

DAY 2 > COMPLICATIONS:
COMPATIBILITY, ACUTE & LONG TERM TRANSFUSION RISKS, & ERRORS -

Acute (Non-Infectious) Reactions

Friday November 19th 2021, 10:15 – 11:00



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Disclosure

- **Relevant relationships with commercial entities:**
 - None
- **Potential for conflicts within this presentation:**
 - Funding from Canadian Blood Services in transfusion reaction research
- **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.**



AHRQ
Agency for Healthcare
Research and Quality
**HEALTHCARE COST AND
UTILIZATION PROJECT**

Roubinian et al. [BMC Health Serv Res.](#) **2014**; 14:213

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



**Reaction rates:
1-10% per
encounter**



**~Half of
transfusions
may be
unnecessary**

Kaufman et al. [Transfusion.](#) **2015**; 55: 144-53.

Hendrickson et al. [Transfusion](#) **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

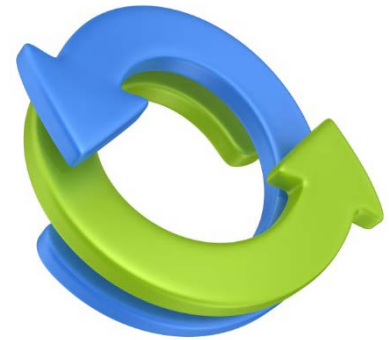
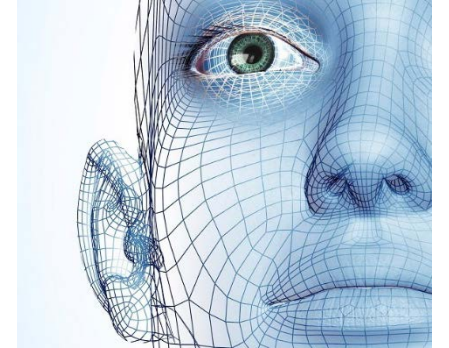


and the guidance
under which the system is regulated”



Objectives – Hemovigilance **Philosophies**

- **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 – *Entities to Know*

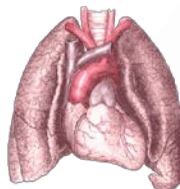


- Describe presentation, frequency, and management of the **3 most commonly encountered but minor** adverse transfusion events
- State the **3 most important causes of transfusion-related mortality and severe morbidity**, ie- **potentially life-threatening acute transfusion reactions** and how we mitigate the risks for these events

febriles

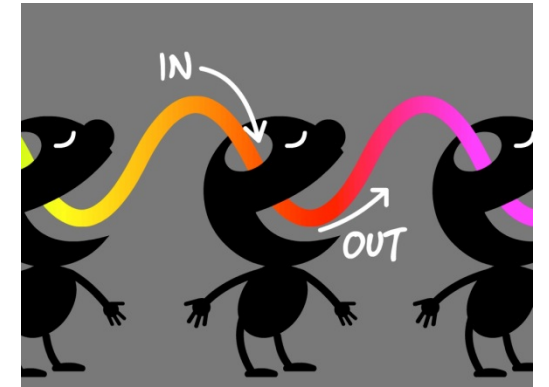


*deep-stuff:
cardiorespiratory
(dyspnea, shock)*



*surface-stuff:
skin (rash)*

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 – 2012

133 million components

AFFSSaPS - France

Biovigilance Network - US

SHOT - UK

TTISS - Canada

TRIP- Netherlands

Politis et al. *Vox Sang.* **2016**; 111(4):409-417.

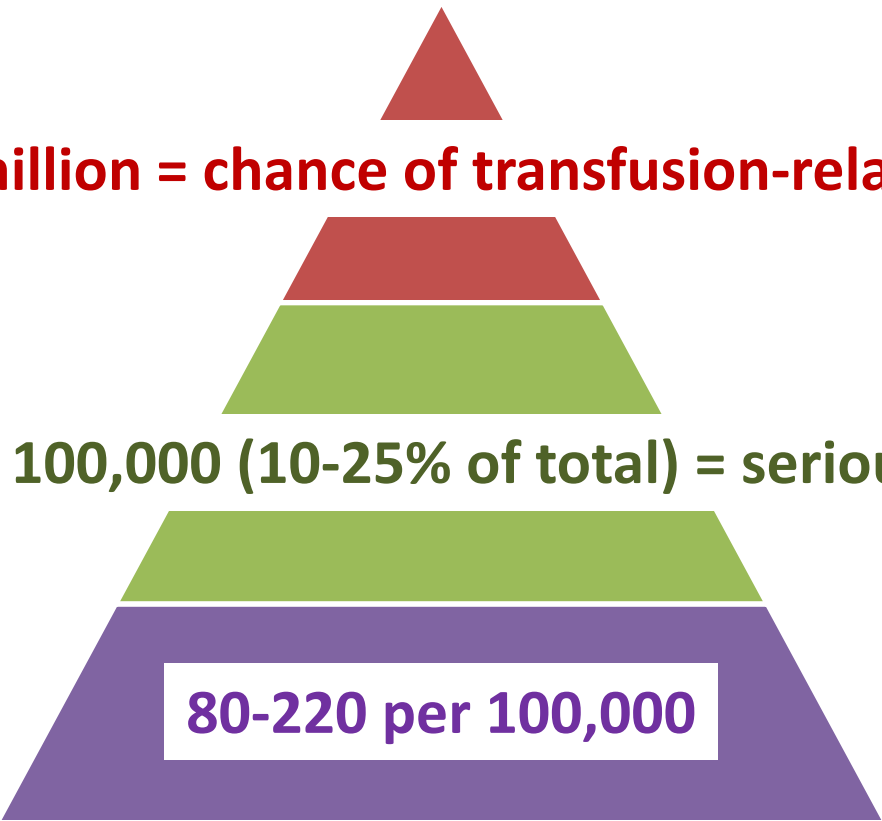
NHSN - National
Healthcare Safety Network
Hemovigilance Module of
the CDC **USA**

2013 – 2015

8 million components

Kracalik et al. *Transfusion* **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

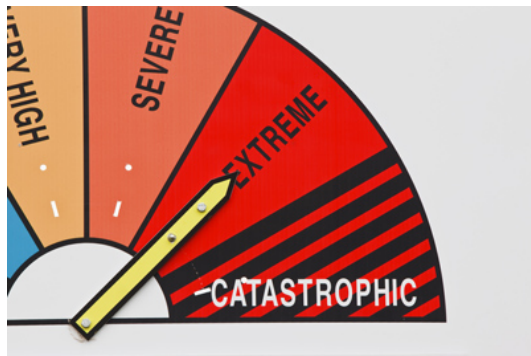
80-220 per 100,000

Qualifying the Event: Provisional Adjectives

- SEVERITY

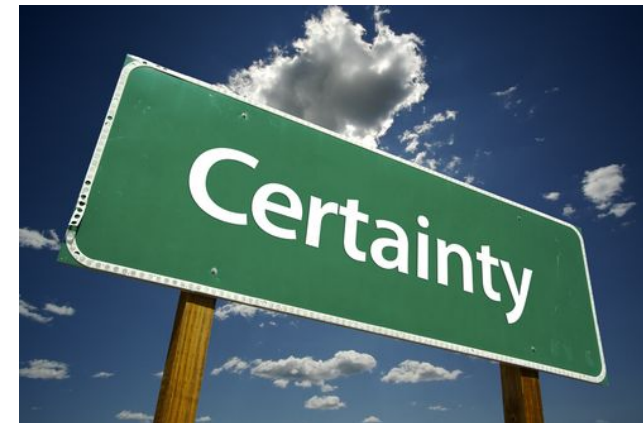
- Grade 1 (non-severe)
 - Mild
 - Moderate

- Grade 2 (severe)
- Grade 3 (life-threatening)
- Grade 4 (death)

