Irradiation of Blood Products: Why, When, How, and Why Not

Gary Bachowski MD, PhD
American Red Cross Blood Services
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Outline

- Residual lymphocytes (leukocytes) in blood products or other transplanted tissue can cause Graft vs. Host Disease (GVHD). While this is a rare occurrence, it can be fatal, so a preventive measure –irradiation – is often required to ensure safe transfusion. In this session the participants:

  - Will learn about GVHD and its cause
  - How irradiation can prevent transfusion associated GVHD (TA-GVHD)
  - Which groups of patients are most susceptible to GVHD and require irradiated blood products
  - What effects does irradiation have on the blood products and what are the resulting disadvantages

Graft versus Host Disease General Definitions

GVHD in organ/stem cell transplantation

- Complication of an allogeneic (donated) tissue transplant, in which cells from a donor trigger an autoimmune-like response in the recipient, causing the body to attack its own tissues.
- Acute vs Chronic = before or after 100 days from transplant

- Symptoms: most common organ systems
  - **Gastrointestinal**: Occurring in 75% of acute cases
  - **Skin**: Occurring in 70% of acute cases
  - **Liver**: Occurring in 44% of acute cases

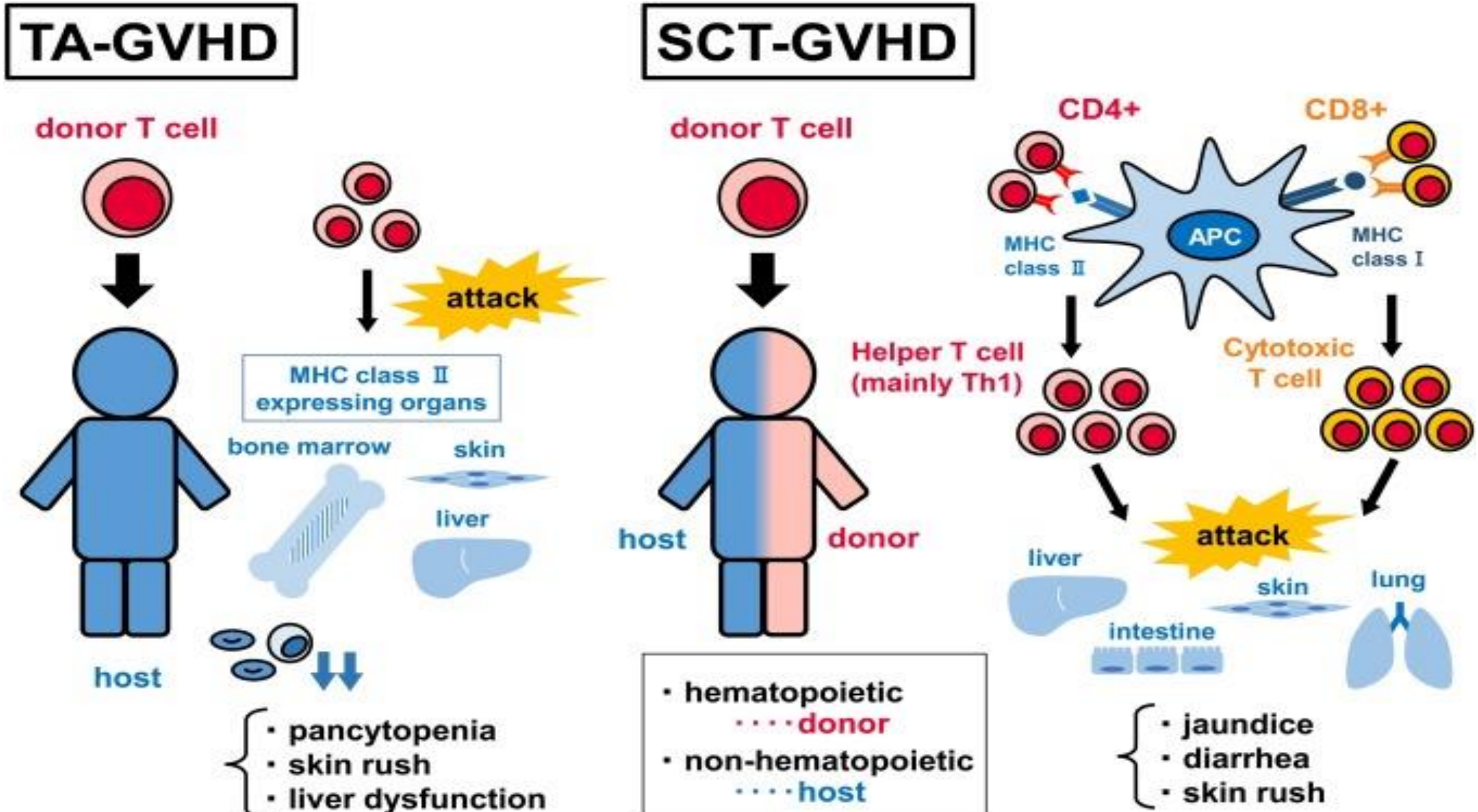
Mechanism

- Donor immune system cells (T-lymphocyte directed) recognize the recipient as “foreign” and trigger an immune response.
  - HLA antigens are key identifiers

- HLA = Human leukocyte antigens (HLA) are **key sites in the histocompatibility complexes (MHC) that help differentiate between self and non-self**

How does transfusion-associated graft-versus-host disease compare to hematopoietic cell transplantation-associated graft-versus-host disease?

