ORBCoN
Ontario Regional Blood Coordinating Network

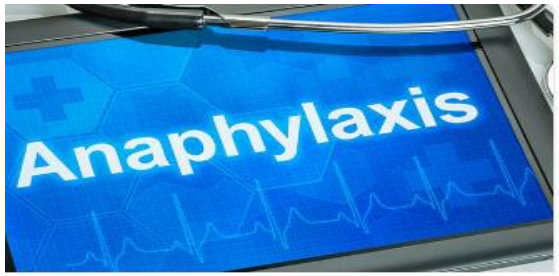
Transfusion Medicine Boot Camp for Nurses
Patient Experiences – Lessons for Learning!

bloody easy

Anaphylactic Transfusion Reactions

Wednesday, November 22, 2023, 9 a.m. – 12 p.m. (EST)

Farzana Tasmin, Transfusion Safety Officer
University Health Network



UHN
Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
Michener Institute

Learning Objectives

- Overview of Allergic reaction spectrum
- Pathophysiology
- Clinical presentation
- Responsibility of the clinician and the Blood Bank
- Recommended Investigations
- Reaction reporting and Hemovigilance

Disclosure:

- No conflicts of interest to disclose

- Ontario Transfusion Transmitted Injuries Surveillance System (TTISS-ON): Education Committee member

University Health Network - Annual Activity

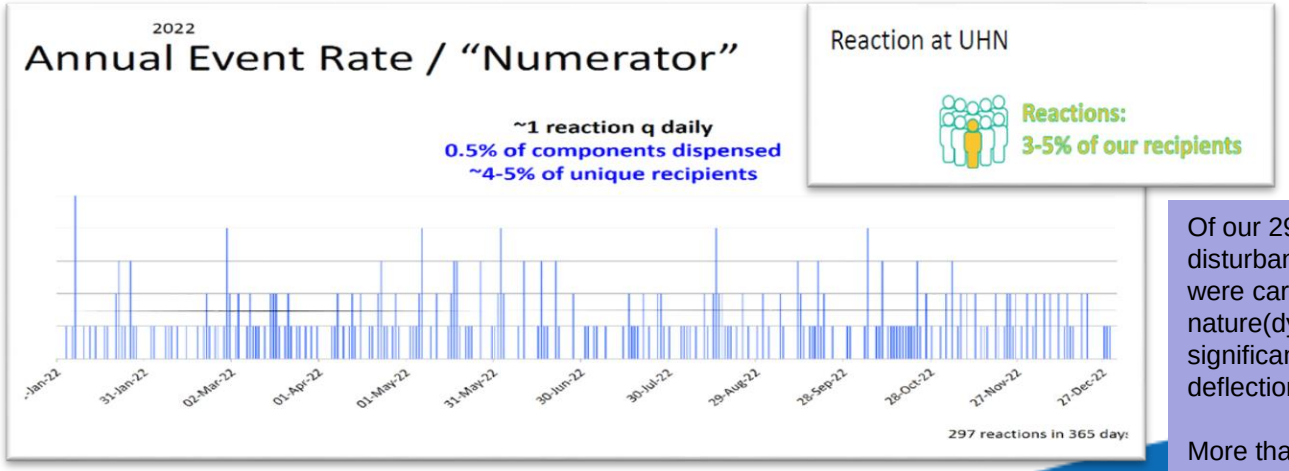
	Toronto General Hospital	Princess Margaret Cancer Center	Toronto Western Hospital
Programs & Special Populations Served	• Red Blood Cell Disorders Program • Multi-Organ Transplant Program • Peter Munk Cardiac Centre • Surgery & Critical Care • Apheresis Program	• Medical Oncology & Hematology: • Chemotherapy & Transfusion Centre • Blood & Marrow Transplant Program	• Surgery & Critical Care • Krembil Neuroscience Centre • Arthritis Program