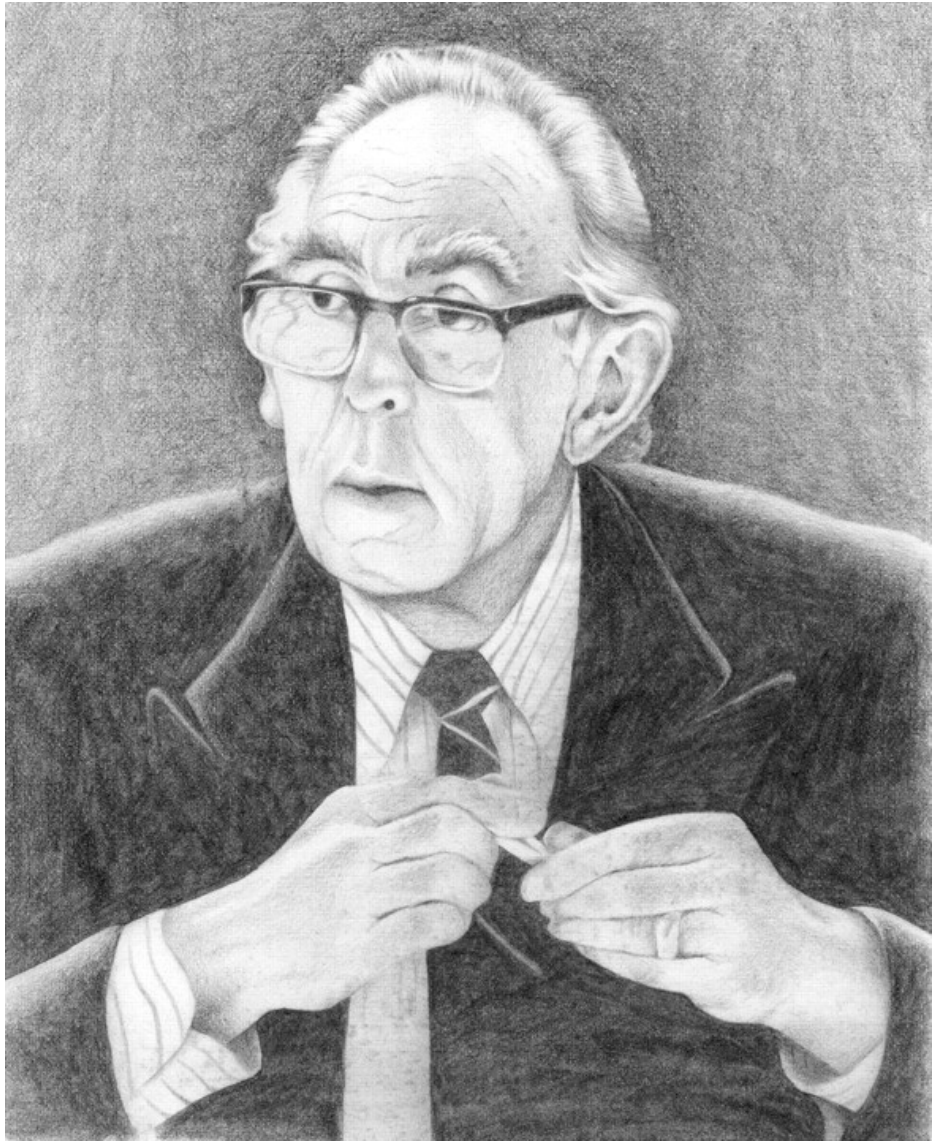
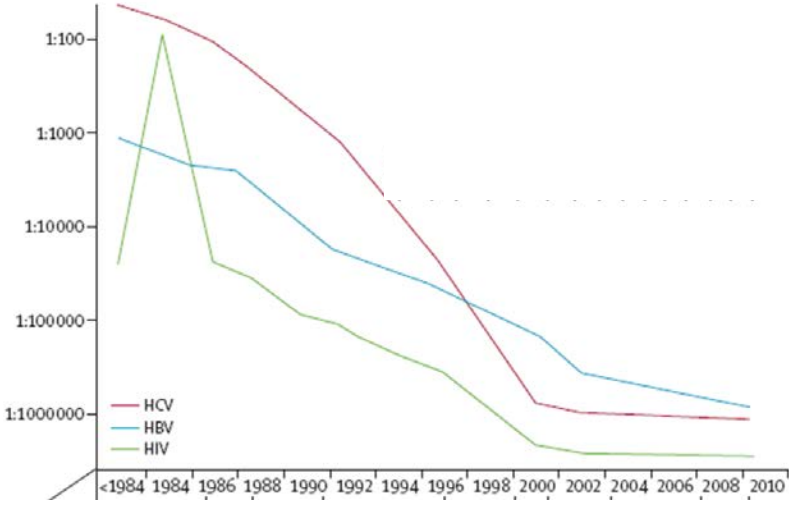


- IMPUTABILITY

- Definite (certain)
- Probable (likely)
- Possible
- Unlikely (doubtful)
- Excluded

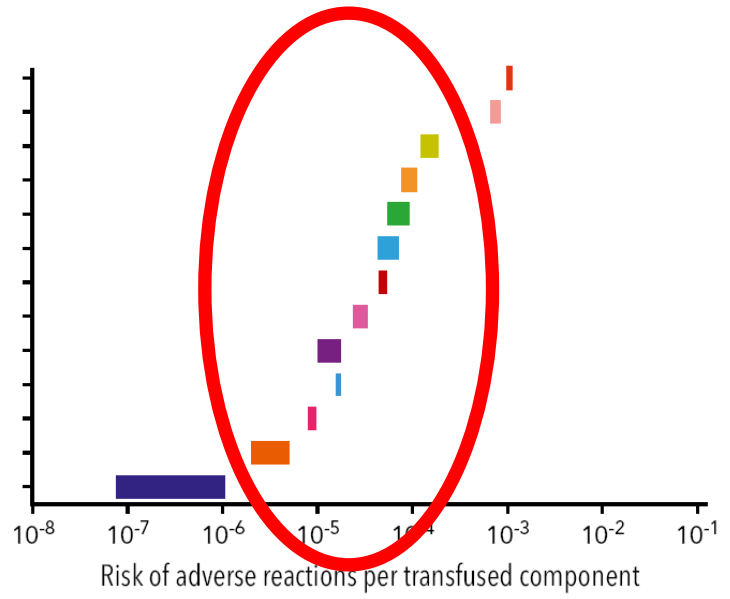


Aggregate Transfusion Transmitted Viral Infection (TTVI) hazards: $< 1/10^5$



Justice Horace Krever

Aggregate non-TTVI hazards: $> 1/10^5$

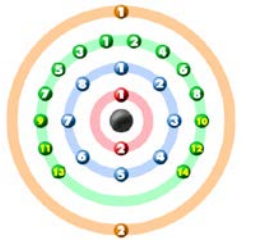


Andrzejewski Jr et al. *Int J Clin Transfus Med.* **2014**; 2: 45-57.

Goel et al. *Blood* **2019**; 133: 1831-9

Minimum Disclosure Framework

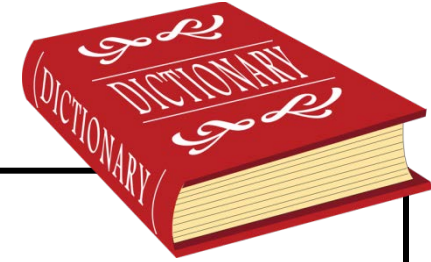
in Layman's Terms & Logscale Frequencies



logscale
1
2
3
4
5
6

| | |
|---|--|
| Common, minor events (1 / 10 ¹ -10 ²) | non-serious fever non-serious hives make antibodies to donor antigens (RBC, HLA) |
| Serious, potentially fatal events (1 / 10 ³ -10 ⁵) | <u>breathing</u> trouble: –volume-driven fluid excess –immune injury-driven fluid leaks –anaphylaxis / severe bronchospasm <u>bacterial</u> contamination of unit <u>botched</u> process (wrong sample or bag) |
| 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: |
| TACO | –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) |
| TTVI | -viral contamination of unit |
| Emerging infections | -new, unexpected bugs |
| TA-GVHD, PTP | -fatal immune “take-over” by product |



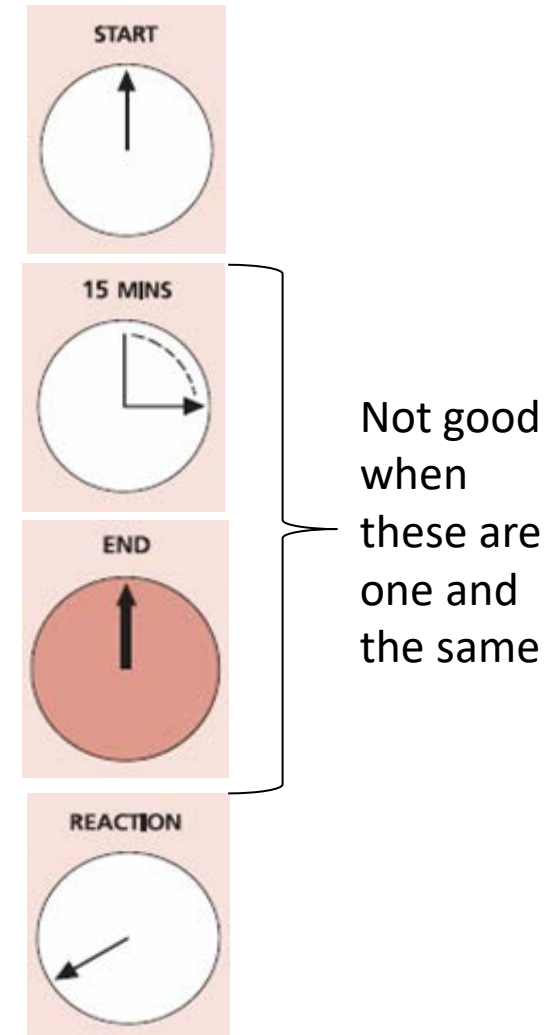
Secret Decoder Slide

| | |
|--------------------|---|
| 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

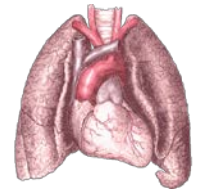
- time 0: vital signs
- 1st 15 minutes: SLOW infusion (50cc/h)
- **at 15 minutes:** vital signs re-check
- end: must be within 4 h;
re-check vital signs
- reaction: vital signs

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





Febrile



Cardiorespiratory

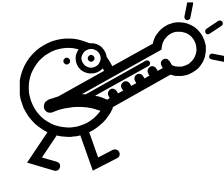


Allergic

When Is It A Fever (Pyrexia) ?



