Delayed Transfusion Reactions

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Canadian Blood Services
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Disclosures & Conflicts of Interest

- Educators for Abbott Laboratories and Immucor
- Data Safety Monitoring Board for Velico

Objectives

- List the types of delayed hemolytic transfusion reactions

- Describe the presentation, mechanism, treatment and prevention of
  - *Delayed hemolytic transfusion reaction (DHTR)*
  - *Transfusion associated graft vs host disease (TA-GVHD)*
  - *Post-transfusion purpura*
  - *Iron Overload*

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Objectives

- Identify 3 delayed transfusion reactions
- Describe clinical presentation, diagnostic work-up, treatment, and implications:
  - *Delayed hemolytic transfusion reactions (D-HTR)*
  - *Post-transfusion purpura (PTP)*
  - *Transfusion-associated graft vs. host disease (Ta-GVHD)*
- Contextualize importance of transfusion history

Delayed hemolytic transfusion reaction (DHTR)

RBC Antigens are Complicated

- More than ABO and Rh D
- 36 blood antigen systems recognized by ISBT
- Many systems are composed of multiple antigens
- Patients can express one or more antigen variant(s) depending on the underlying genetics
- Standard practice considers ABO and Rh D compatibility, but does not consider other antigen status of donor or recipient in absence of antibody

Reid, M et.al. The Blood Group Antigen FactsBook, Third Edition. Academic Press, 2012

RBC Antibodies Develop After Transfusion

- ~5% of patients who receive repeated transfusions develop antibody
- Older age, female sex, RhD negative status are predictive
- Clinical history can impact risk (e.g. SCD 19%-43%)
- Pregnancy is a risk factor for RBC antibody even without transfusion
- This is why we have to perform an antibody screens
- Provide antigen negative blood where indicated

Karafin, M, et. al. British Journal of Haematology 2018;181; 672–681
Karafin, M, et. al. Transfusion 2019;59;217–225

RBC Antibodies Are Dynamic

- Evanescence: some antibodies fade over time
- HTR due to non-ABO alloantibodies third leading cause of transfusion-associated death
  - *US Food and Drug Administration from 2011 to 2015*
  - *24 cases (14% of the reported fatalities)*
  - *6 additional cases in FY 2017*

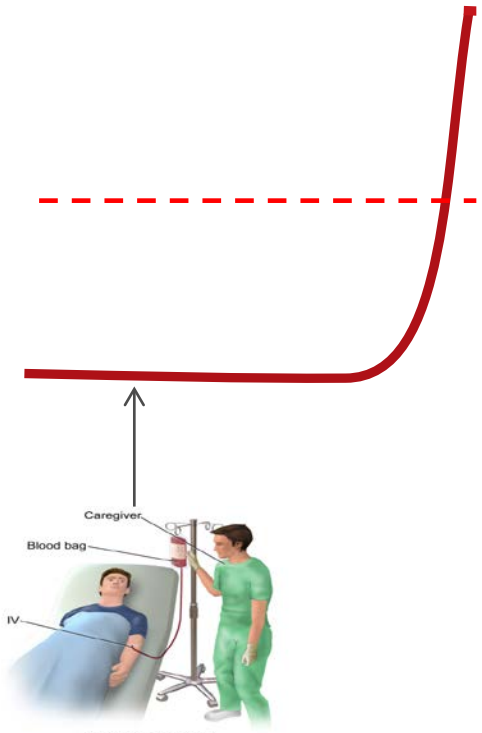
Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2015 https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM518148.pdf

DHTR: Overview

- HTR days to weeks after the transfusion
  - *3 days to 2 weeks after red cell transfusion*
  - *Anamnestic response increases*
- Patients with a red cell antibody not identified on antibody screen
  - *Antibody titer too low to be picked up on testing*
  - *Improperly performed antibody screen*
- Development of clinical hemolysis

