Irradiation of Blood and Blood Components

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- Why to Irradiate blood
- Transfusion Associated Graft versus Host Disease (TAGVHD)
- Indications of Irradiated Components
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Background

- For Prevention of Transfusion Associated Graft versus Host Disease (TAGvHD)
- Irradiation: induces DNA crosslinks, prevents (dividing) lymphocyte proliferation

Transfusion Associated Graft versus Host Disease (TAGvHD)

- Delayed Immune transfusion reaction.
- Results from engraftment of foreign T cells.
- Clinically similar to Graft versus Host Disease (GvHD) except **pancytopenia** is a prominent feature.
- Usually arises 3 to 30 days after transfusion.
- Onset of symptoms occur early with signs and symptoms of bone marrow aplasia.

Factors for developing TA GvHD

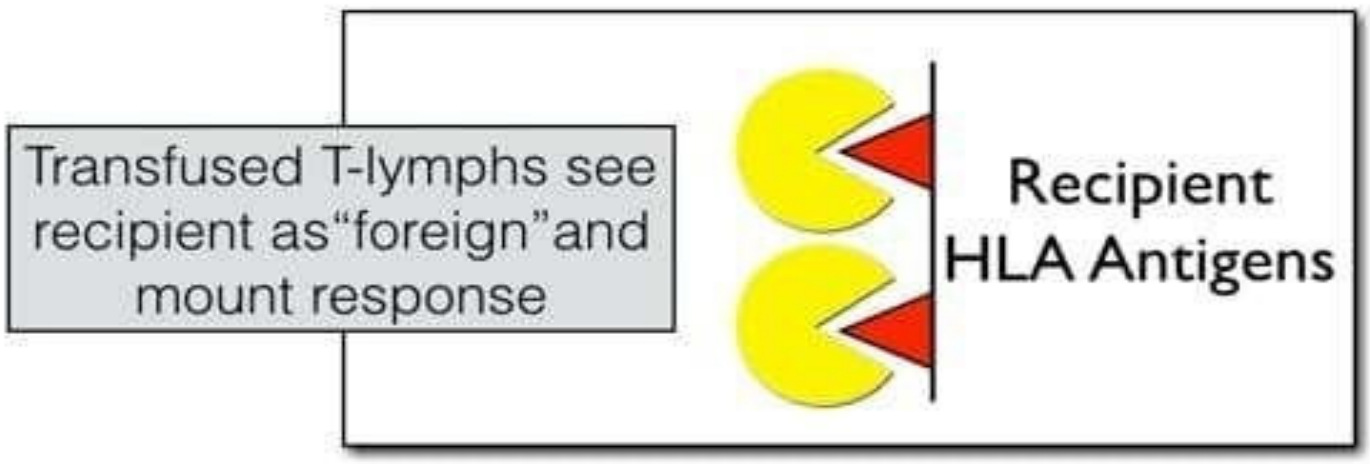
- **Predisposing conditions-**
  - HLA antigen difference between donor & recipient
  - Presence of donor immunocompetent cells in blood component
  - A recipient incapable of rejecting donor immunocompetent cells
- The number of lymphocytes in a bag is determined by the age of the blood component and the irradiation status.
- Fresher blood components contain more viable T lymphocytes.

Pathophysiology

- **Immuno-compromised host –** Congenital/Acquired- lack the ability to reject the donor T cells
- **Immuno-competent host – When donor is** Homozygous and recipient is heterozygous for HLA haplotype (sp Class I) – Host does not recognize donor lymphocytes as foreign