Keiko Aizawa Daniel Peltier Eri Matsuki Tomomi Toubai Published:February 16, Transfusion and Apheresis Science VOLUME 61, ISSUE 2, 103405, APRIL 01, 2022



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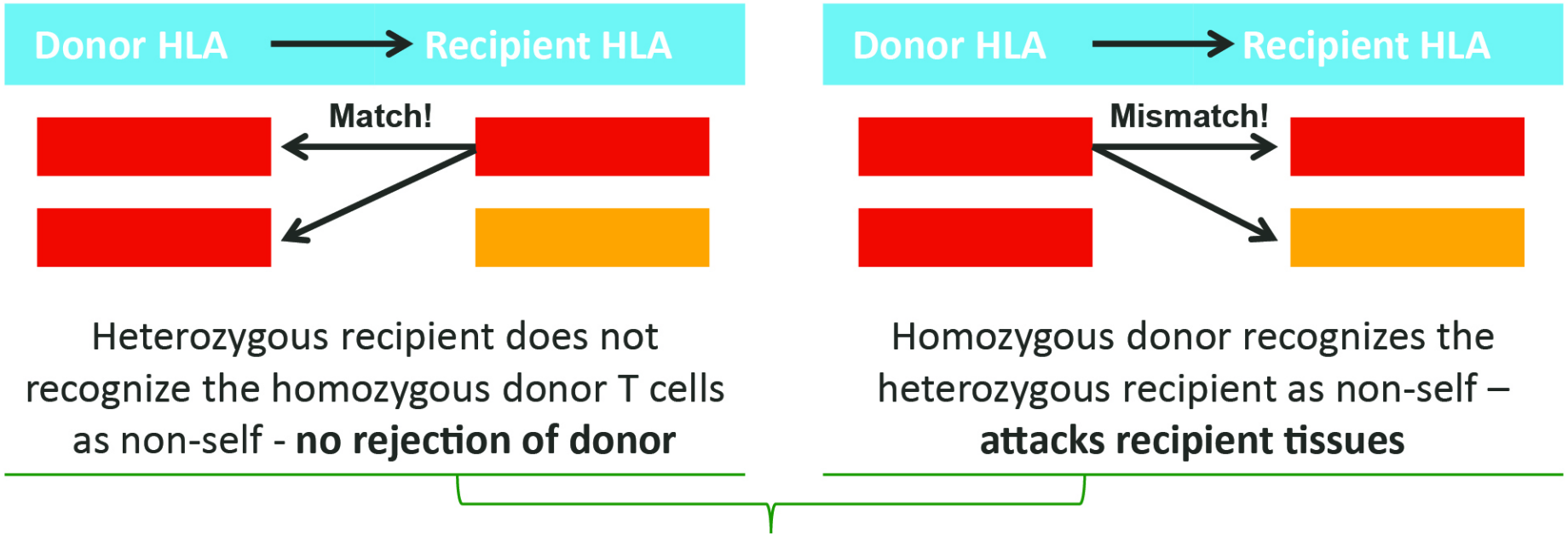
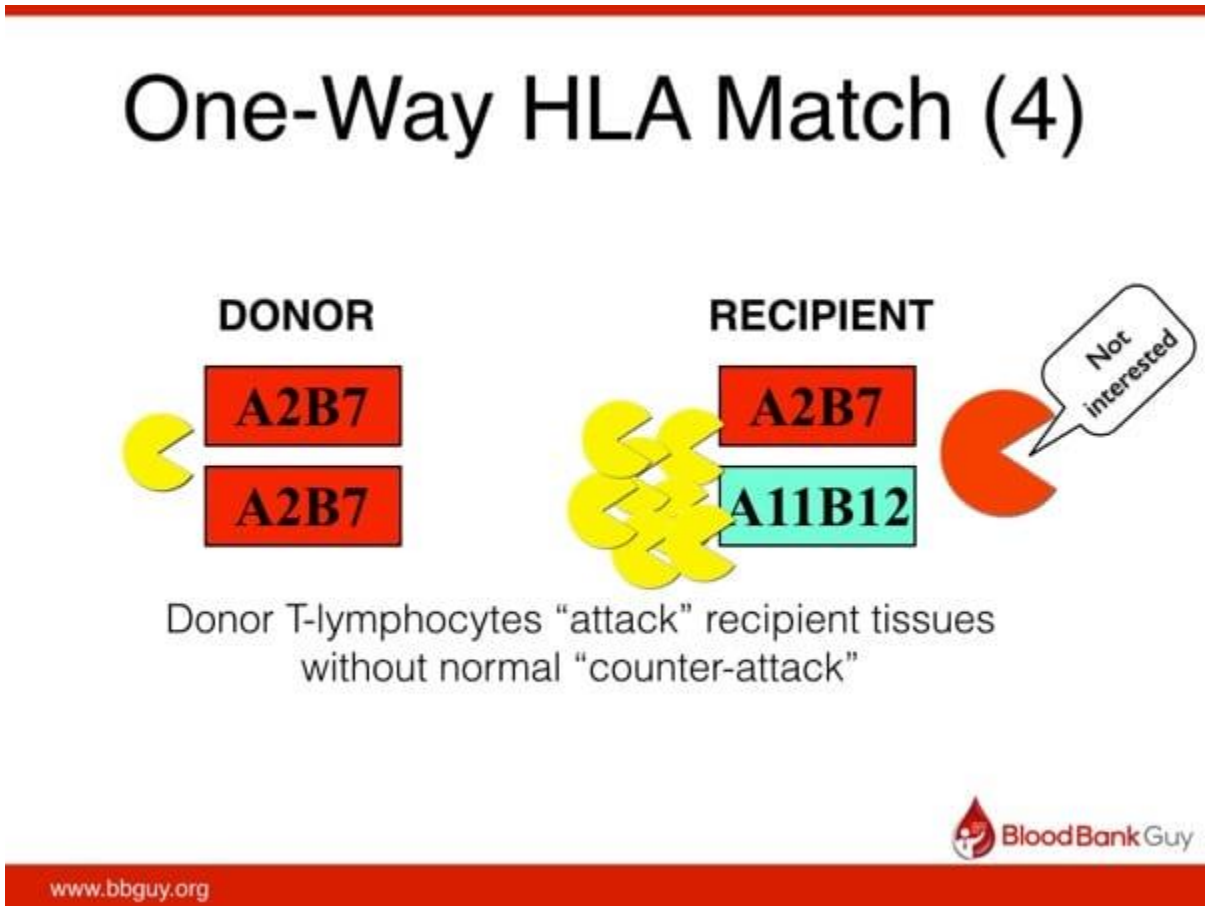


