorespiratory dysfunction
  - MI, CHF, diuretics, abnormal cardiac studies
  - tachypnea, hypoxia, rales, S3/S4
- **R**enal dysfunction
- **A**ge
  - youngest
  - oldest (>60-70 years)
- **P**ositive fluid balance
  - weights, ins/outs, physical signs

- small receiver: low body weight
- ++anemic: hyperdynamic?
- heavy-handedness:
  - unspecified (runaway) or too fast rate
  - unassessed patient
  - big order
  - preceding crystalloids: “STACO”

TACO: How to Change the Order to Reduce the Risk

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

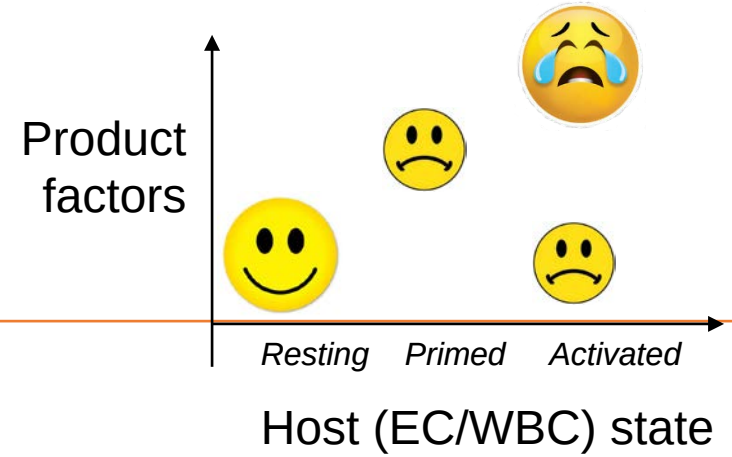
Flash Non-Cardiogenic Pulmonary Edema:



?Transfusion Related Acute Lung Injury (TRALI)

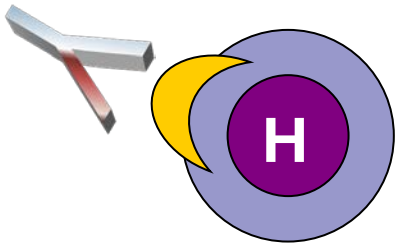
Wong et al. *A life-threatening transfusion reaction.* Transfusion 2017.

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



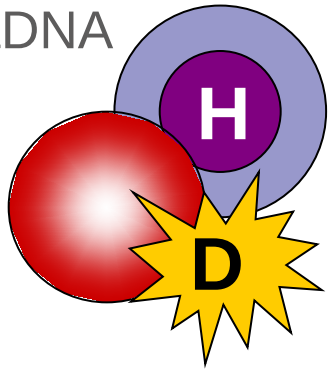
- **<u>donor</u>: anti-leukocyte antibodies (ALA)**
  - ALA (HLA [**II**>I], H**N**A)
  - ALA in most cases

D



cognate Ag binding → activation (TRAIL)*

- **product toxins/biologic response modifiers (BRM)**
  - products release:
    - biologically active lipids, lysoPC, microparticles
    - cytokines, chemokines (HMGB1, sCD40L)
    - NETs, mtDNA



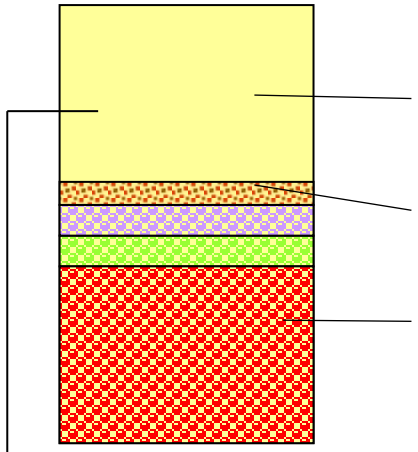
donation stews harmful humours

Sachs. *Recent insights into the mechanism of TRALI.* Curr Opin Hematol 2011.
Kopko et al. *Antibodies associated with TRALI: differences in clinical relevance.* Transfusion 2019.

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 foreknowledge”

OR ~ ½



WHOLE BLOOD:
plasma for “recovery”/fractionation (pooling = dilution)

platelets in platelet additive solution

red cells still used for direct component therapy

apheresis or whole blood plasma *if for direct component therapy*: **MEN or NULLIPARAS**

Transfusion Related Acute Lung Injury (TRALI)

A + B + C:

A.