- $T > 38^{\circ}\text{C}$ AND \uparrow by $\Delta 1^{\circ}\text{C}$



OR

- the cytokine-provoked equivalent of chills or rigors



febriles



Fever's Differential Diagnosis



HIGH RISK FEVER

danger gradient



acute hemolytic transfusion reaction (AHTR)

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

fever due to underlying disease



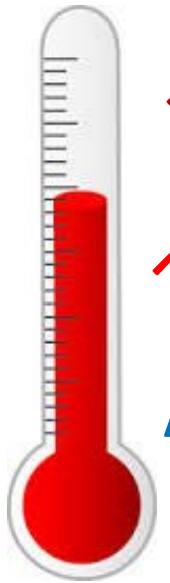
LOW RISK FEVER

febrile non-hemolytic transfusion reaction (FNHTR)



frequency gradient

The “High Risk” Fever: *?BacOn ?Bad Match*

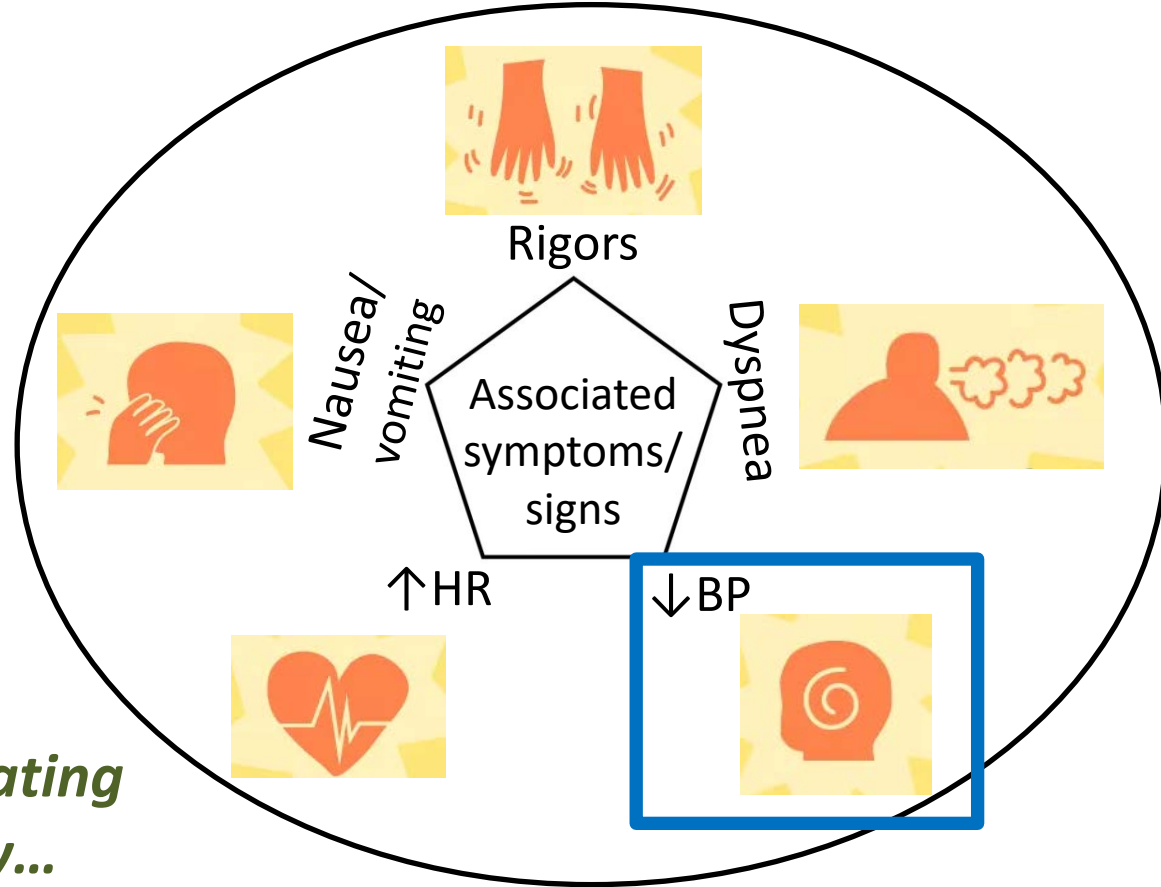


↑Δ1°C to ≥39°C

↑Δ1°C to ≥38°C + any...

Antipyretic + any...

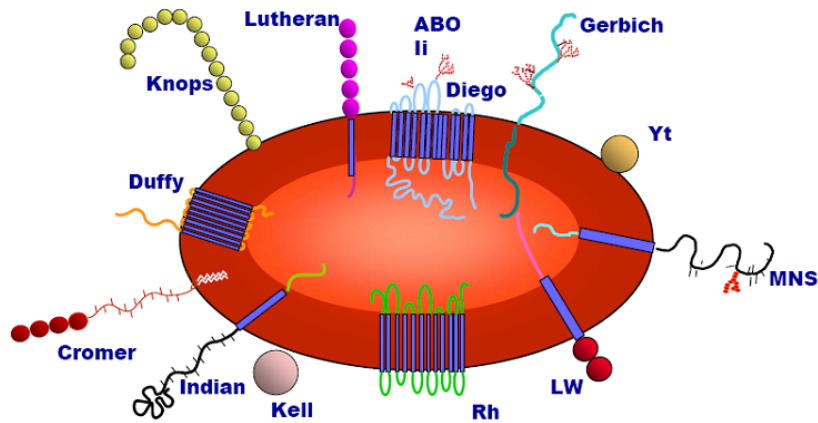
Early interim volume associating with ↑Δ1°C to ≥38°C, or any...



As of 2020:

3 9 blood group antigen systems

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



• © Jill Storry



ERYTHROGENE

4 3

RBC blood group related genes

2 1 0 4 1 2

RBC blood group genetic alleles

1 2 4 1

RBC blood group coding region variants

3 6 5

RBC antigens (known to provoke antibodies)

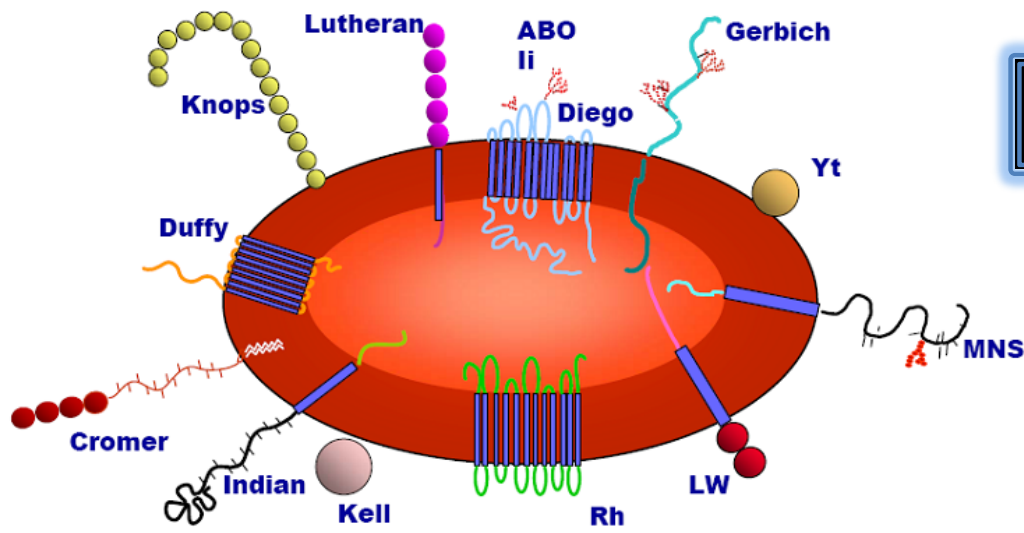
- Storry et al. *Vox Sang* **2019**; 114: 95-102. <http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/>
- Möller et al. *Blood Advances*, **2016**; 1(3):240-249. <http://www.erythrogene.com/>

As of 2021:

4 3

blood group antigen systems

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



© Jill Storry

4 7

RBC blood group related genes

2 1 0 4 1 2

RBC blood group genetic alleles

1 2 4 1

RBC blood group coding region variants

3 8 1

RBC antigens (known to provoke antibodies)