Antibody Concentration

Primary
Response



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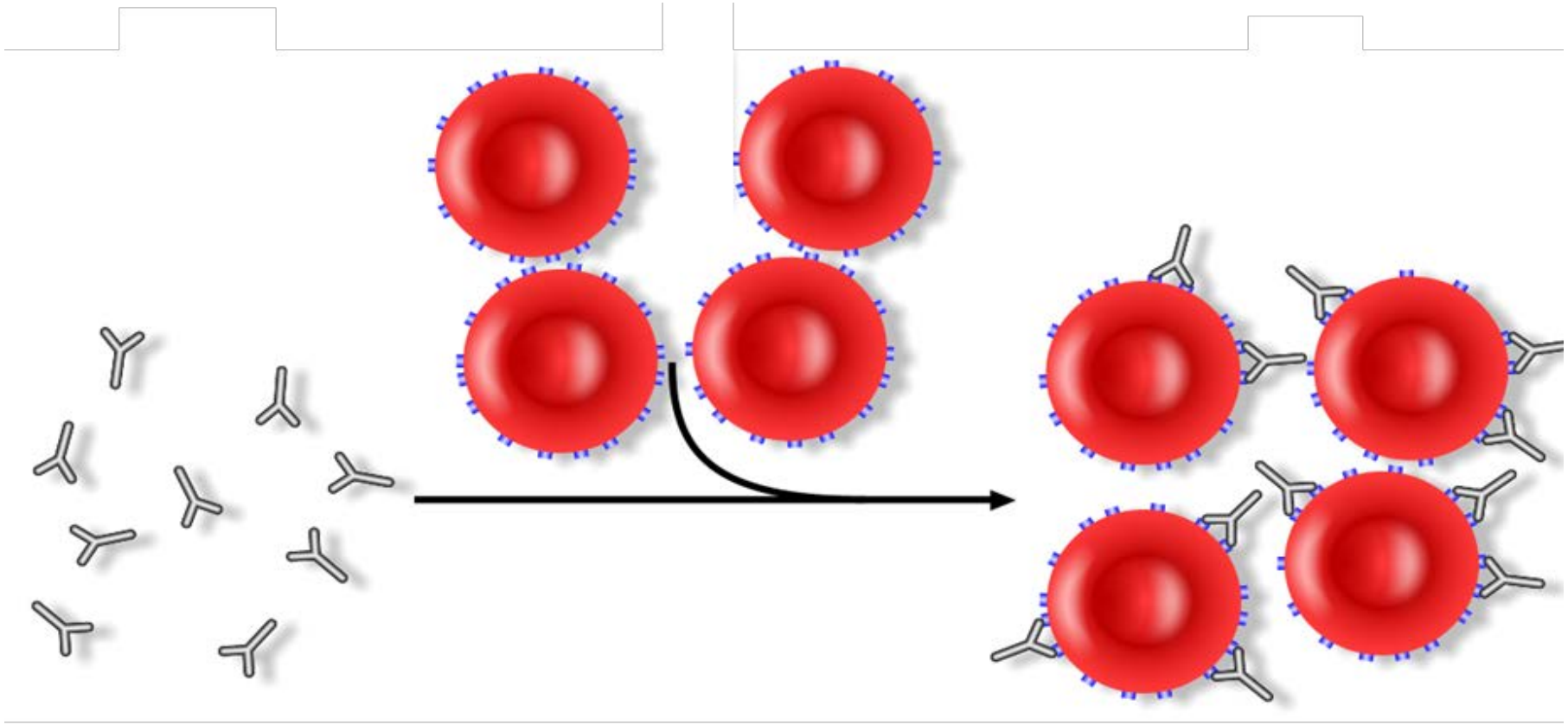
Antibodies Bind Antigen Positive Red Cells



Modification of image by A. Rad at English Wikipedia

DHTR: Presentation

- Occurs in ~ 1 in 7000 transfusions
- Clinical presentation:
  - *Previously transfused or pregnant patient*
  - *Unknown or not investigated transfusion history*
  - *Presents with fever, chills, new jaundice, unexpected anemia, and recent transfusion*
- Accurate transfusion / pregnancy history is VERY important!

DHTR: Laboratory

- Positive antibody screen with specific antibody identified
- Positive direct antiglobulin test (antibodies coating red cells)
- Eluate shows antibody against specific antigen
- Hemolysis labs abnormal
  - *Elevated bilirubin (mild, indirect)*
  - *Elevated LDH*
  - *Can have decreased haptoglobin*

DHTR: Additional Features

- History of previous transfusion or pregnancy
  - *Antibody identified on previous prenatal or blood bank sample?*
- Patient negative for antigen against which antibody is directed
- Patient was transfused with antigen positive cells
- Commonly implicated antigens are (in order of frequency):
  - *E, Jka, c, Fya, K*
- *Similar pathophysiologic mechanism to IVIG related hemolysis