Uneventful Transfusion

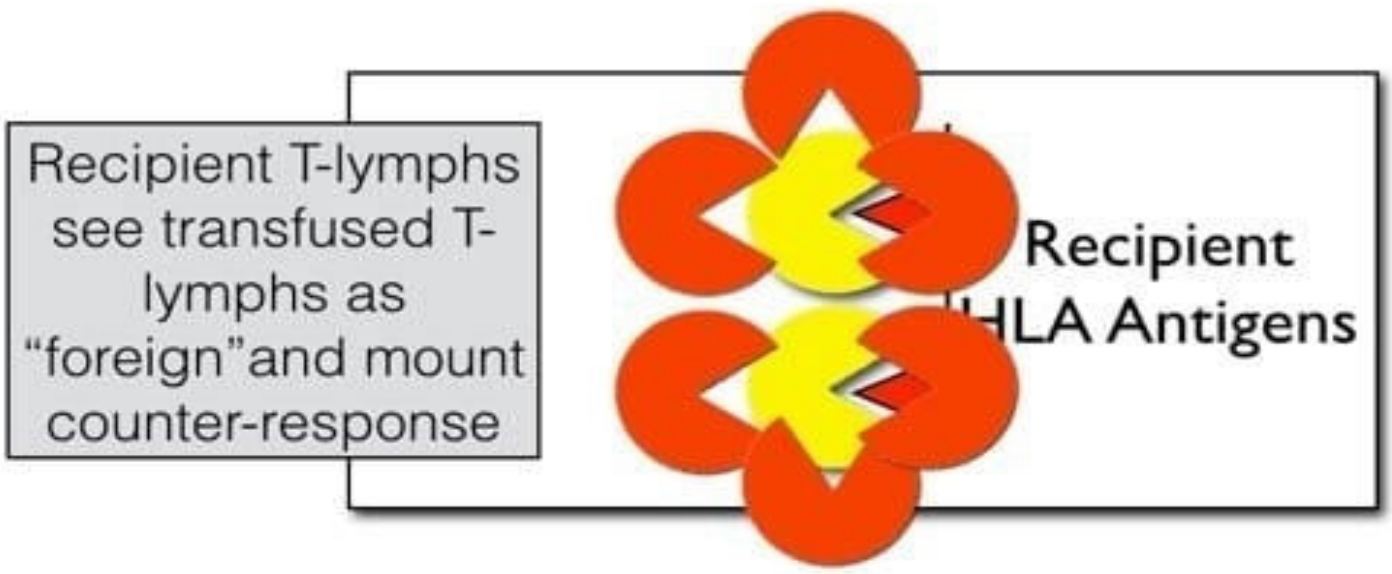
Normal Events



Attack!