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

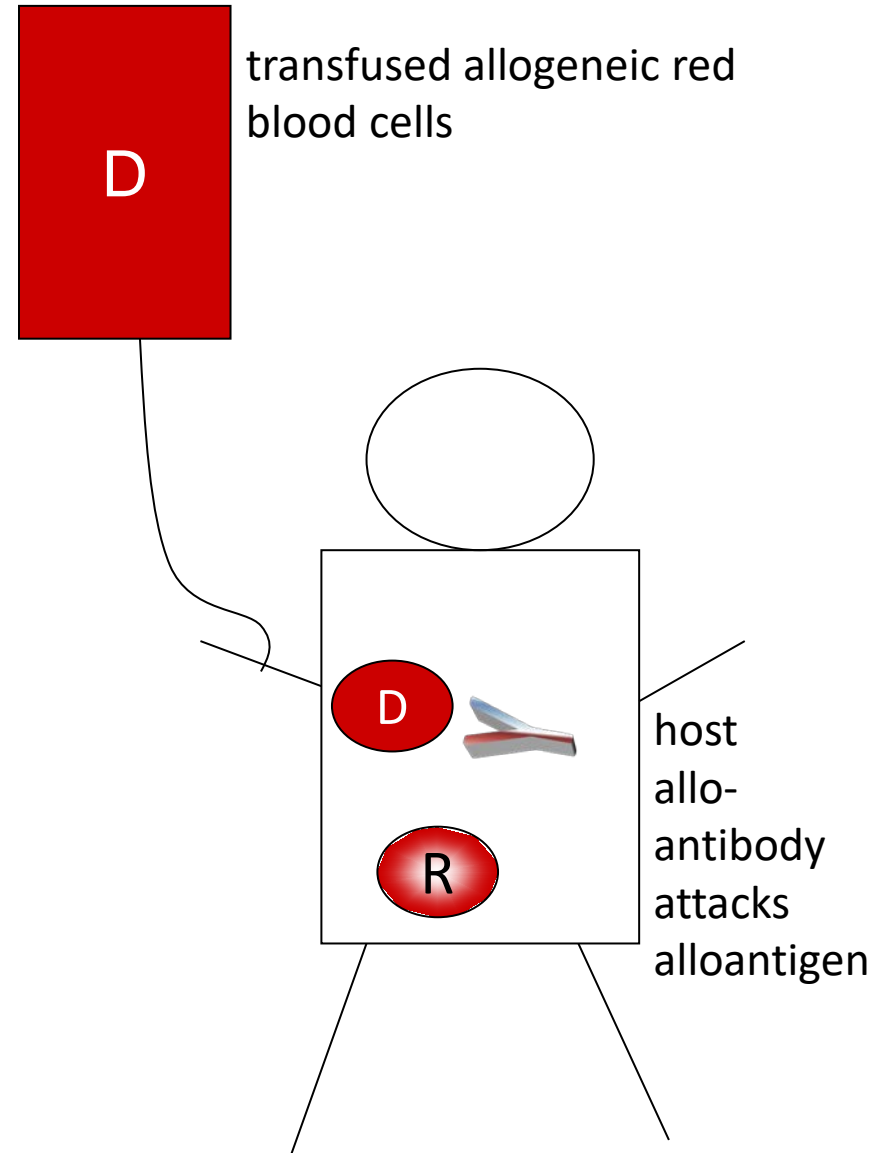


Acute (or Delayed) Hemolytic Transfusion Reaction

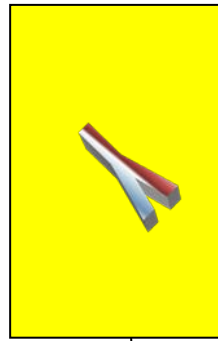
- **active** AHTR = MAJOR INCOMPATIBILITY

– recipient makes antibodies that destroy foreign RBC

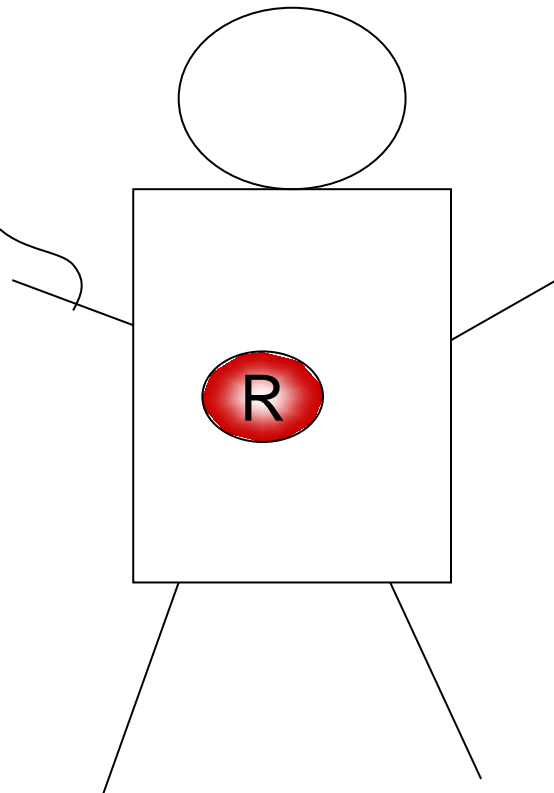
eg. RBC incompatible for (ABO or non-ABO-blood) antigens



Acute (or Delayed) Hemolytic Transfusion Reaction



high plasma-volume (or plasma antibody-) containing products (platelets, IVIG)