Annual UHN Blood Utilization

Denominator Component Activity

	TGH	PMH (68% of platelets)	TWH	UHN total
RBC units transfused	28,559 4%↓	9,560 14%↓	3,200 4%↑	**41,319** 6%↓
platelet units (adult doses) transfused	2,857 13%↓ (277 apheresis & 2580 BCP)	6,750 5%↓ (959 apheresis & 5791 BCP)	386 6%↓ (44 apheresis & 342 BCP)	**9,993** 7%↓ (1280 apheresis & 8713 BCP) 1 : 6.8
plasma units (250cc dose equivalents) transfused	11,551 26%↑ (6788 FP 17%↑, 4763 SDTP 42%↑)	119 88%↓ (119 FP, 0 SDTP)	1104 21%↓ (900 FP, 204 SDTP)	**12,774** 11%↑ (7807 FP, 4967 SDTP)
Components issued:	42,967 (2%↑), 67%	16,429 (14%↓), 26%	4,690 (4%↓), 7%	**64,086** (3%↑)
Derivative items or orders:	**41,298**			**7,417** (6%↑) unique recipients served
Dispensation sum estimate:	**105,384**			
% cellular products irradiated:	**27.4%** (3%↑)			

UHN 2022 (Jan 1 – Dec 31, 2022)



Of our 297 investigated transfusion disturbances in 2022, 47 (16%) were cardiorespiratory in nature(dyspnea or hypoxia or significant hemodynamic deflections).

More than a third (17= 36%) were severe or worse in nature.

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab Michener Institute

Questions: Pre Knowledge

- What kind of blood products can cause an anaphylactic transfusion reaction?
  A. Plasma and Platelets only
  B. Blood components (RBC, Plasma or Platelets) only
  C. Fractionated plasma products (IVIG or Fibrinogen) only
  D. Any blood products

Questions: Pre Knowledge

- What is the mechanism of anaphylactic transfusion reactions
  A. Anti-IgA in an IgA deficient recipient
  B. IgE mediated/allergen dependent
  C. Antibodies to polymorphic forms of serum proteins (i.e. haptoglobin)
  D. All of the above

Questions: Pre Knowledge

26-year-old woman with severe aplastic anemia awaiting for SCT, had experienced anaphylactic transfusion reaction to platelets while receiving the transfusion in an outpatient clinic. She reported feeling drowsy with blurred vision and developed hives >2/3 BSA towards the end of the transfusion. Her BP went down to 89/55 from baseline 103/70 and patient had a syncopal episode. She was given hydrocortisone 100 mg IV and an NS bolus with pressure bag. A code blue was called, and the team administered a second dose of hydrocortisone 100 mg IV, Benadryl 50 mg IV and 0.5 mg of epinephrine IM.

- What precaution should be taken/recommended for next transfusion:
  A. Pre- medication with antihistamine
  B. Blood Product modification- plasma volume reduced/ washed blood products
  C. Send samples for anti-IgA testing
  D. A and B only
  E. All of the above

Anaphylactic Transfusion Reactions

- The International Society of Blood Transfusion (ISBT) and International Hemovigilance Network (IHN) has defined anaphylactic reactions as,
  - mucocutaneous symptoms (itchy rash, hives, swelling of the lips, redness and swelling around the eyes and of the conjunctiva)
  - accompanied by upper or lower airway obstruction and/or severe hypotension occurring during or shortly after transfusion.
- In general, the incidence is higher in blood components containing a high volume of plasma.
- Often happen early in transfusion, during or up to 4 hours post transfusion

Source: Anaphylactic transfusion reactions and IgA deficiency | Professional Education (blood.ca)

Allergic Reaction 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 ± death

Incidence: Severe anaphylactic or anaphylactoid reactions (SAAR)

- 5.3 per year/100,000 units of blood components transfused [2020]

Transfusion Transmitted Injuries Surveillance System Summary Report, 2016 to 2020 - Canada.ca

Source: Dr. Christine Cserti-Gazdewich, TTISS meeting 2018, Topic: Nav–IgA–ting the Threat of IgA Deficiency in Your Nearest OR *(ie- Anticipating/Mitigating Anaphylaxis…)*

Pathophysiology:

- **Allergen-dependent pathways:**
  - **Classic Allergic IgE (**IgE-, mast cell- and histamine-mediated sub-pathway)
    - 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

- **Allergen-independent pathways:**
  - Biological response modifiers (inflammatory cytokines and chemokines that accumulate in stored blood components)
  - Patient factors other than allergens and antibodies (patients with chronic idiopathic urticaria have detectable histamine-releasing activity)