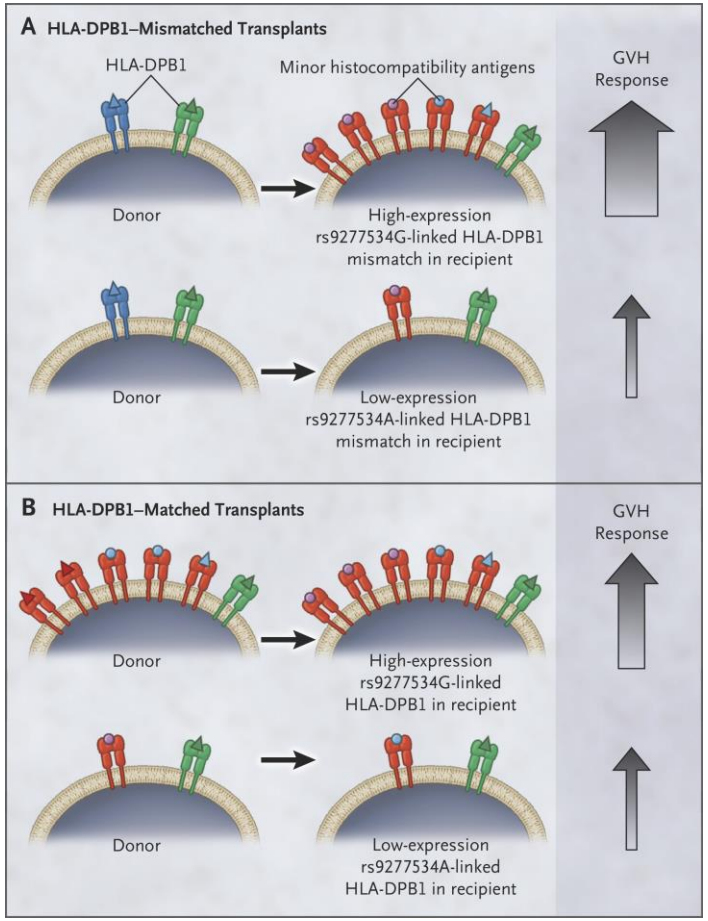
The donor T-cells attack the recipient, but the recipient immune system does not reject the donor T cells.

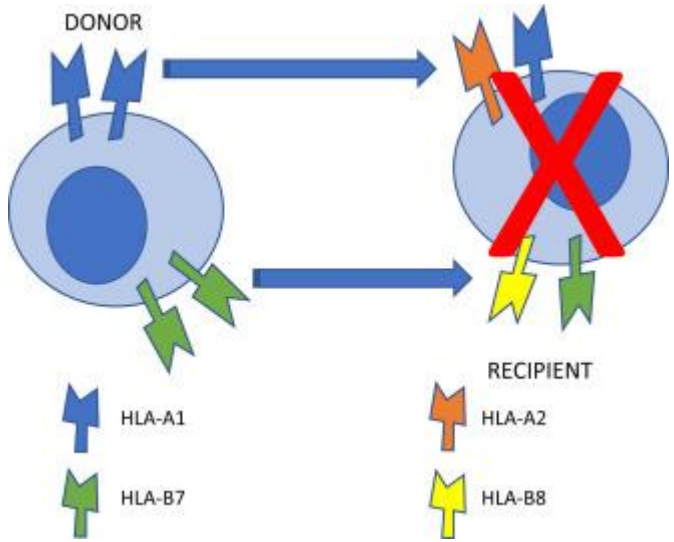
https://www.bbguy.org/2016/07/15/013/



Immunologic Concepts in Transfusion Medicine 2020, Pages 197-204 chapter 12 - Graft-Versus-Host Disease and Transfusion-Associated Graft-Versus-Host Disease

Author links open overlay panel Alex B.RyderMD, PhD YanZhengMD, PhD





B-cell exception

- **Passenger lymphocyte syndrome (PLS)**

  Rare and unique form of GVHD in which activated B-lymphocytes are passively transferred into the recipient circulation. It is **a complication of both solid-organ and stem cell transplants and is caused by donor B lymphocyte production of antibodies causing an immune response to recipient RBCs**