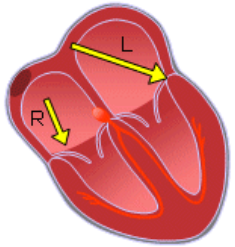
Acute Onset

Hypoxemia

- *paO2/FiO2 ≤ 300*
- *spO2 <90% R/A*
- *Other evidence*

Bilateral Infiltrates

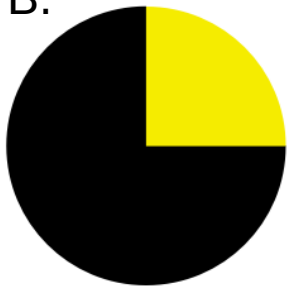
CXR, CT, US



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

Echo, PCWP

B.



Onset during or within **6h** 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*

Vlaar et al. *A consensus redefinition of TRALI.* Transfusion 2019.

TRALI “Types” by Background

TRALI Type I	TRALI Type II
TRALI	possible TRALI (pTRALI)

Disturbance within 6h

No risk factors/features prior

Disturbance within 6h

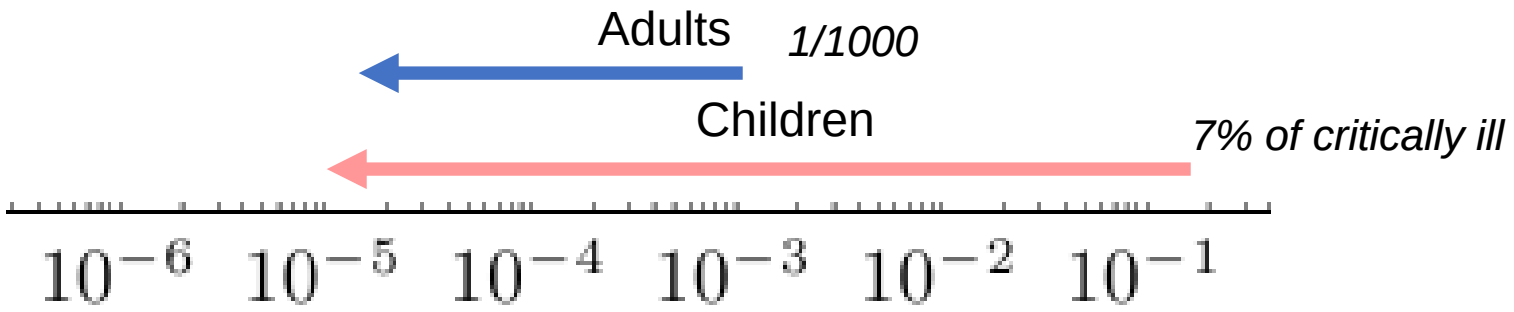
+ Risk factors/features
BUT *stable in the last 12h*

Disturbance within 6h

+ Risk factors/features
& worsening in the last 12h

TARDS

TRALI Epidemiology



Vossoughi et al. *10y of TRALI mitigation: measuring our progress.* Transfusion 2019.

- Transfusion-attributable fatalities:

TTISS (Ontario)	2014-2018: 9/35 (26%)	**16%** (95% CI: **13-19%**)
SHOT (UK)	2010-2020: 7/212 (3%)	
FDA (USA)	2014-2019: 59/225 (26%)	

- IHM: up to 50%
- CFR: 5-25%

McVey et al. *TRALI in the Perioperative Patient.* Anesthesiology 2019.

Why is dyspneic/hypoxic reaction reporting so important?

A. Billings bring revenue

B. Quality signal on dangerous bedside practitioners

C. Reporting improves real-time care

D. Maps to co-component quarantine, donor investigation (+/- deferral)

E. Enables legal actions

Learning objective #3:

Allergic and Other Archetypes

The Allergic Spectrum

frequency gradient

1% overall incidence of any allergic feature

fatal anaphylaxis: 1 in 2-10 million

90% of cases are minor (<2/3 TBSA urticaria)

angioedema (=subcutaneous rather than cutaneous)

respiratory:
- bronchospasm
  - wheezing, stridor, hoarseness, dyspnea, hypoxia, asphyxia/doom

gastrointestinal instability:
- nausea/vomiting/abdominal cramping/diarrhea

cardiovascular instability:
- hypotension, chest pain, tachycardia

anaphylactoid / anaphylactic reaction ± death

danger gradient

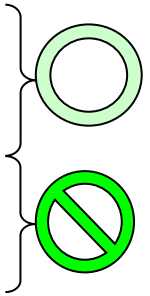
Why Allergic Reactions Happen

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

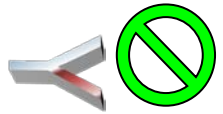
RECIPIENT HAS <u>MISSING OR VARIANT</u> PROTEIN, AND REACTS TO WILD-TYPE PROTEIN