Delayed Serologic Transfusion Reaction

- Same mechanism of action
- Too much time has past to observe laboratory findings of hemolysis
- Transfusion → Hgb drop, antibody appears → Hgb recovering → antibody screen later identifies ‘new’ alloantibody

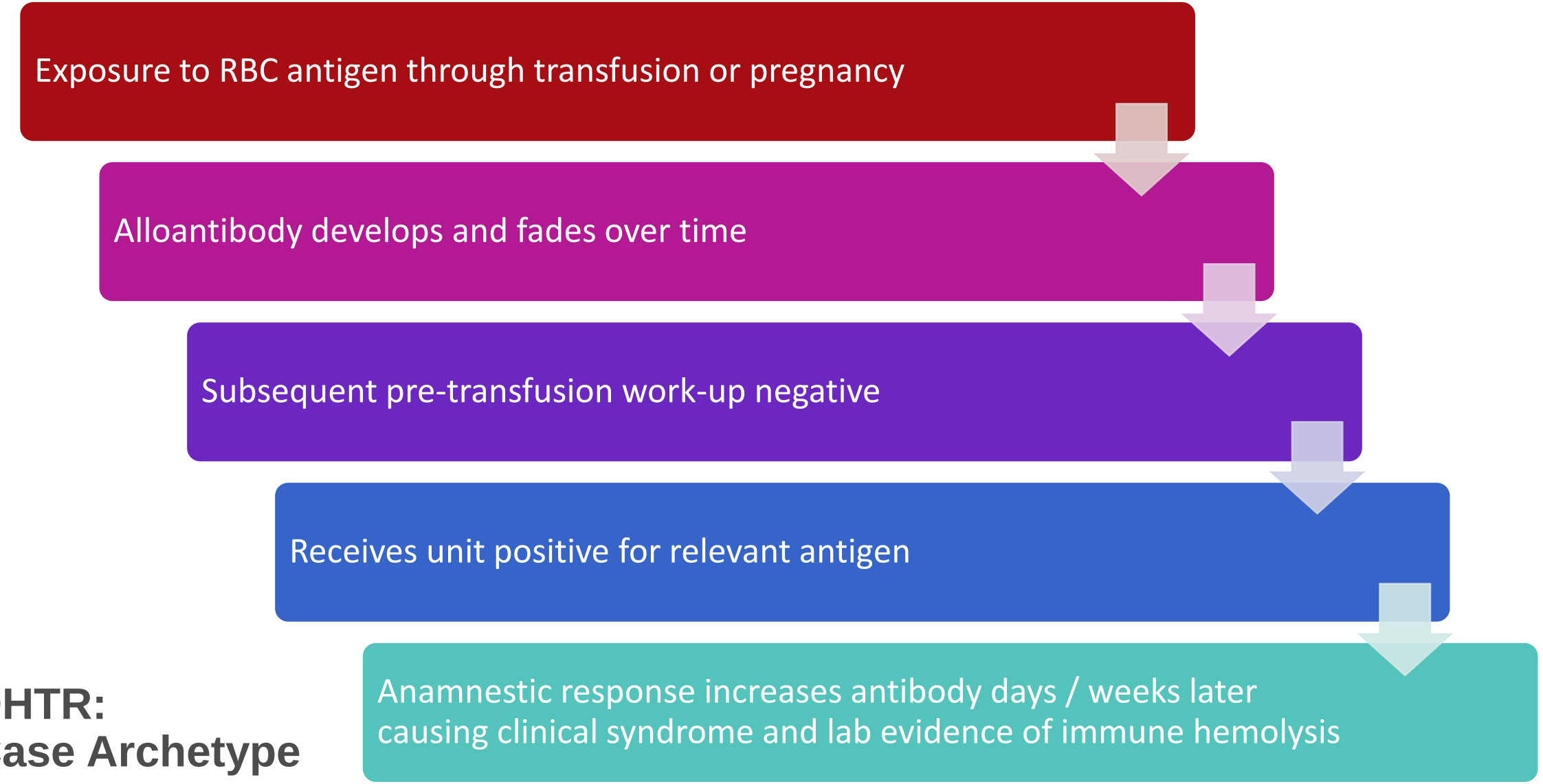
DHTR: Treatment

- Most do not require treatment, but can be severe
- Monitor hemoglobin (should not go lower than pre-transfusion level)
- Follow hemolysis labs for severe cases
- Rarely, severe hemolysis with renal failure – monitor renal function
- Antigen negative blood if transfusion required