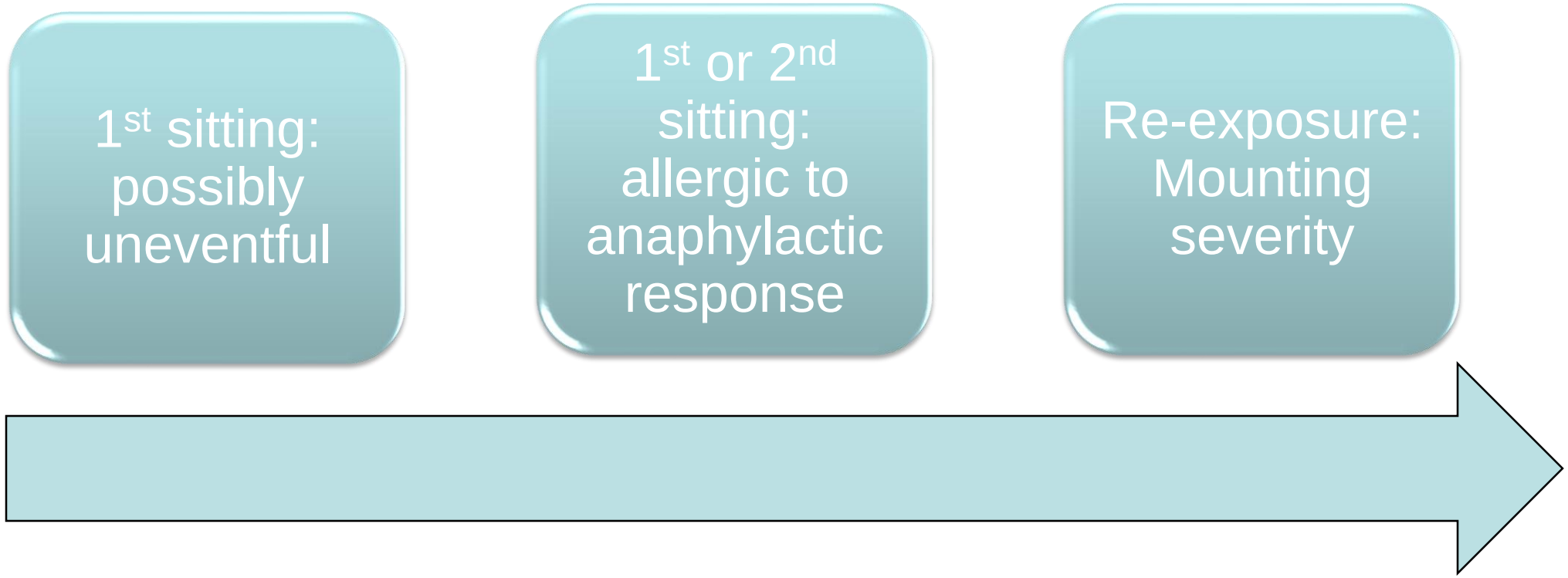
- **Recipient has missing or variant protein and reacts to wild-type protein**
  - e.g. IgA, haptoglobin, complement, albumin, α1anti-trypsin, transferrin
  - anti-protein IgG develops

Implicated Mechanisms

Majority of anaphylactic reactions are unexplainable

- Implicated mechanisms: Is lab confirmation possible?
  - Anti-IgA in an IgA deficient recipient
  - Antibodies to polymorphic forms of serum proteins (haptoglobin)
  - Transfusing an allergen to a sensitized patient
  - Passive transfer of IgE (to drugs, food)

IgA Deficiency – Anaphylaxis Pattern



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(ie- Anticipating/Mitigating Anaphylaxis…)

IgA Deficiency: Testing Anti-IgA antibodies

- Even in the presence of low IgA levels and anti-IgA antibodies, risk of anaphylactic transfusion reaction is low

- Anti-IgA testing is only recommended in selected individuals,
  - patient with a history of an anaphylactic transfusion reaction and undetectable IgA level
  - patient with a history of 2 or more severe allergic transfusion reactions, not quite meeting definition of anaphylaxis