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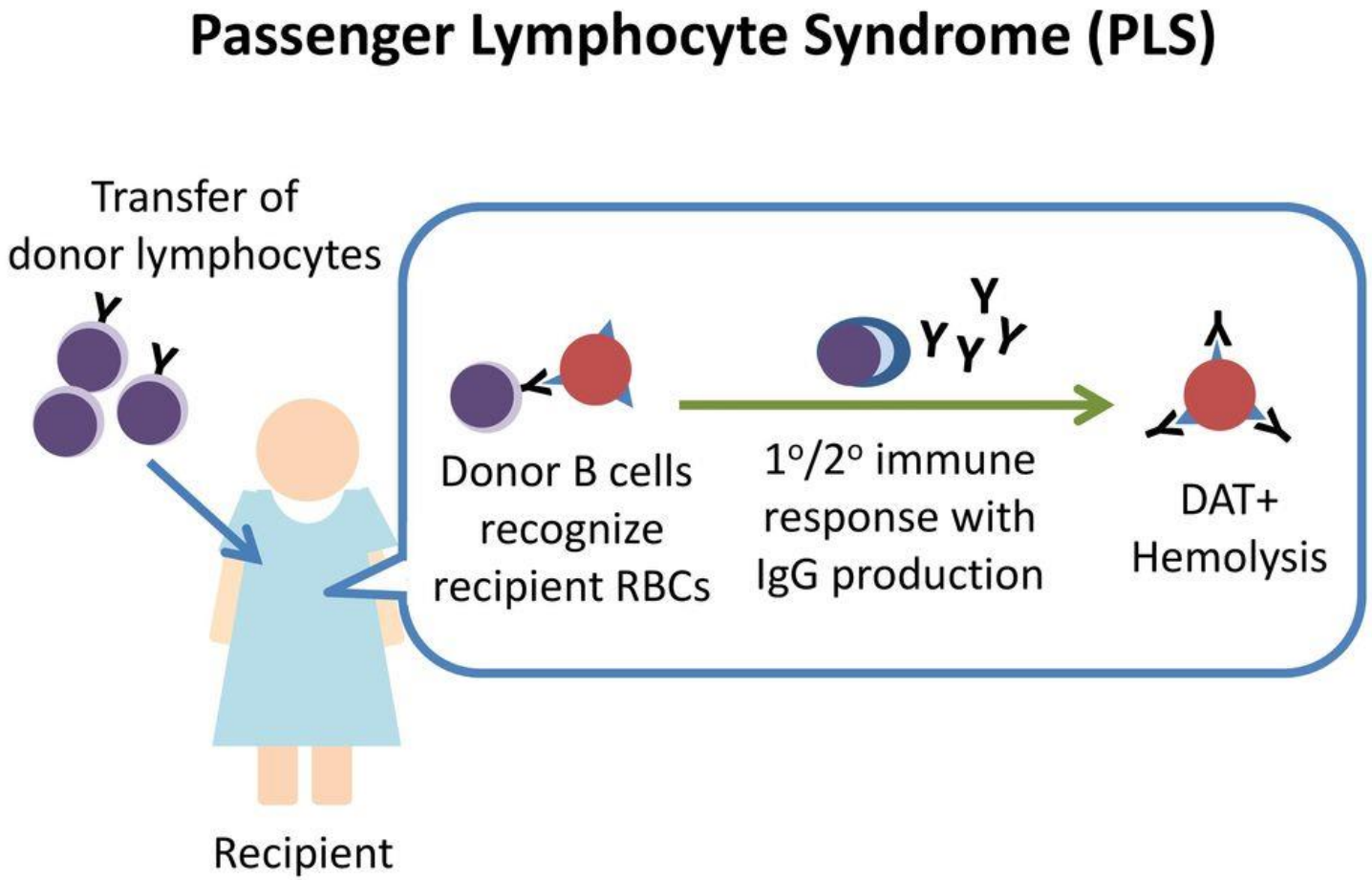
Jean Oak MD,PhD Transfusion Medicine Fellow Stanford University



Other concepts

- Host vs Graft disease = Organ/Tissue Rejection

- Immune suppression often given to prevent rejection
  - Balancing prevention vs. risk for infection
  - Relatively common in transplant medicine

Transfusion Associated GVHD

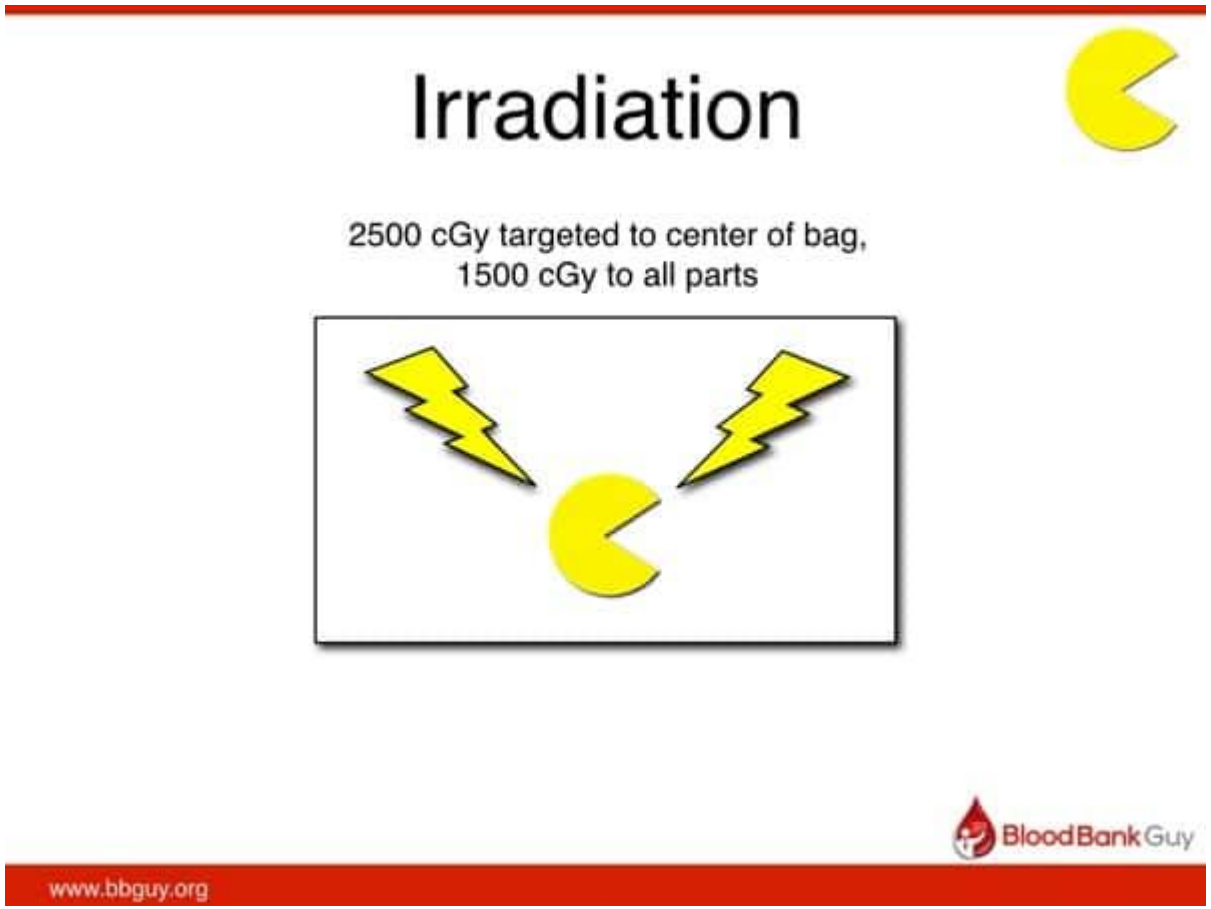
- Transfusion Associated GVHD
  - Mechanism
    - T-cells and HLA immune system recognition
  - Targets bone marrow
    - Also GI, skin
  - 90% fatality?