Tormey CA, Stack G. Arch Pathol Lab Med. 2013 Jun;137(6):861-4

DHTR: Follow-Up

- Blood bank work-up to identify antibody and specify patient phenotype
- Patient should be given materials so that they are aware of their transfusion and antibody history so can report to outside institutions
- Transfuse only antigen negative blood
  - *Should be automatically done by blood bank if history is known, regardless of current screen results*
- Patient goes to a new hospital?



DHTR: Case Archetype

Post Transfusion Purpura (PTP)

PTP–Platelet Antigens

- Platelets have antigens that are specific to platelets (HPA's)
- There is variability related to single nucleotide polymorphisms
- Diallelic, codominant antigens
  - *When both genes present both expressed*
- One gene is predominant; rare to be negative for the common form
  - *E.g. HPA-1a allele much more common than HPA-1b*
  - *Most people will be 1a/1a or 1a/1b*
  - *Few will be 1b / 1b, and therefore negative for 1a*

Antigen	Other names	Glycoprotein location	Amino acid change	Phenotype frequency[a]
HPA-1a	PI^A, ZW	GPIIIa	Leu <-> Pro33	72% a/a
HPA-1b				26% a/b
				2% b/b
HPA-2a	Ko, Sib	GPIb	Thr <-> Met145	85% a/a
HPA-2b				14% a/b
				1% b/b
HPA-3a	Bak, Lek	GPII	Ile:Ser843	37% a/a
HPA-3b				48% a/b
				15% b/b
HPA-4a	Pen, Yuk	GPIIIa	Arg:Gln143	>99.9% a/a
HPA-4b				<0.1% a/b
				<0.1 b/b
HPA-5a	Br, Hc, Zav	GPIa	Glu:Lys505	80% a/a
HPA-5b				19% a/b
				1% b/b
HPA-6bw	Ca^a, Tu	GPIIIa	Arg:Gln489	<1% b/b
HPA-7bw	Mo	GPIIIa	Pro <-> Ala407	<1% b/b
HPA-8bw	Sr^a	GPIIIa	Arg:Cys636	<0.1% b/b
HPA-9bw	Max^a	GPIIIa	Val:Met837	<1% b/b
HPA-10bw	La^a	GPIIIa	Arg:Gln62	1% b/b
HPA-11bw	Gro^a	GPIIIa	Arg:His633	<0.5% b/b
HPA-12bw	Iy^2	GPIb	Gly:Glu15	1% b/b
HPA-13bw	Sit^a	GPIa	Met:Thr799	<1% b/b
HPA-14bw	Oe^a	GPIIIa	Del:Lys611	1% b/b
HPA-15a	Gov	CD109	Tyr:Ser703	35% a/a
HPA-15b				42% a/b
				23% b/b
HPA-16bw	Duv^a	GPIIIa	Thr:Ile140	<1%
NA	NAK^a	CD36 (GPIV)		99.8%

Human Platelet Antigens

International Journal of Clinical Transfusion Medicine 2015, 3:29-40

PTP–Pathophysiology

- Exposure to non-self HPA's (transfusion or pregnancy) can cause alloantibody formation
- Re-exposure to the antigen can result in anamestic response
- Analogous to DHRT for platelets
- ***Antigen negative* patient platelets are destroyed by the alloantibody with the anamestic response***

PTP – Description

- Extremely rare transfusion reaction
  - *UK: ~10 cases per year 1990s, 0-1 per year 2000s*
- More common in females (pregnancy history)
- SEVERE thrombocytopenia 1 – 24 days (mean 9d) post transfusion
- May have purpura / mucous membrane bleeding
- Patients at risk for dangerous bleeds including intracranial hemorrhage
- Mortality 0 – 13% in reported case series

PTP – Diagnosis

- New, severe thrombocytopenia with recent history of transfusion
- Total lack of response to platelet transfusions
- *May be associated with fever, chills, rigors, bronchospasm
- Platelet antibody screen positive
    - *Specific anti-HPA antibody identified*
- Patient is negative for relevant HPA
- Most common offending antigen is HPA-1a (~75% of cases)