Anaphylactic transfusion reactions and IgA deficiency | Professional Education (blood.ca)

IgA Deficient Patient with a Severe Allergic-Spectrum Reaction:

anti-IgA IgG + (or pending)	anti-IgA IgG -
IgA deficiency safe products	Can be re-challenged under controlled circumstances…. But if reaction recurs, then earns IgA deficiency safe products

Haptoglobin Deficiency

A novel method for the laboratory workup of anaphylactic transfusion reactions in haptoglobin-deficient patients

Katie L Thoren [1], Scott T Avecilla [1], Virginia Klimek [2], Cheryl Goss [1]

Affiliations + expand

PMID: 31975382 PMCID: PMC8204907 DOI: 10.1111/trf.15657

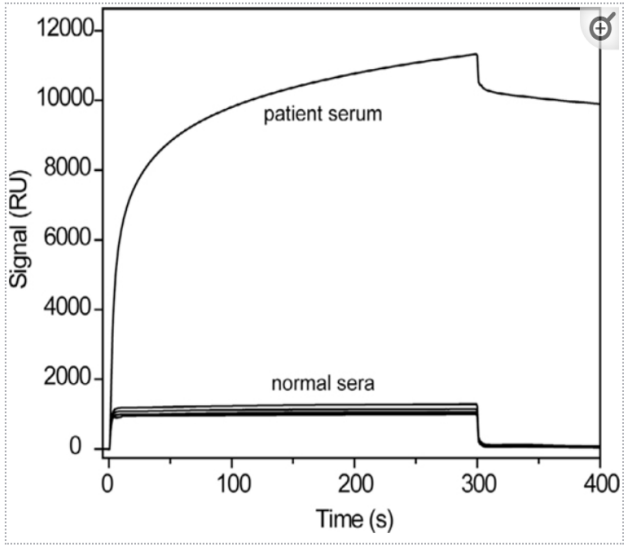
Free PMC article

Abstract

Background: Patients with congenital haptoglobin deficiency can develop anti-haptoglobin antibodies after exposure to blood products, and they can suffer from life-threatening anaphylactic transfusion reactions. Here, we present a case of a 57-year-old Chinese male with myelodysplastic syndrome who manifested an anaphylactic transfusion reaction during the transfusion of platelets. The only abnormality detected during his reaction laboratory workup was an undetectable haptoglobin level in the absence of evidence of hemolysis.

Surface plasmon resonance (SPR) was explored as a method to be able to detect the presence of anti-haptoglobin antibodies in serum

An IgG anti-haptoglobin antibody was detected in the patient's serum with SPR.



Katie LT, Scott TA, Virginia K, Cheryl G Transfusion. 2020 Apr; 60(4): 682–687.

Transfusing an allergen to a sensitized patient

Identification of Peanut allergen in a transfused blood product causing transfusion associated anaphylaxis

Waseem Anani, Sarah Dobrozsi, Rowena Punzalan

First published: 18 May 2020 | https://doi.org/10.1111/trf.15774 | Citations: 2

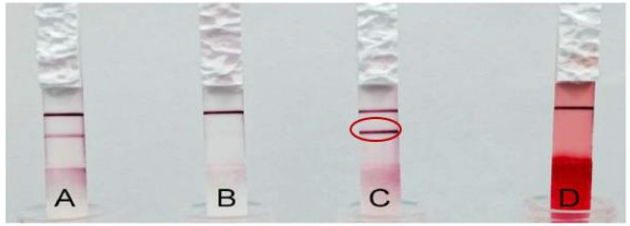
Find it @ UHN

A 4-year-old male with acute lymphocytic leukemia was sequentially transfused a unit of RBC and platelets.
The RBC transfusion was uneventful.
However, after 23 mL of the platelet transfusion, patient experienced an anaphylactic reaction with the symptoms of hives, facial edema, wheezing, and hypoxia.

The transfusion reaction workup revealed a documented patient history of a severe peanut allergy, and his symptoms mirrored past exposures to peanuts.

The blood product donors were contacted for pre-donation peanut intake:
the RBC donor did not recall ingesting peanuts, and
the platelet donor recalled eating peanut butter for breakfast the morning of donation!