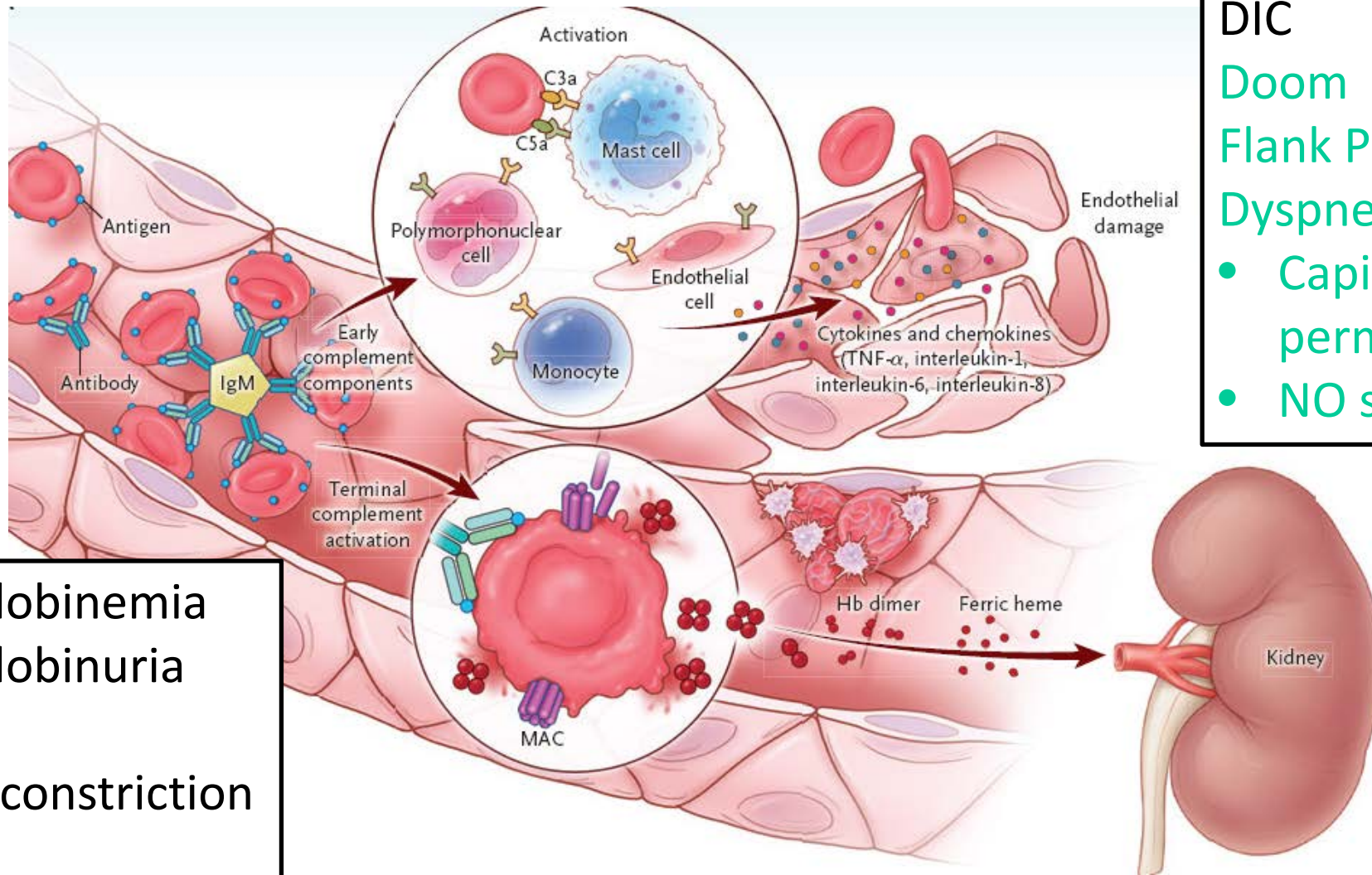


- **passive** AHTR =
MINOR INCOMPATIBILITY

– product contains antibodies that destroy host RBC

eg. ABO antibodies (“isohemagglutinins”) targeting recipient

(A)HTR

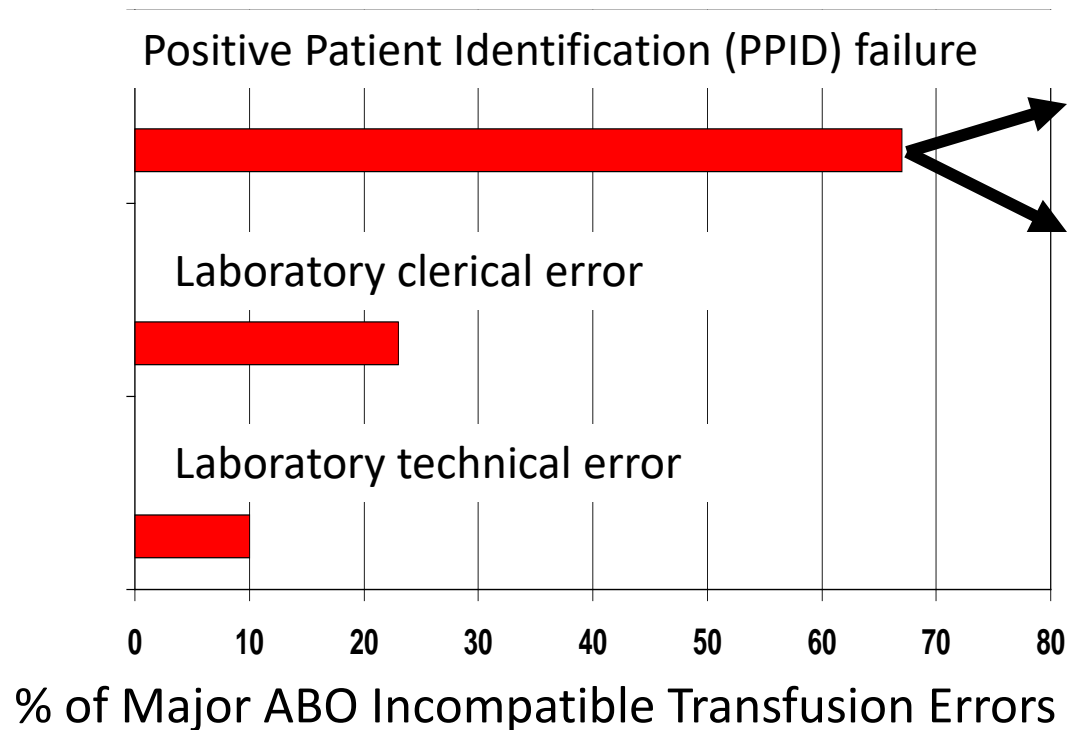


- Shock
- Fever
- DIC
- Doom
- Flank Pain
- Dyspnea
- Capillary permeability
- NO scavenging

- Hemoglobinemia
- Hemoglobinuria
- AKI:
 - Vasoconstriction
 - ATN

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 \uparrow safety by >5 -fold beyond manual/human processes

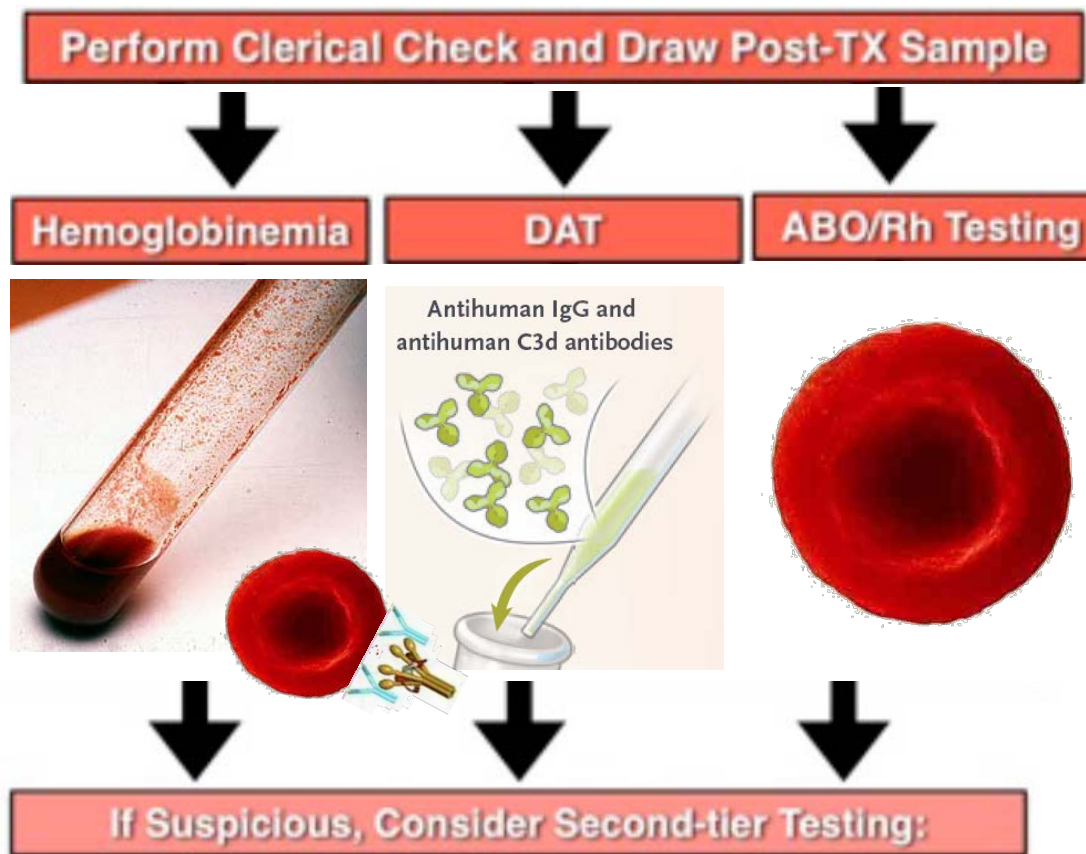
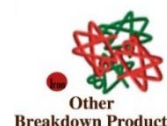
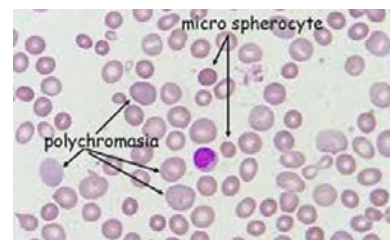
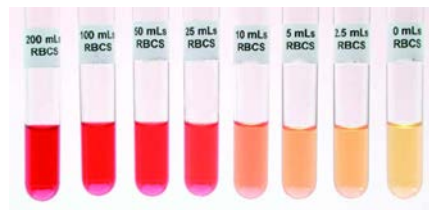


How Do You Prove It?

look at labels

look for 'lysis

- ↑ reticulocytes (± spherocytes)
- ↑ LDH (& AST > ALT)
- ↑ bilirubin (unconjugated-predominant)
- ↓ haptoglobin
- hemoglobinuria/hemosiderinuria, ATN
- DIC
- C3/C4, ferritin