PTP – Treatment

- First line therapy IVIG 1g/kg daily X 2 days
  - *Platelet count start to increase 1 – 4 days after treatment*
- Antigen negative platelets:
  - *May not be effective pre-IVIG treatment*
  - *Can be used to prevent antigen re-exposure*
- Subsequent transfusion with antigen negative products where possible
- Affected patients and their relatives are at risk for PTP and NAIT and should be counseled regarding this possibility

Rafei,H. et. al. Post-Transfusion Purpura: A Case Report of an Underdiagnosed Phenomenon

Previous exposure to blood through pregnancy or transfusion

Develops SEVERE thrombocytopenia days to weeks post transfusion of cellular product

Refractory to platelet transfusions +/- mixed febrile – allergic reactions to platelets

Positive platelet antibody screen with antibodies against non-self platelet antigens

IVIG often effective at restoring platelet count over days

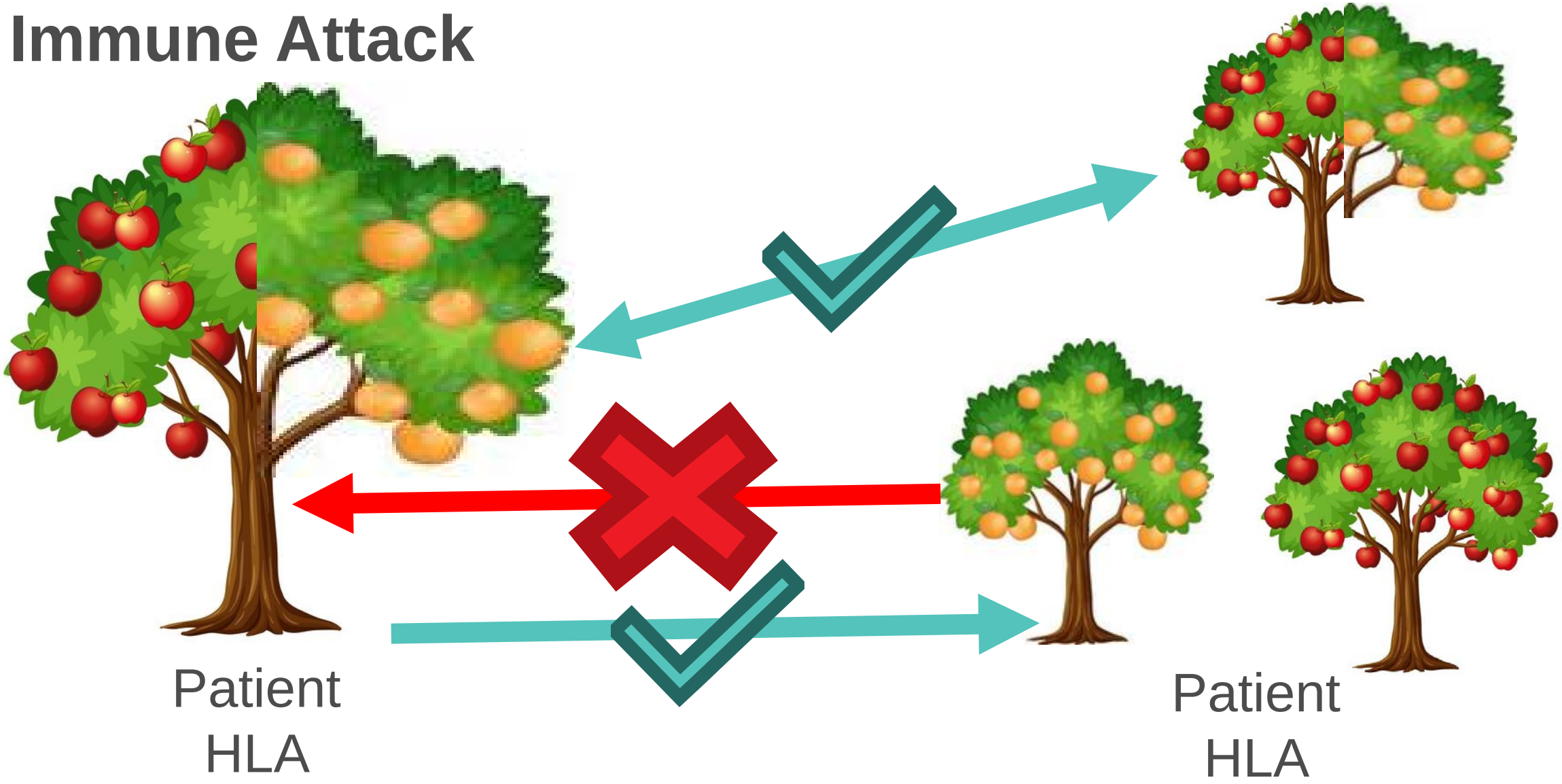
PTP Case Archetype

Transfusion-associated Graft vs. Host Disease (TA-GVHD)