Allergen detection - Peanut peptide detection with lateral flow device



Anani W, Dobrozsi S, Punzalan R. Identification of Peanut allergen in a transfused blood product causing transfusion associated anaphylaxis. Transfusion. 2020 May;60(5):1108-1109

Case 1: Clinical Presentation

- 54 year old female with CNS DLBCL presented to outpatient clinic with a platelet count of <3.
- H/O 2 consecutive minor allergic reactions the month before
- Blood Bank issued an ABO identical, day 7, irradiated buffy coat pooled Platelets, no premedication prior to transfusion
- While almost 3/4th of the bag had been transfused, patient experienced dyspnea, swollen face, dysphagia (felt like a lump in the back of her throat) and chest tightness.
- Transfusion was stopped immediately

Case 1: Patient Management

- A code medical emergency was called and patient was placed on NRB with SpO2 100%.
- Post medication: Epi 0.3mg IM + Diphenhydramine 25 mg IV + Hydrocortisone 100 mg IV
- Patient was transferred to Emergency room where she received another dose of Epi 0.5mg IM enabling a taper of the O2 to 2 L/min and significant reduction of angioedema and resolution of dyspnea.
- Platelet increment was good (<3 to 28)

Case 1: Lab Investigation

- Reaction was reported to Blood Bank
- Transfusion reaction sample was processed and no serological incompatibility detected.
- Product sent to Micro- no growth detected
- Sample sent for Anti-IgA IgG testing to CBS

Case 1: Recommendation for future transfusion

- Pre- medication
- Modified Blood Products
  - Plasma volume reduced Platelets
  - Washed pRBC
- Transfusion at a slower rate with very close monitoring

Case 1: Follow up

4 months later:

- Blood Bank received the result for anti-IgA IgG- Not detected
- No further reaction- received 4 PVR'd Platelets and 7 washed RBCs
- Patient was re-assessed for modified Blood Products
  - Continue provide PVR'd platelets
  - Unmodified RBC was recommended, as agreed upon in the circle of care

Impression

- Reaction: Anaphylactic reaction
- Relationship of Adverse event to transfusion: Definite
- Severity: Grade 2 (Severe)
- Outcome of Adverse event: Major sequelae
- Reported to CBS and TTISS

Case 2: Clinical Presentation

- 49 year old woman with liver disease associated GI bleed, required transfusion with Fibrinogen Concentrate for a baseline level of fibrinogen <0.40
- Received 25% albumin previously (3 months prior to this event)- no transfusion reaction
- Tolerated an earlier platelet transfusion on the same day, achieving a good rise from 41 to 62
- ~150 mL into the 4g prescribed dose of FC, experienced diffuse pruritis with stridor and voice change, implying upper airway angioedema.
- Transfusion was stopped immediately

Case 2: Patient Management

- Post medication: Diphenhydramine 25 mg IV + Epinephrine 0.5 mg IV+ Famotidine 20 mg IV + Methylprednisolone 30 mg IV + inhaled Salbutamol
- Placed on cardiac monitor and requested CCRT consult for close monitoring post Anaphylactic reaction
- Patient's hoarseness much decreased following Epinephrine and steroid
- Reaction was reported to Blood Bank

Case 2: Lab Investigation

- Transfusion reaction sample was processed and no serological incompatibility detected.
- Pre reaction IgA level: No IgA deficiency

Component	Ref Range & Units	3 mo ago	7 mo ago
IgG Quantitation	7.0 - 16.0 g/L	14.9	11.5
IgA Quantitation	0.70 - 4.00 g/L	5.94 ^	4.87 ! R
IgM Quantitation	0.40 - 2.30 g/L	5.11 ^	3.75 ! R
Resulting Agency		TGH	HISTORICAL CONVERSIONS LAB

- Haptoglobin: went down post reaction from previously detectable range i.e. not a congenital ahaptoglobinemia

Component Ref Range & Units	8 mo ago (9/3/23)	8 mo ago (5/3/23)	10 mo ago (31/12/22)	11 mo ago (14/12/22)	1 yr ago (6/10/22)	1 yr ago (4/5/22)
Haptoglobin		CM	<0.03 v R	<0.03 v R	<0.03 v R	0.20 ! R

Case 2: Lab Investigation

- Post-reaction Tryptase (4.3) and IgE levels (46) were normal.