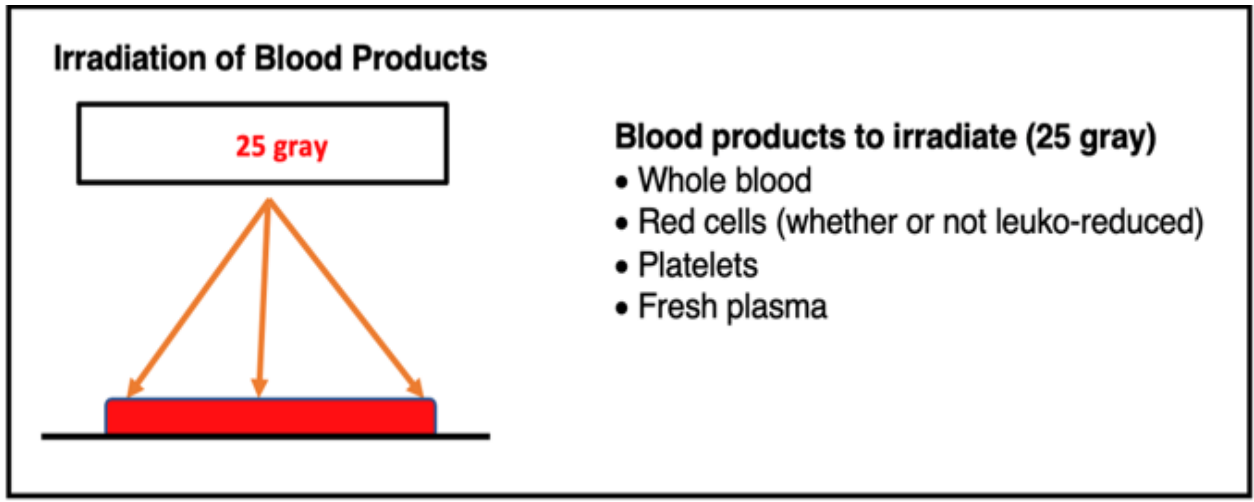
- Transfusion as “tissue transplant”
  - Contains leukocytes (T and B lymphocytes with HLA antigens)

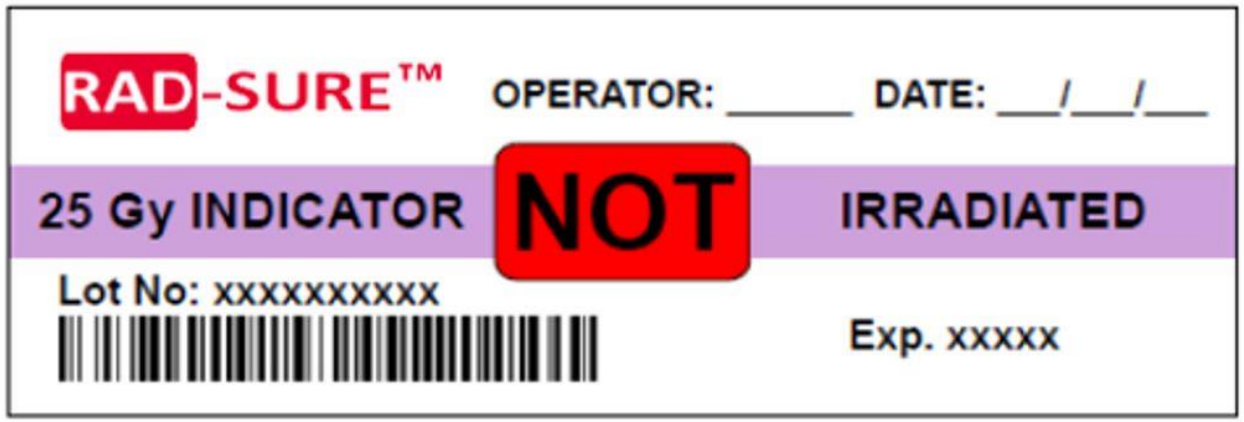
Transfusion Medicine and Hemostasis (Third Edition)
Clinical and Laboratory Aspects 2019, Pages 261-265
Chapter 42 - Irradiation of Blood Products Richard O.Francis MD, PhD

Gamma-irradiation or X-ray, is performed to prevent transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD is a rare and almost universally fatal complication of blood transfusion that has no consistently successful treatment options. It is caused by the infusion of viable lymphocytes that engraft in the recipient and mount an immune response against the host. Irradiation results in the generation of electrons that damage lymphocyte DNA, rendering the lymphocytes unable to proliferate.