<5% of cases

- eg **IgA**, haptoglobin, complement, albumin, α1anti-trypsin, transferrin

- anti-protein IgG develops



Hypotension

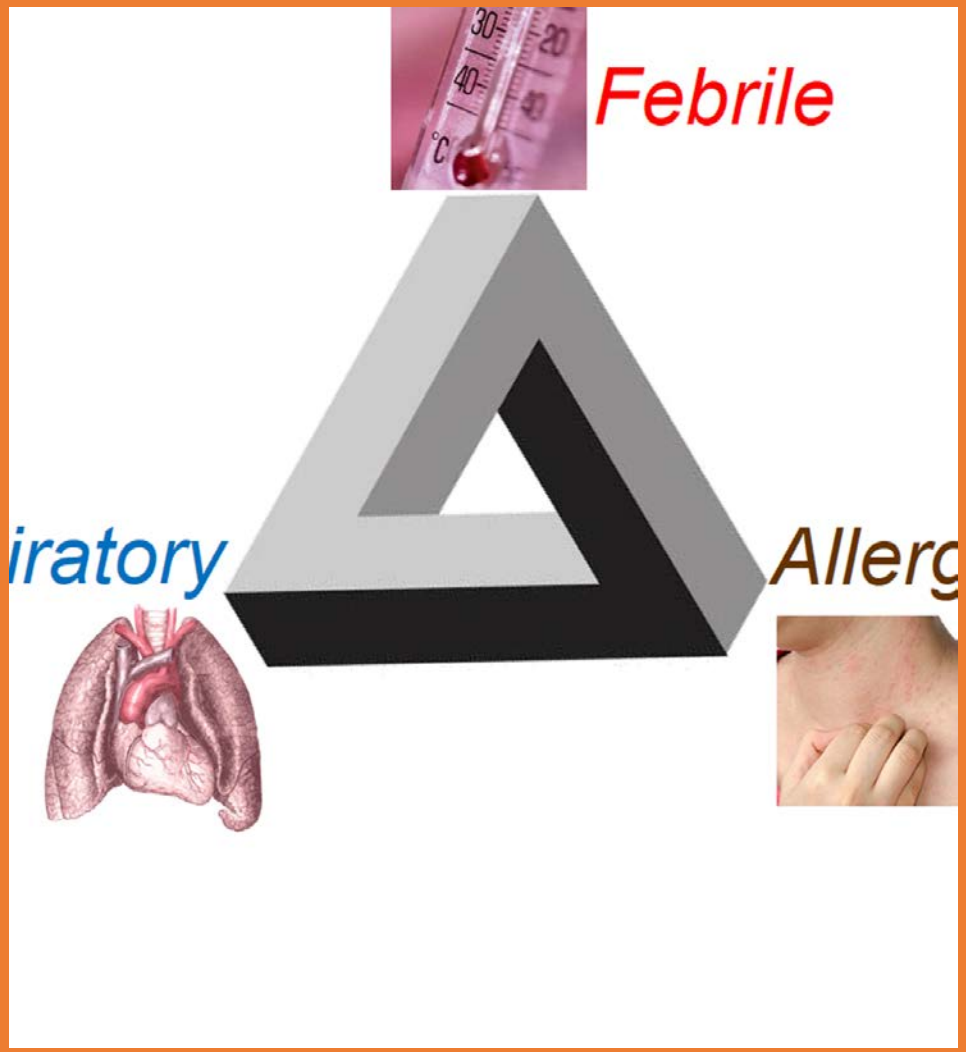
acute hemolytic transfusion reaction (AHTR)

bacterial contamination (BaCon)

severe allergic transfusion reaction / anaphylaxis

bradykinin shock?

Key Learnings and Take Aways



1. Expectations

you report to us, & we report within and to outside channels

Presentation Archetype	Testing Reflex		Management: Supportive Care
	Blood Bank Sample (r/o Hemolytic Incompatibility)	**Microbiology** Samples (r/o Septic Reactions)	
High Risk Fevers	✓ +hemolysis w/u	✓	✓
Dyspneic Reactions	✓ +/- CXR, BNP +/- TRALI w/u	✓	✓
Shock	✓	✓	✓
Anaphylaxis / Anaphylactoid	✓ +/- IgA deficiency w/u	✓	✓

2. Truths

- what COULD go wrong (3 tiers: common, serious, rare)

ATR / ETR / STR / TACO — 10^1-10^2

Resp / BaCon / HTR — 10^3-10^4

TTVI / new pathogen / GVHD — 10^5-10^6

- most common (acute) killers: TRALI & TACO, AHTR-IBCT, TAS

  (delayed) killer: SCD: DHTR-HHS

- the only measure with power to mitigate EVERY single transfusion reaction type, is AVOIDANCE of the order itself…

Happy Transfusion Endings…

Thank you.

Canadian Blood Services

Laboratory Medicine & Pathobiology
UNIVERSITY OF TORONTO