Bilirubin



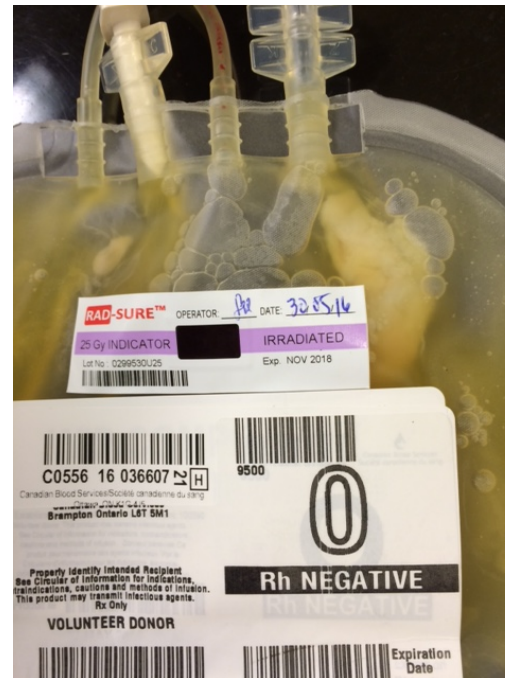
Heme



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



*irradiation is not a
decontamination measure*

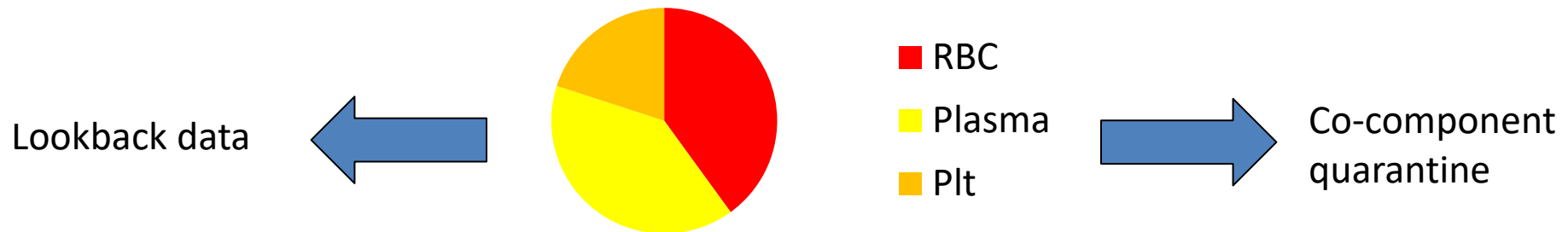


The most BaCon-ific
product of all... 1 / 1000?

Culture / Investigation Pathway

| PRE | POST | CONCLUSIONS |
|---------|---------|---------------------|
| PATIENT | PRODUCT | |
| | | Pre-existing sepsis |
| | | Definite BaCon |
| | | Probable BaCon |
| | | Possible BaCon |
| | | 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

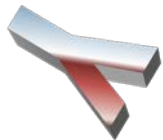
- **recipient has anti-leukocyte antibodies**

(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 → Respiratory Distress

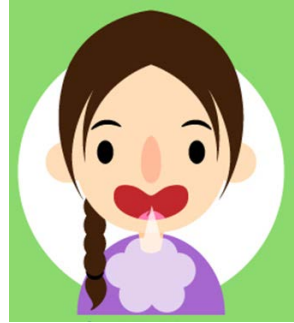
Most “important” of all transfusion hazards

High case morbidity
& mortality rates, at
high frequency



Accounting for 60% of
transfusion-related
deaths

deep-stuff:
cardiorespiratory (dyspnea)



Dyspnea



cardiogenic

transfusion-associated circulatory overload (TACO)

non-cardiogenic

transfusion-related acute lung injury (TRALI)

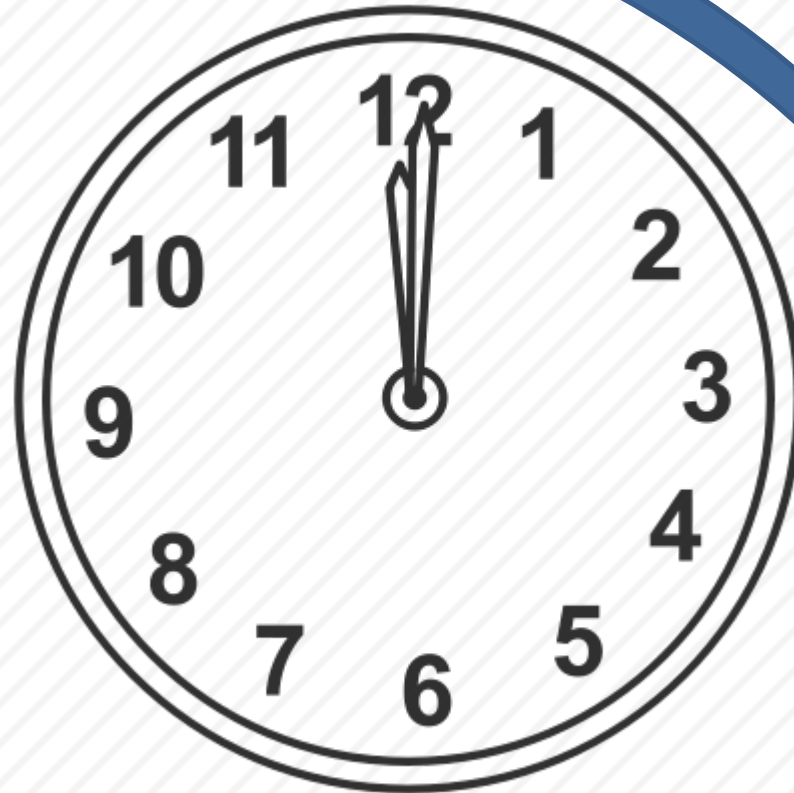
allergic reaction (bronchospasm)

bacterial contamination or incompatibility reaction (off-target)

underlying disease process

transfusion-associated dyspnea (TAD)

STOP ASAP



REPORT
DISTRESS
EVENTS WITHIN
6-12H OF
PRODUCT

1 Volume Status as the Discriminant (exam)

2 Structure: Infiltrates?



3 Function: Hypoxia?

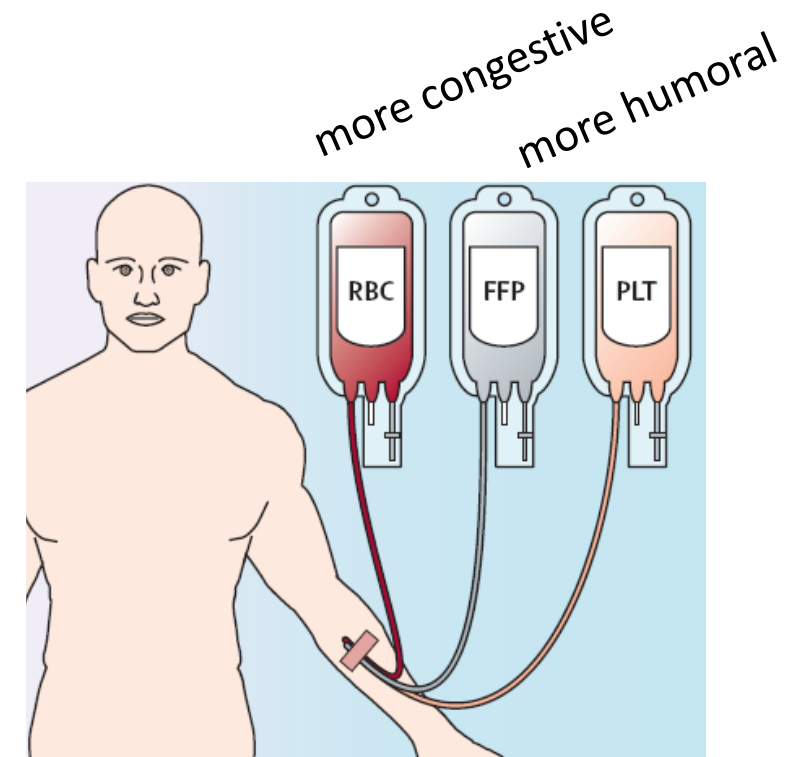
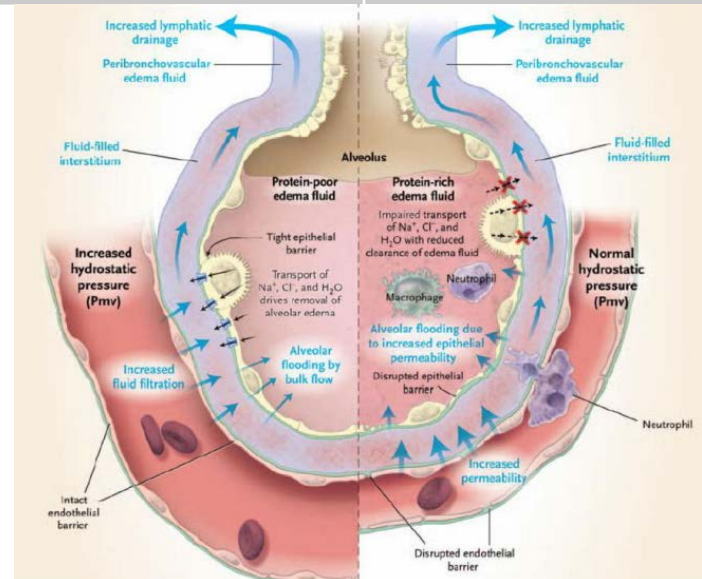


transfusion-associated circulatory overload (TACO)

transfusion-related acute lung injury (TRALI)

Shared: 2-hit model

| Fluid driver: | hydrostatic | permeability/leak |
|---------------|------------------|-------------------|
| Immunology: | - | + |
| Agent: | dangerous doctor | dangerous donor |
| Biomarker: | cardiac stress | leukoagglutinins |



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

Transfusion Associated Circulatory Overload (**TACO**):

≥ 1 REQUIRED:

OCCURRING
WITHIN ≤ 12H
AFTER
TRANSFUSION



Respiratory Distress

eg-

- tachypnea
- dyspnea
- cyanosis
- ↓spO₂ % 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:



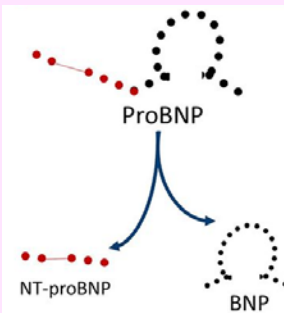
Cardiovascular system changes not from underlying condition

- 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 CRITERIA**

TACO Landscape



- Common – **1-10%** of encounters

Hendrickson JE et al, [Transfusion](#) **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% (95% CI: 33-41%) |
| SHOT (UK) 2010-2020: 104/212 (49%) | | |
| FDA (USA) 2014-2019: 72/262 (27%) | | |

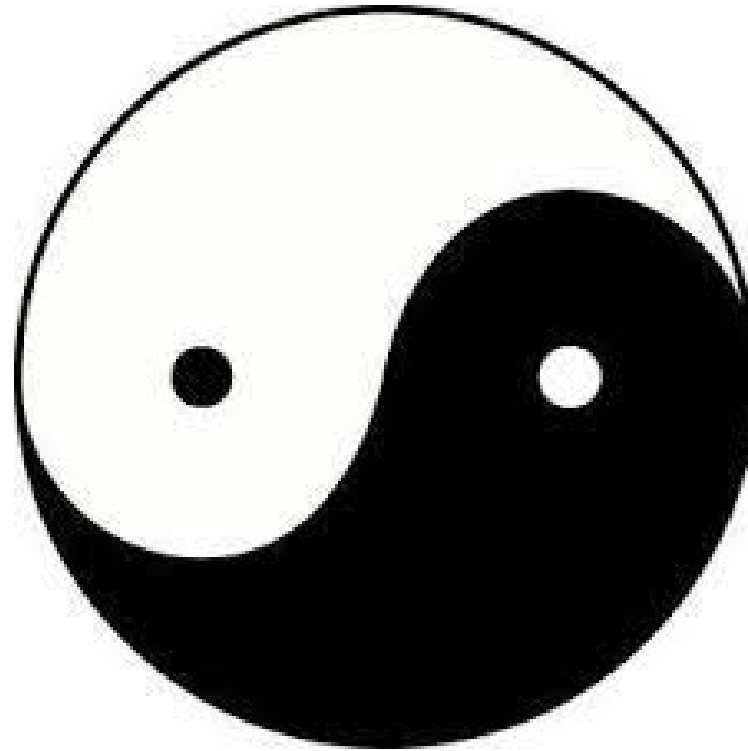
- Often serious (**1/5 to ICU**) ...

LOS effects...

CFR: 1-10%

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

**IDENTIFYING
WHO IS AT RISK**



**MODIFYING 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)

- cardiorespiratory 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]

- renal dysfunction

- age

- youngest
- oldest (>60-70 years)

- positive fluid balance

- weights, ins/outs, physical signs



- small receiver: low body weight
- anemic hyperdynamism
- heavy-handed giver:

- unwritten orders (verbal)
- unassessed patient
- big order
- too fast
- preceding crystalloids: “STACO”

- Li et al. [Transfusion](#) **2011**; 51:338-43.
- Lieberman et al. [Transfus Med Rev](#) **2013**; 27:206-12.
- Andrzejewski Jr et al. [Transfusion](#) **2013**; 53:3037-47.
- Alam et al. [Transfus Med Rev](#) **2013**; 27:105-12.
- Clifford et al. [Anesthesiology](#) **2015**; 122:21-8.
- Roubinian et al. [Crit Care Med](#) **2018**; 46:577-85.

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



Flash *Non-Cardiogenic*

Pulmonary Edema:



?Transfusion Related Acute Lung Injury (TRALI)

Transfusion Related Acute Lung Injury (TRALI):

A + B + C:

A.



Acute Onset

- $paO_2/FiO_2 \leq 300$
- $spO_2 < 90\%$ on room air
- Other clinical evidence

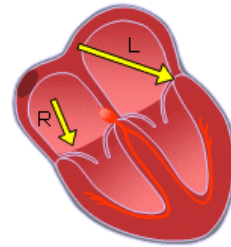


Hypoxemia



Bilateral Infiltrates

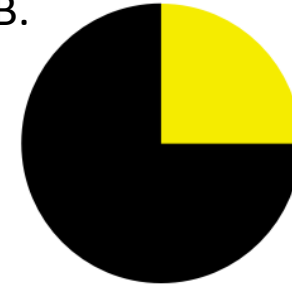
CXR, CT, US



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*

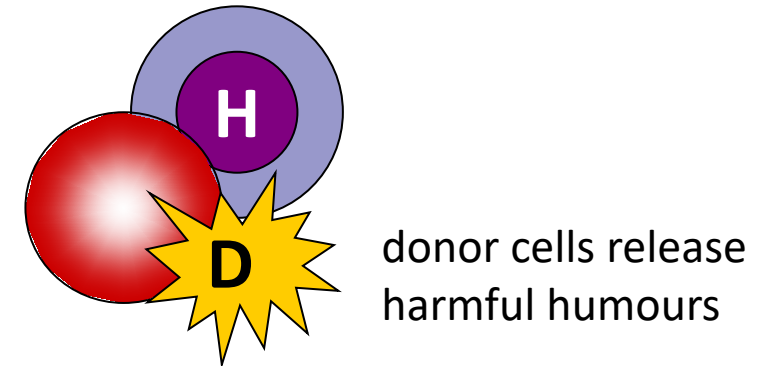
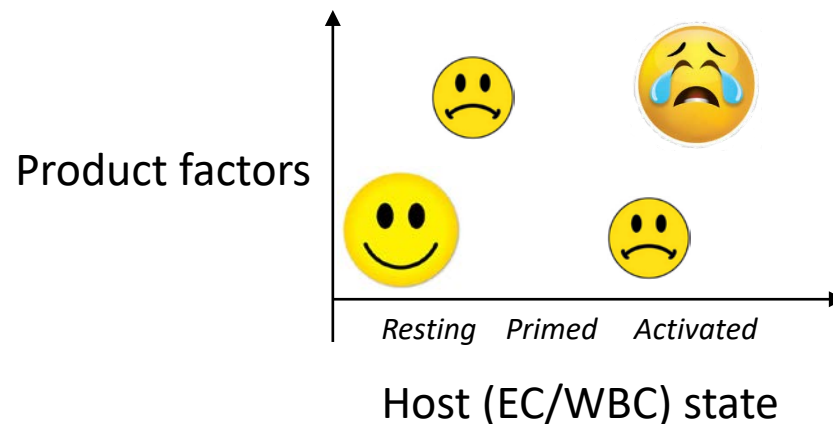
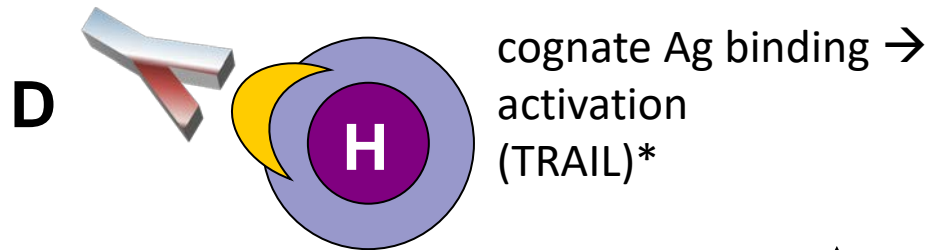
TRALI: How It Happens: 2nd Hit[s] (*in a 1st-Hit Host*)

- **donor** had incidental anti-leukocyte antibodies (ALA) collected into product