https://www.bbguy.org/2016/07/15/013/



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25 Gy INDICATOR
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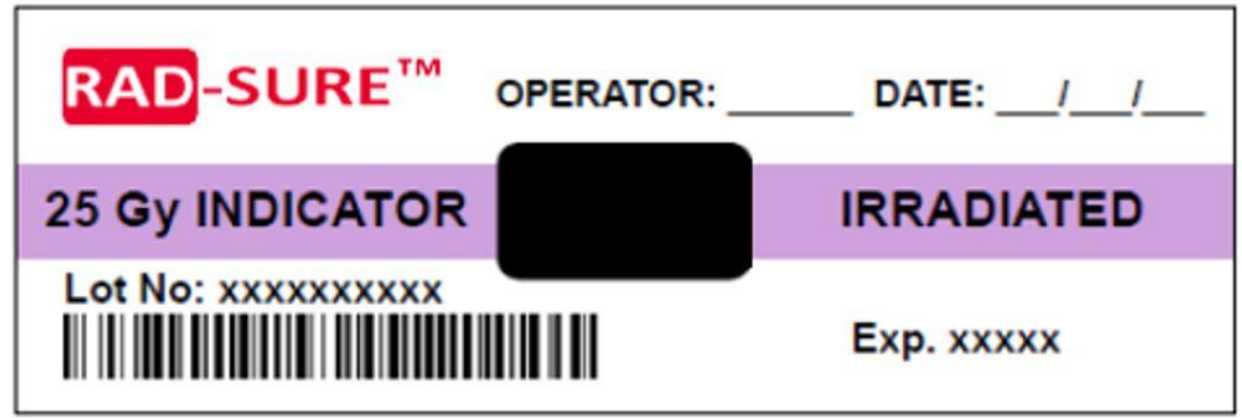
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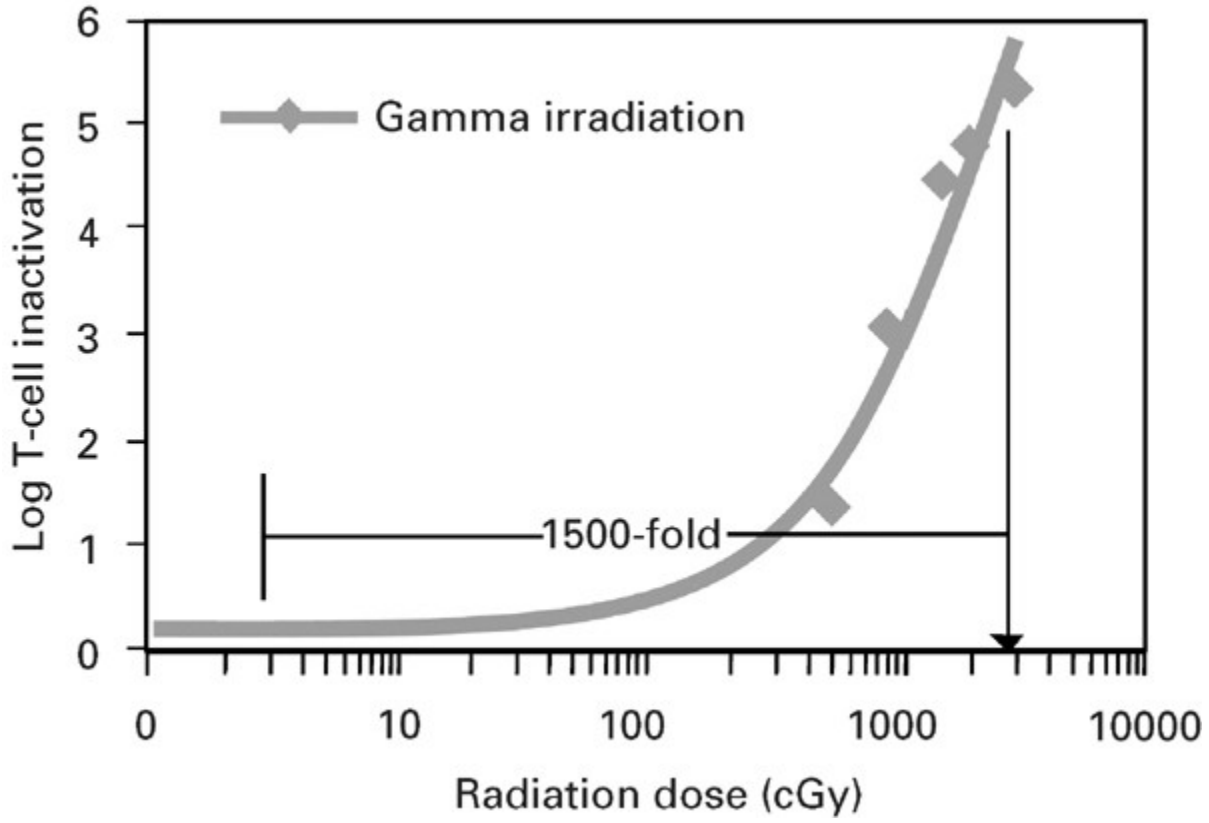
Under-Irradiated
Central Dot lighter than minimum reference color

Within Recommended Dose Range
Central Dot between minimum and maximum reference color

Over-Irradiated
Central Dot darker than maximum reference color

- Because the identification of all individuals at risk of TA-GVHD may not always be successful, some institutions and countries irradiate all cellular blood products (universal irradiation); however, policies for irradiating cellular blood products only for those patients at increased risk for developing TA-GVHD are more common. For irradiation of cellular blood products to be successful in preventing TA-GVHD, the irradiation dose must be sufficient to inhibit lymphocyte proliferation.

Irradiation and Effects in Prevention



Effective dose

- Studies indicate that 25 Gy, measured at the mid-plane of a component, completely abolishes mixed lymphocyte responses

  AABB *Standards for Blood Banks and Transfusion Services*, 32nd Edition, recommends a dose of 25 Gy to the central area of the component with no portion receiving <15 Gy, but sets no upper limit.

  The Japanese Society of Blood Transfusion's Guidelines recommend a similar dose.

  In the UK, a minimum of 25 Gy is recommended, but with the dose to any bag in the container not exceeding 50 Gy.

FDA device requirements

- **Devices using x-rays** (*NRC requirements do not apply*).
  Two examples from FDA's website:
  - **RAD SOURCE X-RAY BLOOD IRRADIATOR, MODEL RS-3400**
  - **Raycell Mk2** 510(k) Premarket Notification and **2016 510(k)**

- **Devices using gamma rays** from either cesium-137 or cobalt-60 sources (*extensive Nuclear Regulatory Commission (NRC) requirements*).
  - ELIMINATION OF DEVICES USING CS-137
    The goal of the **Cesium Irradiator Replacement Project** and the **Off-Site Source Recovery Program** is to **eliminate the use of blood irradiation devices that rely on cesium chloride (Cs-137) in the United States** through voluntary replacement. **Section 3141** of the **John S. McCain National Defense Authorization Act for Fiscal Year 2019** includes a provision that requires the Administrator for Nuclear Security to ensure that goal is met **by December 31, 2027**.