TA-GVHD

- Transfused T-cells “engraft” and attack the host
- Requires:
  - *Viable, immunocompetent T-cells in the transfused product*
  - *Host has HLA antigens not present on the donor (i.e. donor cells see host as “not self” and reject host)*
  - *Host tolerant of infused cells (i.e. recipient immune system damaged, or sees donor cells as “self”)*

Immune Attack



Bahar, B. & Tormey, C. Prevention of Transfusion-Associated Graft-Versus-Host Disease With Blood Product Irradiation The Past, Present, and Future. Arch Pathol Lab Med 2018; 142: 662-667.

TA-GVHD

- Occurs in Recipients that are either:
  - *Severely immuno-compromise*
  - *Related to or an HLA-match with the donor*

- "The majority of cases in our review were attributed to cellular, non-leukoreduced, nonirradiated components that were stored for less than 10 days"

Kopolovic, I, et al. Blood. 2015 Jul 16;126(3):406-14

TA-GVHD – Clinical Presentation

- Immunocompromised patient or patient receiving blood from related or HLA-matched donor
- Develops fever, skin rash, severe watery diarrhea, abdominal pain, jaundice / elevated liver enzymes, pancytopenia (marrow aplasia)
- Typically 8 – 10 days post transfusion
- Patients typically die 1 – 3 weeks post presentation due to hemorrhage or infection

TA-GVHD – Diagnosis

- Rapidly progressive acute GVDH clinical picture
- GVHD histological appearance on skin, GI, liver, marrow biopsies
- No standard test regimen to make diagnosis
- Goal is to demonstrate significant presence of donor T-cells, in particular in tissue being damaged by process
  - *Serological or molecular HLA-typing strategies*
  - *PCR-based molecular studies such as micro-satellite repeat sequences (Short Tandem Repeats)*

TA-GVHD – Treatment and Prevention

- Treatment is supportive (blood products, antibiotics) but is 90% fatal
  - *Recent review identified a few cases of possible "mild" Ta-GVHD*
- Immunosuppressive regimens used for SCT GVHD are not effective
- Case reports curative stem cell transplants
- Irradiation of cellular blood products prior to transfusion in at risk patients prevents GVHD
  - *Prevents infused T-cells from proliferating*
  - *Pathogen reduction technology*

Kleinman, S & Stassinopoulos, A. Transfusion,2018;58;2545–2563

Ta-GVHD – Prevention

- Patients at risk for Ta-GVHD should receive irradiated blood
- Effective in preventing Ta-GVHD, but identifying at risk patients extremely complex
- SHOT: Large number of inadvertent transfusions of nonirradiated components to immunocompromised recipients without a single instances of Ta-GVHD

Kopolovic, I, et al. Blood. 2015 Jul 16;126(3):406-14

Who Needs Irradiated Blood?

- HLA-matched platelets, directed donations from relatives, granulocyte transfusions
- Allogeneic or autologous stem cell transplant / candidate
- Hodgkin's lymphoma, at any stage
- Other Hematologic malignancies / Aplastic anemia – only where otherwise indicated due to matched blood or drug exposure
- Solid organ transplant – only where otherwise indicated due to matched blood or drug exposure
- Exchange transfusions, extremely low birth weight infants, congenital T-cell immunodeficiency, intrauterine transfusions

http://www.nacblood.ca/resources/guidelines/downloads/Recommendations_Irradiated_Blood_Components.pdf

Who Needs Irradiated Blood?