- ALA (HLA [II>I], HNA) delivered IV
- ALA account(ed) for most cases

- **product toxins/biologic response modifiers (BRM)**

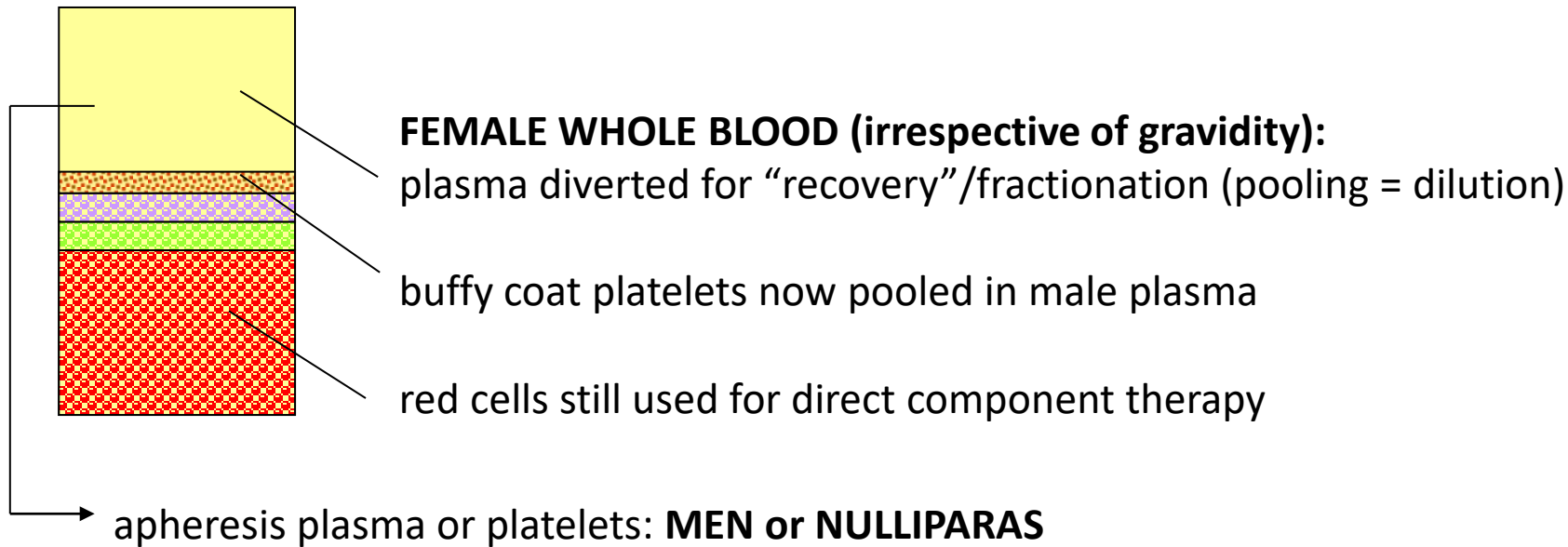
- products release biologically active lipids
 - biologically active lipids, lysoPC, microparticles
 - cytokines, chemokines (HMGB1, sCD40L)
 - NETs, mtDNA



Mitigating **Femme Fatale**: 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”

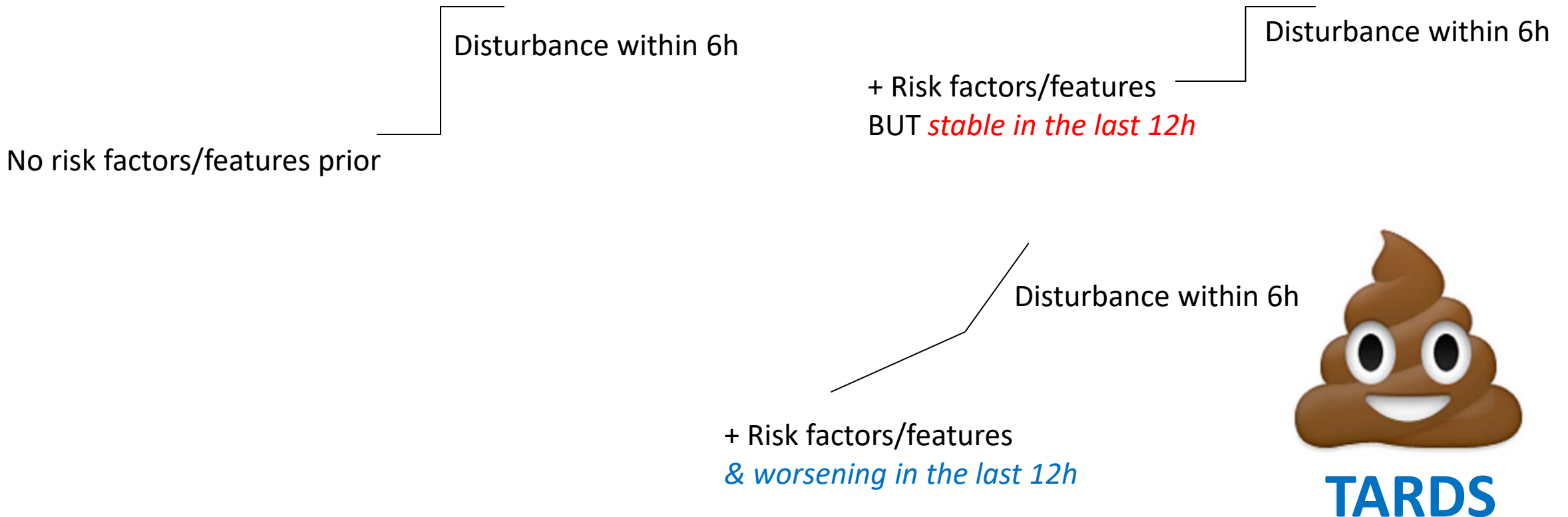
OR ~0.5



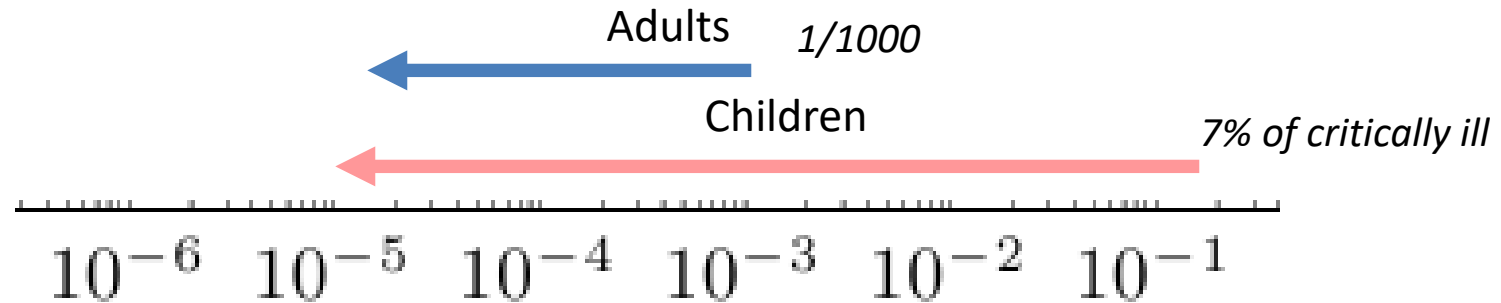
- Muller et al. [Transfusion](#). 2015; 55(1):164-75.
- Schmickl et al. [Crit Care Med](#). 2015; 43(1):205-25.

Culpability/Certainty Spectrum:

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



TRALI Epidemiology



Vossoughi et al. [Transfusion](#) **2019**; 59: 2567-74

- 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. [Anesthesiology](#) **2019**; 131: 693-715.

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:
 - 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 \pm death

frequency gradient

1% incidence

90% of
ATR
cases

danger gradient

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

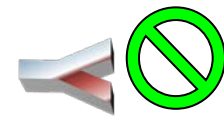
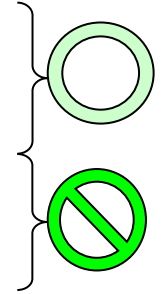


RECIPIENT HAS MISSING OR VARIANT PROTEIN AND REACTS TO WILD-TYPE PROTEIN

<5% of cases

- eg **IgA**, haptoglobin, complement, albumin, α 1anti-trypsin, transferrin

- anti-protein IgG develops



Hypotension



acute hemolytic transfusion reaction (AHTR)

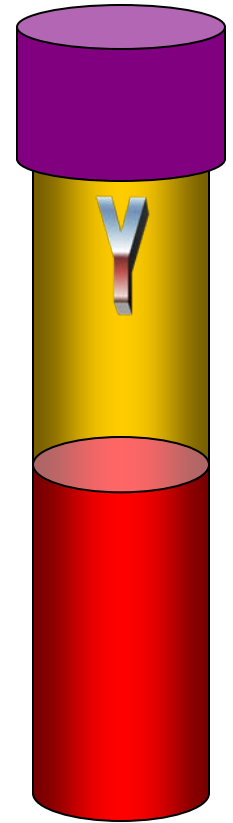
bacterial contamination (BaCon)

severe allergic transfusion reaction / anaphylaxis

bradykinin shock?

Testing Approach

- We investigate with the following panels for:
 - **Febriles:** hemolysis, microbiology
 - **Dyspneics:** hemolysis, microbiology, CBS (donor ALA)
 - **Hypotensives:** hemolysis, microbiology
 - **Anaphylactics:** hemolysis, ?IgA/anti-IgA IgG
(?other protein deficiencies)



Blood bank
sample:
BIAS = exploration
for immune
hemolytic
incompatibility

Major Take-Home Messages

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

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

| | | | |
|--|-------------------------------|---|-------------------------------|
| | <i>ATR / ETR / STR / TACO</i> | <i>Respiratory / BaCon / mix-up: AHTR</i> | <i>TTVI / rare bug / GVHD</i> |
| | common, 10^1 - 10^2 | serious, 10^3 - 10^4 | rare) 10^5 - 10^6 |
- 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...