Susceptible Patients (who needs irradiated blood)

- Fetal and neonatal recipients of intrauterine transfusions
- Selected immunocompromised recipients
- Recipients of cellular components known to be from a blood relative
- Recipients who have undergone marrow or peripheral blood progenitor cell transplantation
- Recipients of cellular components whose donor is selected for HLA compatibility

Hospital Policies are more specific and vary in strictness

NON-Indications

- Acute leukemia
- Non Hodgkin Lymphoma
- Rituximab
- Solid Organ Transplant
- Multiple sclerosis
- Aplastic anemia

Alternatives

Leukoreduction (UK guidelines)

- Current specification is that >99% of components should contain <5 × 10^6 leucocytes per unit and >90% <1 × 10^6 per unit.
  - Process fails occasionally: residual risk of issuing a unit above these specified levels
    - Likelihood of RBC unit containing more than 1 × 10^6 leucocytes is 1:230, and >5 × 10^6 leucocytes is 1:1881
    - For apheresis platelets 1:321 and 1:8154 respectively
    - For pooled platelets 1:75 and 1:3205
- Consider the risk of issuing a non-LD component and its potential clinical consequences
  - TA-GvHD is usually fatal(?)
  - Recent international systematic review of 348 cases of TA-GVHD, LD components were implicated in 17% of cases where LD status was reported (6·6% overall cases).
  - In about half of cases the level of leucocyte depletion was below current standards in the UK
  - Not aware of any country that relies on leucocyte depletion alone for prevention of TA-GVHD

- **Recommendation:** There is insufficient evidence to recommend leucocyte depletion alone to prevent TA-GvHD in susceptible patients

2021 Dec;195(5):681-688.

Guideline development for prevention of transfusion-associated graft-versus-host disease: reduction of indications for irradiated blood components after prestorage leukodepletion of blood components

Johanna C Wiersum-Osselton [1], Jennichjen Slomp [2], J H Frederik Falkenburg [3], Tessa Geltink [4], Hans L P van Duijnhoven [5], Tanja Netelenbos [6], Martin R Schipperus [7]

TA-GVHD is a rare, commonly fatal complication of transfusion preventable by irradiation of blood units. Revision of the Dutch transfusion guideline addressed whether irradiation is still necessary if blood components are prestorage leukodepleted. We searched for published cases of TA-GVHD following transfusion of prestorage leukodepleted blood and through contacting haemovigilance systems. Six presumed cases were found, dating from 1998 to 2013. Four out of six patients had received one or more non-irradiated units despite recognized indications for irradiated blood components. In the countries providing information, over 50 million prestorage leukodepleted, non-irradiated, non-pathogen-reduced cellular components were transfused in a 10-year period.

Potential benefits of lifting indications for irradiation (and/or avoiding blanket policies)

- Costs (€ 1.5 million annually in the Netherlands)
- Less donor exposure for neonates
- Most recommendations were unchanged
  - except 6 or 12 months after autologous or allogeneic stem cell transplant

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Pathogen Inactivation

- Systems to pathogen inactivate platelets also inactivate lymphocytes
  - Manufacturers therefore claim that these systems can be used as an alternative to irradiation for the prevention of TA-GvHD
  - Many centers that have implemented this technology have stopped irradiating platelets. Although these systems are considered by some authors as potential future solutions for prevention of TA-GvHD, they are not yet used in the UK, and similar systems in development for red cells are not yet licensed with limited data available.

- BBTS 32nd Edition (Effective July 1, 2020)

- **Standard Number 5.19.4.1**
- Methods known to prevent transfusion-associated graft-vs-host disease shall be used, and include either irradiation or the use of a pathogen reduction technology that is known to inactivate residual leukocytes and is cleared or approved by the FDA or Competent Authority.

- **FDA**
  - "Manufacture of Blood Components Using a Pathogen Reduction Device in Blood Establishments: Questions and Answers Guidance for Industry."

    U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research November 2021
  - As described in the FDA-approved labeling, the INTERCEPT® Blood System for Platelets can be used as an alternative to gamma irradiation for prevention of transfusion-associated graft versus host disease (TA-GVHD)

Effect on RBCs

- Significant changes in some markers of RBC quality
  - Increased hemolysis
  - Increased potassium leakage
  - Can increase microparticles though no adverse effects reported
  - **No clinically significant effect** on pH, glucose consumption, ATP or 2,3-diphosphoglycerate (DPG)

- Effects dependent upon age of RBCs prior to irradiation, dose of irradiation and length of storage once irradiated.
  - Irradiation of RBCs in the last few weeks of their normal shelf life, currently permitted by AABB standards (*Standards for Blood Banks and Transfusion Services*, 32nd Edition), and Council of Europe guide (*Guide to the Preparation, Use and Quality Assurance of Blood Components*, 20th Edition, 2020)
    - Results in increased hemolysis of and reduced post-transfusion RBC recovery, although recovery is still above the minimum defined as acceptable by US FDA (75%)
    - Versus UK standard
      - RBCs irradiated up to 14 days post collection and stored a maximum of 14 days more without loss of viability or hemolysis
      - Little operational gain in enabling irradiation later in shelf life in the UK, so recommended that RBCs are irradiated within 14 days from collection, and stored for a maximum of 14 days after irradiation.

RBCs cont. UK guideline analysis

- Both gamma- and X-irradiation of RBCs result in significantly accelerated leakage of potassium and increase extracellular potassium
  - Small volume transfusions given at standard flow rates do not constitute a risk of hyperkalemia, even when given to premature neonates
  - Potassium load may be clinically important in rapid large-volume transfusions, such as neonatal exchange blood transfusion (EBT) or IUT, therefore the shelf life is restricted to 24 h following irradiation and by the end of Day 5 from collection to reduce the risk of hyperkalemia.
  - Restrictions also recommended for infants receiving other large volume transfusions such as for cardiac bypass or extracorporeal membrane oxygenation (ECMO):
    - Small infants are particularly susceptible to hyperkalemia due to their small size compared to extracorporeal circuits and potential for high transfusion rates relative to weight.