APPENDIX B: Quick reference of potent immunosuppressive medications cited to increase TA-GVHD risk, and for which irradiated component transfusion should be considered

GENERIC Name	TRADE Name*
Fludarabine	Fludara
Cladribine or 2-CDA	Leustatin
Deoxycoformicin	Pentostatin or Nipent
Alemtuzumab (anti-CD52)	Campath, Lemtrada
Bendamustine	Treakisym, Ribomustin, Levact and Treanda
Clofarabine	Clolar
Anti-thymocyte globulin (ATG), rabbit or horse - When used in the setting of severe aplastic anemia only	Rabbit: Thymoglobulin Horse: Atgam

* *Note:* This list of pharmaceutical trade names may not be exhaustive, due to the nature of branding changes.

http://www.nacblood.ca/resources/guidelines/downloads/Recommendations_Irradiated_Blood_Components.pdf

Transfused patient receives viable donor T-cells and either severely immunocompromised or received HLA matched or blood from relatives

Rapidly progressive GVDH syndrome including diarrhea, skin rash, elevated liver enzymes, pancytopenia

8 – 10 days after having received non-irradiated cellular blood product

Rapidly progresses to death

Donor T-cells identified on molecular studies

Ta-GVHD Case Archetype

Uchida S, et. al. Transfus Med. 2013 Dec;23(6):416-22

Iron Overload

Iron Overload

- Chronically transfused patients receive 250 mg of iron for every RBC unit given
  - *Commonly observed in thalassemia, SCD, MDS, etc*
  - *Patients receiving >10-20 RBC units are at risk*
  - *No physiologic mechanism to remove excess iron*
- Excess iron deposits in organs causing long term damage

Rasel M, Mahboobi SK. Transfusion Iron Overload. [Updated 2021 Sep 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Symptoms and Laboratory Findings of Iron Overload

- Fatigue
- Breathlessness
- Hepatic failure (coagulation factor deficiency, albuminemia)
- Cardiac disease (dilated/restrictive cardiomyopathy, MI, arrhythmia)
- Endocrine contions (DM, hypogonadism, hypothyroidism, hypopituitarism)
- Skin pigmentation
- Arthritis

Rasel M, Mahboobi SK. Transfusion Iron Overload. [Updated 2021 Sep 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Diagnosis and follow up

- Serum ferritin
  - *Thal patients >2500 ng/dL have >80% of cardiac mortality*
  - *Liver biopsy*
- Baseline free thyroxine (T4), thyroid-stimulating hormone (TSH), calcium, phosphate, 25-OH vitamin D, fasting blood sugar, echocardiography, bone mass densitometry
- MRI of the liver and heart once a year
- Q3month serum ferritin and transferrin testing

Rasel M, Mahboobi SK. Transfusion Iron Overload. [Updated 2021 Sep 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Treatment/Management

- Prophylactic iron chelation therapy
  - *Start before clinically significant findings*
  - *Deferoxamine*
    - *Chelates free iron in blood and tissue*
    - *Excreted in the urine and bile*
    - *IV, subQ*
  - *Deferasirox*
    - *Tissue iron chelation*
    - *Excreted in bile*
    - *Oral administration*
- Goal serum ferritin <1000 micrograms/L

Rasel M, Mahboobi SK. Transfusion Iron Overload. [Updated 2021 Sep 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Return to the Learning Objectives

- Describe clinical presentation, diagnostic work-up, treatment, and implications for 3 delayed transfusion reactions:
  - *Delayed hemolytic transfusion reactions*
  - *Post-transfusion purpura*
  - *Transfusion-associated graft vs. host disease*
- Contextualize importance of transfusion history

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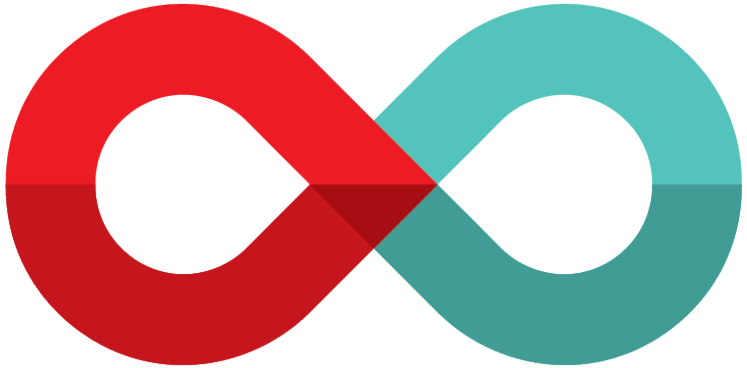

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