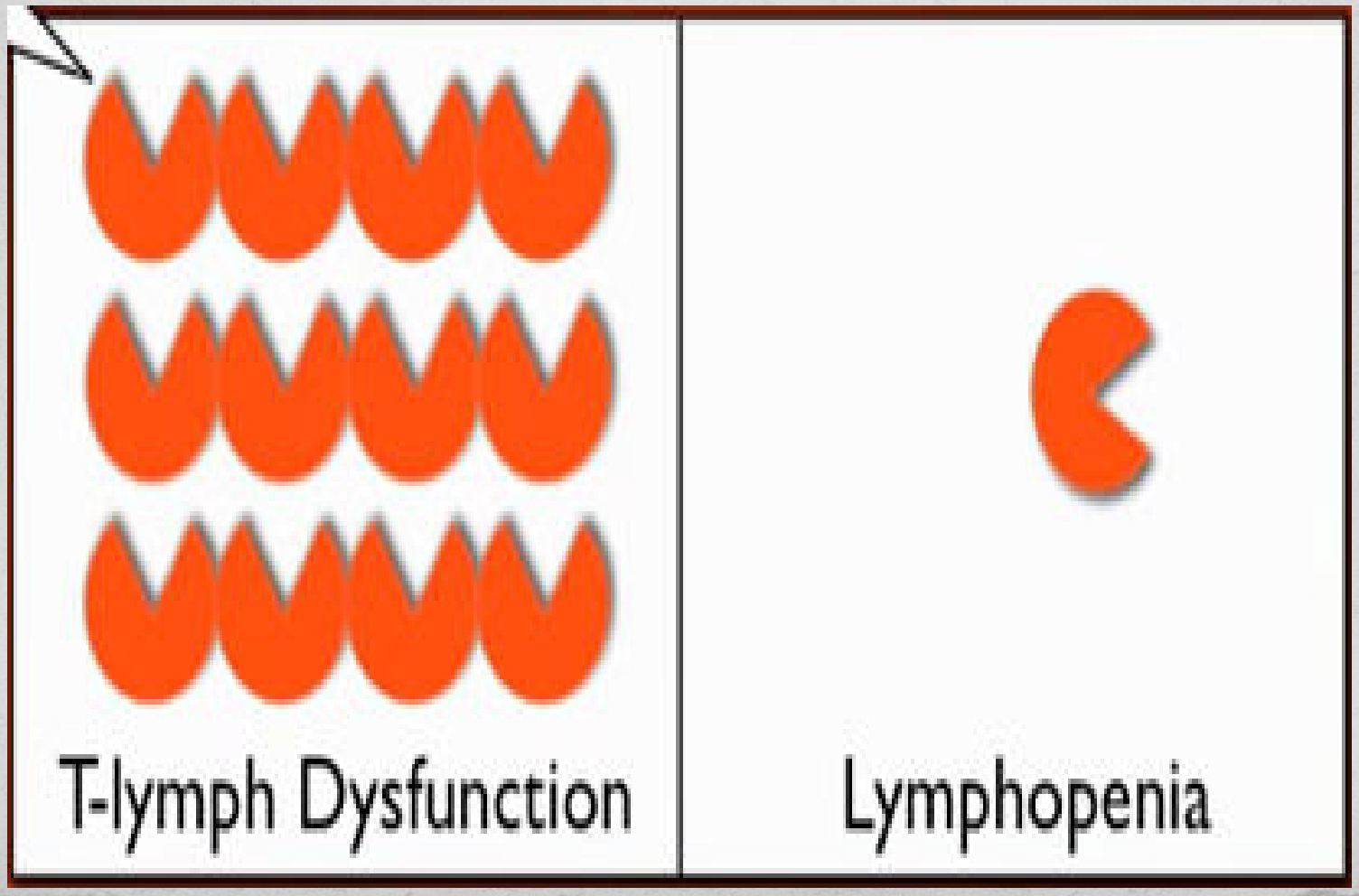
Uneventful Transfusion

Normal Events



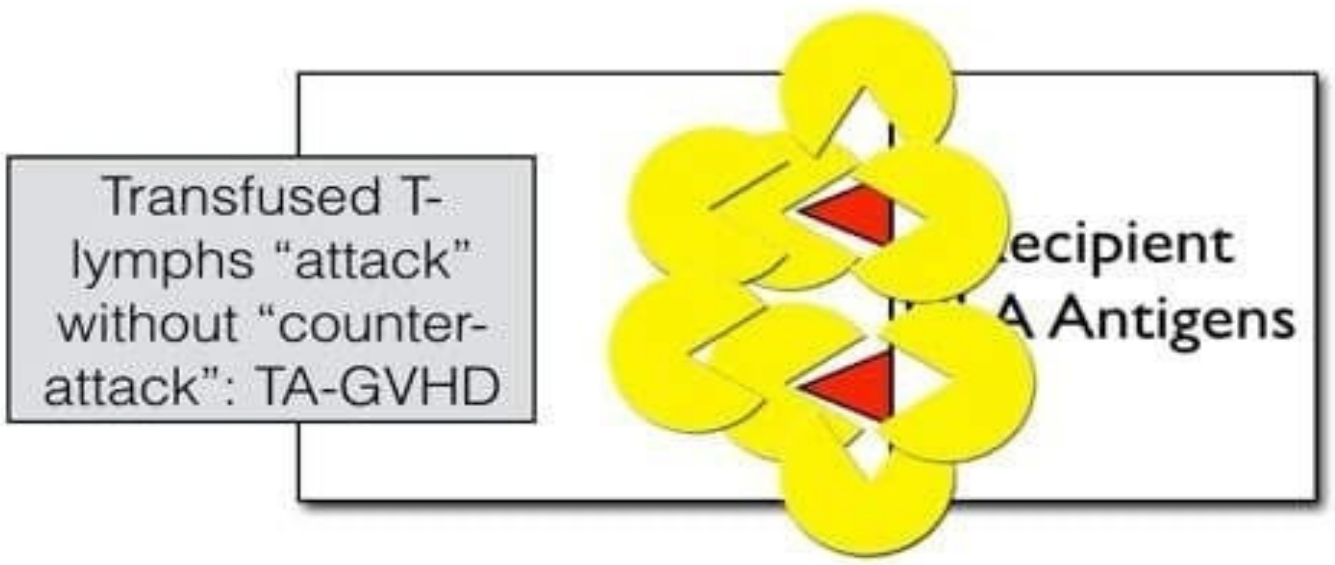
Counter-Attack!