RBCs cont. (More UK guideline tidbits)

- Probably safer to avoid transfusion of irradiated blood for MTP, unless irradiated blood is otherwise indicated, as rapid infusion of irradiated red cells for patients on MTP could contribute to hyperkalemia

- In a recently published retrospective study, prolonged storage of irradiated red cells was associated with a significant increase in non-allergic transfusion reactions. Overall, the leading type of reaction being febrile non-haemolytic transfusion reaction. (Bolton-Maggs, P, personal communication from SHOT data).

Effect on platelets

- Although recent laboratory studies suggest that irradiation may result in proteomic/metabolomic changes in platelets, irradiation <50 Gy has not been shown to produce significant clinical changes in platelet function.[58, 72-74]

Recommendation

- Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection.

What about cold storage, or 7 day platelets, or 14 day cold storage platelets?

Effect of granulocytes

- The evidence for irradiation damage to granulocyte function is conflicting, but in any case, granulocytes should be transfused as soon as possible after production and irradiation, as granulocyte function declines rapidly with time.

Recommendation

All granulocytes should be irradiated before issue. They should be transfused with minimum delay

Pediatric practice UK

- Risk of TA-GvHD in the fetus and neonate, especially if preterm, is thought to be higher than in older recipients. Contributing factors:
  - Immunological immaturity
  - Use of fresher blood
  - Relatively large transfusion volumes in situations such as neonatal EBT

- In some countries and institutions, irradiation is undertaken for blood for older children because of concerns for unrecognized immunodeficiency. However, potential benefits of universal irradiation need to be balanced against the ability to use multiple ‘pedipacks’ for neonatal transfusions to reduce donor exposure (not practical in the UK if universally irradiated by blood centers) and the potential risk of hyperkalemia following rapid transfusion of older irradiated blood to a neonate.

- **Recommendations**

  Red cells for IUT and neonatal EBT should be irradiated and then transfused within 24 h

Congenital immunodeficiencies in infants and children e.g. DiGeorge Syndrome (UK)

- **Recommendation**

Neonates and infants with T-lymphocyte count is >400 cells/µl, of which 30% are naive T lymphocytes, there is no need to irradiate red cells or platelets. If it is not possible to undertake T-cell investigations prior to surgery, irradiated cellular blood components should be given until immunological investigations have been undertaken.

Adults, and children aged > 2 years without a significant history of unexplained infection or in whom DiGeorge anomaly is not suspected, do not need irradiated cellular blood components

- **Viral infection T-cell deficiencies/HIV**
  - No indication for irradiation of cellular blood components for infants or children with temporary defects of T-lymphocyte function as the result of a viral infection. No indication for irradiation of cellular blood components for adults or children who are HIV-antibody positive or who have AIDS

- **Allogeneic hematopoietic stem cell transplantation (HSCT)**
  - All recipients of allogeneic HSCT should receive irradiated blood components from the time of initiation of conditioning chemo/radiotherapy regardless of the underlying diagnosis.
  - Irradiated components should be continued until all of the following criteria are met:
    - >6 months have elapsed since the transplant date
    - The lymphocyte count is >1·0 × 10e9/l
    - The patient is free of active chronic GvHD
    - The patient is off all immunosuppression
  - If chronic GVHD is present or continued immunosuppressive treatment is needed, irradiated blood components should be given indefinitely
  - Treatment with irradiated blood components should continue indefinitely if required based on previous diagnosis or treatment (e.g. purine analogue treatment or Hodgkin Lymphoma)

- **Autologous stem cell transplantation (ASCT)**
  - All patients undergoing ASCT should receive irradiated cellular blood components from initiation of conditioning chemo/radiotherapy until 3 months post-transplant (6 months if total body irradiation was used in conditioning) unless required based on previous diagnosis or treatment (e.g. purine analogue treatment or Hodgkin Lymphoma.

Hodgkin lymphoma (HL) - indefinite

Patients treated with purine analogues (regardless of the underlying condition)

- The purine analogues fludarabine, cladribine and pentostatin induce profound lymphopenia with low CD4 counts that may persist for several years after treatment. There are case reports of TA-GvHD following treatment of low-grade B-cell malignancies with fludarabine and cladribine.

- Hematology patients and patients with rare types of immune dysfunction **treated with alemtuzumab (campath) or anti-thymocyte globulin (ATG)**

- **Chimeric antigen receptor T-cell (CAR-T) therapy**
  - In addition to immunosuppression associated with CAR-T, the process autologous lymphocyte collection by apheresis; so the apheresis product could theoretically contain viable lymphocytes, which could contaminate the final product and lead to TA-GvHD.
    - Therefore, it is recommended that the guidance for autologous stem cells also be followed for CAR-T
      - No cases of TA-GvHD secondary to CAR-T cells administration have been reported to SHOT
      - No cases found in the literature review
      - It is expected that patients receiving CAR-T therapy will have other indications for irradiation.

Case 1

- Sister (JK3 negative) donates RBCs for her 47 year old brother (Hgb 7.3) who is having surgery for esophageal cancer.
    - 4 RBC units requested but only 2 frozen RBCs available from rare donor program
    - Patient history does not indicate any need for routine irradiation of blood products

Case 2

- 63 year old male who had an autologous stem cell transplant 8 years ago for multiple myeloma. Now comes in for cardiac surgery and 4 RBCs are requested for type and cross.

B-negative with anti-e and Jka historically

Patient has normal CBC and differential

Hospital policy has been to maintain use of irradiated blood products indefinitely

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Summary

TA-GVHD is caused by contaminating T-lymphocytes in blood tissue ‘transplants’

- Rare but often fatal (non-fatal may be under-recognized)
  - 1 in a million? 1 in 10 million?
- T-cells in RBCs, platelets, granulocytes, (liquid plasma?)
- Risk is greater in closely related/HLA matched transfusions
- Risk applies mainly to select groups

Selected patient groups most susceptible to GVHD and require irradiated blood products

- Congenital T-cell deficiency, intrauterine/neonatal, BMT, Hodgkin Lymphoma, granulocyte transfusion, related or HLA matched, purine analog chemotherapy
- Not needed for HIV, leukemia, other types of chemotherapy

Disadvantages of irradiation include logistical, regulatory, and cost problems in addition to the potential to damage blood products

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