- The fibrinogen level, despite the 3 (rather than 4) grams given, rose to 1.03 (per the next day's measurement).

Case 2: Recommendation for future transfusion

- Provide FC from different lot number or the alternative brand
- Pre- medicate the patient
- Suggest conventional triggers to follow for subsequent transfusion
  - <70 if stable/non-bleeding or at symptomatic/bleeding thresholds for RBC (1u at a time)
  - adult dose platelet concentrate for bleeding at <50 or for prophylaxis if <10
  - If bleeding, may also use plasma (15cc/kg or typically a 4u dose) if bleeding at INR >2.

Case 2: Follow up

- Subsequent transfusions with components (RBC, Platelets and Plasma) and blood derivatives (25% albumin)- no reaction reported
- Not re-exposed to any FC

Impression

- Reaction: Anaphylactic reaction
- Relationship of Adverse event to transfusion: Probable
  - Product Imputability: FC or Platelet?
- Severity: Grade 2 (Severe)
- Outcome of Adverse event: Minor sequelae
- Reported to Manufacturer, TTISS and Health Canada

Received: 12 April 2023 | Revised: 12 June 2023 | Accepted: 18 July 2023
DOI: 10.1111/trf.17521

TRANSFUSION

CASE REPORT

An outbreak of anaphylactic transfusion reactions to group B plasma and platelets and its possible relationship to Alpha-Gal syndrome

Colleen W. Gilstad[1] | Kathleen Conry-Cantilena[2] | Roya Zarpak[1] | Anne F. Eder[3]

Case Report Summary

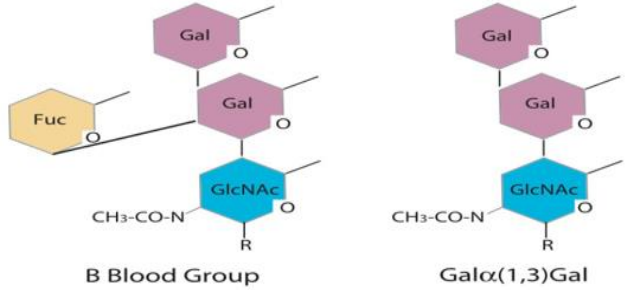
Anaphylactic transfusion reactions were observed for 3 patients in two Washington, D.C. hospitals.

All 3 recipients were group O, received group B plasma/platelets and resided in southern Maryland where alpha-gal syndrome was prominent

	Case 1	Case 2	Case 3
Allergies	H/O anaphylactic reactions to cat *Donor had pet cats	No known allergies Reported “passing out” after eating hamburgers and unexplained GI symptom	Dogs, cats, horses, grass
H/O tick bites	--	Yes	Yes
Alpha gal IgE	Not done	↑	↑
Transfusion History	Yes- no reaction	Yes- reported multiple severe allergic reaction (twice with B Plasma)	No transfusion

Alpha Gal Syndrome (AGS) is an emerging, tick bite–associated allergic condition characterized by a potentially life-threatening immunoglobulin E (IgE)–mediated hypersensitivity to galactose-alpha-1,3-galactose (alpha-gal), an oligosaccharide found in most nonprimate mammalian meat and products derived from these mammals.

Galactose-α-1,3-Galactose is antigenically similar to the B blood group antigen.



Millard & Sandrin (Tissue Antigens 2006)

Could it be an allergic reaction to the B antigen??

- We don’t know…. Further research needed!
- We do know that platelets express ABO antigens and ABO antigens are present in plasma

Why this matters?

Emerging life threatening problem: Implication for blood transfusion practice

- there is no recommendation regarding Blood Transfusion, further research is warranted

What can we do?