Host is Immuno-compromised



Host is Immuno-compromised

TA-GVHD



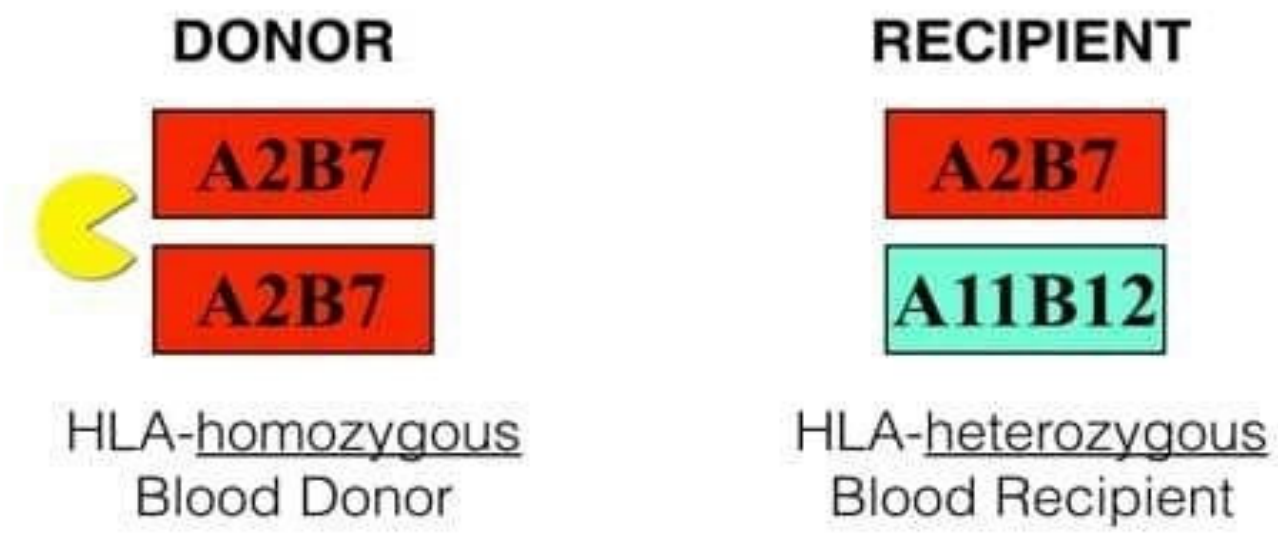
Skin, liver, GI tract, Bone marrow

Host is Immuno-competent

- **Directed Donation** (One way HLA match)- Most Common
- **Recipients of fresh blood** with lot of viable T-lymphocytes (granulocytes, fresh whole blood)
- **Cardiac bypass surgery** (In Japan)

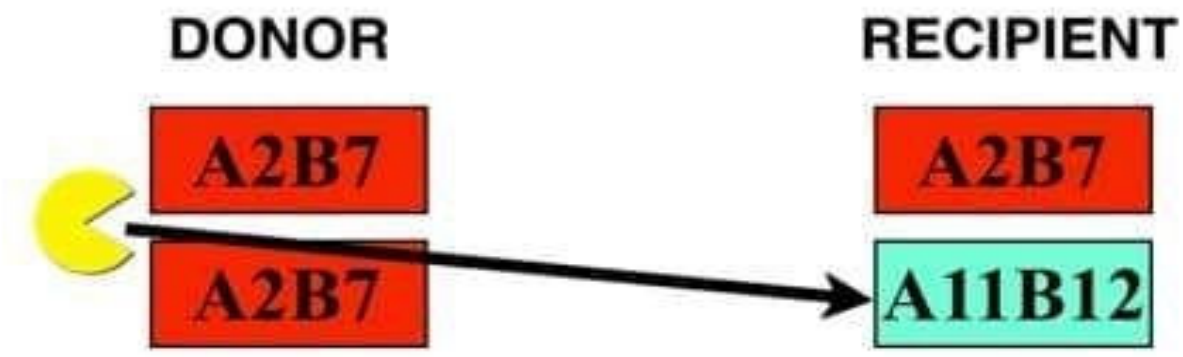
Host is Immuno-competent

One-Way HLA Match (1)