- Patients, their health care providers and the blood bank must be informed if there is added risk
  - Systems can be put in place for these patients (ie, avoid group B blood components, give ABO-compatible platelets/plasma)

- If there is an unexplained anaphylactic transfusion reaction, consider alpha gal and investigate

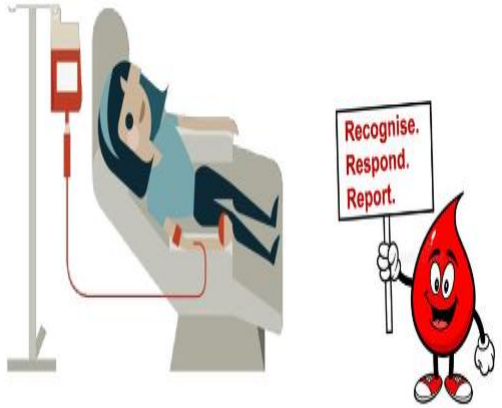
Responsibility of the Clinician

- Informed Consent for Blood Transfusion:
  - a description of blood component
  - the associated risks and benefits, including special or unusual risks
  - alternative therapies, if appropriate to the clinical circumstances
  - the likely consequences of not having the treatment

- Patient monitoring:
  - Start transfusion with a slower rate 50ml/hr for first 15 minutes
  - Obtain vitals at baseline, 15 minutes and completion
  - Closely observe the patient throughout the transfusion and for an appropriate time thereafter for any adverse reaction
  - Instruct the patient to report any symptoms and notify the nurse

Management Guideline

- Stop the Transfusion
- DO NOT restart the transfusion
- Promptly administer **epinephrine**, corticosteroids, diphenhydramine, vasopressors, and supportive care as required
- Initiate the lab investigation
- Return blood products to blood bank
- **Notify Blood Bank immediately**
  - Blood Bank record update
  - Consult with transfusion medicine physician, if further testing required
  - Detailed review of the reported reaction
  - Reporting obligation- required by Health Canada



Recommended Investigation

- Transfusion reaction work up:
  - Group and screen and DAT
- If patient experienced dyspnea and hypoxia:
  - Chest X-Ray, Echo, ABG
- Haptoglobin
- IgA level
- Anti IgA testing
- Serum Tryptase

As suggested by Transfusion Medicine physician

- Precautionary measure for future transfusion
  - Premedication
  - washed or plasma depleted blood components
  - If a patient is found to be IgA-deficient with anti-IgA who had an anaphylactic reaction, IgA-deficient blood products from IgA deficient donors, available from CBS

Reaction reporting and Hemovigilance

Severe Allergic/ anaphylactoid/Anaphylactic reactions- ***Reportable*** reaction

Who to report to: based on the Product imputability

- Blood component: reportable to
  - Canadian Blood Services(CBS)->will report to Health Canada
  - The Transfusion Transmitted Injuries Surveillance System (TTISS-ON)
- Fractionated Plasma products:
  - TTISS-ON
  - Manufacturer
  - Canada Vigilance (as per Vanessa's law).

References:

- Gilstad CW, Conry-Cantilena K, Zarpak R, Eder AF. An outbreak of anaphylactic transfusion reactions to group B plasma and platelets and its possible relationship to Alpha-Gal syndrome. Transfusion. 2023. https://doi.org/10.1111/trf.17521
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- Thoren KL, Avecilla ST, Klimek V, Goss C. A novel method for the laboratory workup of anaphylactic transfusion reactions in haptoglobin-deficient patients. Transfusion. 2020 Apr;60(4):682-687. https://doi.org/10.1111%2Ftrf.15657 Epub 2020 Jan 23. PMID: 31975382; PMCID: PMC8204907.
- Anaphylactic transfusion reactions and IgA deficiency | Professional Education (blood.ca), a “textbook” chapter: https://professionaleducation.blood.ca/en/transfusion/publications/anaphylactic-transfusion-reactions-and-iga-deficiency
- TTISS-ON Acute Transfusion Reaction Chart: https://ttiss.mcmaster.ca/wp-content/uploads/2020/10/TTISS-2020-10-08-Symptom-Transfusion-Reaction-Chart.pdf
- Bloody Easy 5.1: Blood Transfusions, Blood Alternatives and Transfusion Reactions. A Guide to Transfusion Medicine, Fifth Edition Handbook, July 2023.
- The Ontario Guide for Reporting Transfusion Reaction: https://ttiss.mcmaster.ca/wp-content/uploads/2019/12/Guide_Reporting_Transfusion_Reactions_V3_Nov2019.pdf

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- Thanks! Questions??