Host is Immuno-competent

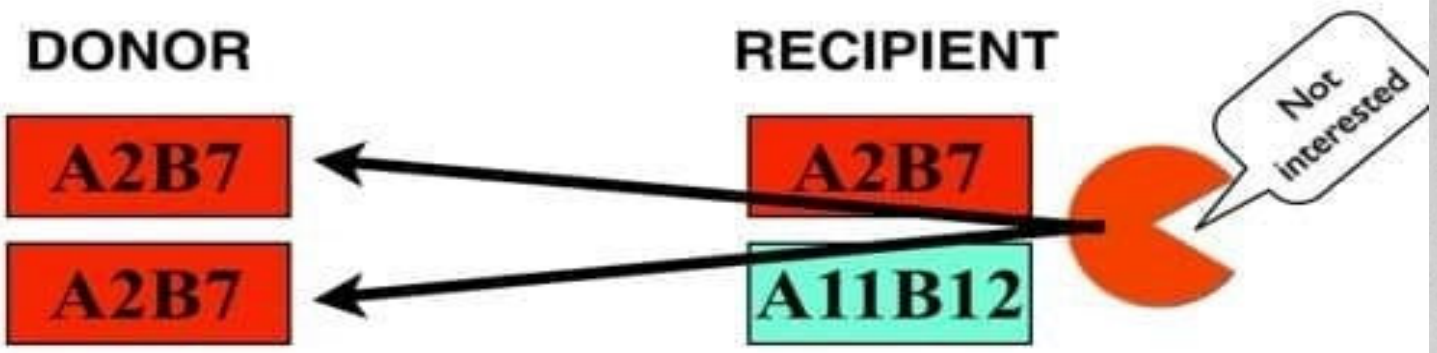
One-Way HLA Match (2)



Donor recognizes recipient as "foreign"
due to A11B12

Host is Immuno-competent

One-Way HLA Match (3)



Recipient does NOT think donor is "foreign"
(A2B7 is shared)

Host is Immuno-competent

Clinical Presentation

- Signs and symptoms usually begin 3-30 days after transfusion.
- Initially fever with skin manifestations
- Gastro Intestinal manifestations
- Hepatic dysfunction
- BM failure with pancytopenia
- Death often occurs with infection or bleeding manifestations

Skin Manifestations

- Erythematous maculopapular rash
- Pruritic
- Involves palms and soles and spreads throughout the body
- Blisters and ulcers - in severe cases.

GIT - Manifestations

- Diarrhoea – secretory, voluminous (>2L/day)
- Bleeding - life threatening intestinal hemorrhage.
- Nausea, vomiting.
- Anorexia
- Abdominal pain

Liver

- Jaundice and hepatomegaly
- Mainly cholestatic hepatitis
  - lymphocytic infiltration of portal tracts
  - damage to bile duct epithelium
  - consequent destruction of bile ducts.
- Increased liver enzymes
- Increased serum billirubin

Diagnosis

- TA-GVHD is probably underdiagnosed since it may be wrongly attributed to
  - Intercurrent infection
  - Severe drug reaction
  - Auto immune diseases
- Histopathological/hematological features and detection of donor lymphocytes or DNA (mixed chimerism)

Diagnostic testing

- **Skin biopsy**
  - superficial perivascular lymphocyte infiltrate
  - necrotic keratinocytes
  - bullae formation
- **Bone marrow examination**
  - Hypocellular/aplastic marrow
  - Only macrophages present
- **Liver biopsy**
  - Small bile duct degeneration & eosinophilic necrosis
  - Intense periportal inflammation
  - Lymphocytic infiltration

Definitive diagnosis-

Identification of donor derived lymphocytes in recipient circulation/tissues+ presence of clinical symptoms

Differential diagnosis

- Acute viral hepatitis
- Severe drug reaction
- Dengue fever and leptospirosis
- Acute sero-conversion illness due to HIV infection

Prognosis

- **Fatality**
  - Profound marrow aplasia
  - Mortality>90%(1-3weeks)

Management of Suspected/proven disease

- Must be treated in a specialized unit
- **High dose steroids** –First line - antilymphocyte and antiinflammatory activity
- **Methotrexate & Cyclosporine-A** – to prevent the disease
- **Steroid refractory GvHD**
  - – Anti-thymocyte globulin (ATG)
  - – Azathioprine
  - – Intravenous immunoglobulins
- **Supportive therapy** – Antibiotics
- **Stem cell transplantation**

Prevention

- Prevention is better than cure
- Gamma Irradiation of cellular Blood component

  - **25Gy**- centre of blood bag

  - **15Gy**-peripheral part of blood bag
- Photochemical treatment of platelets & plasma

When to Irradiate

- **At a minimum, cellular components shall be irradiated when:**

  1.A patient is identified as being at risk for TAGVHD

  2.The donor of the component is a blood relative of the recipient

  3.The donor is selected for HLA compatability, by typing or crossmatching.

AABB Technical Manual
Clinical Indications for Irradiated Components

- **Well-documented indications**
  - Intrauterine transfusions
  - Premature, low-birthweight infants
  - Newborns with erythroblastosis fetalis
  - Congenital immunodeficiencies
  - Hematologic malignancies or solid tumors (neuroblastoma, sarcoma, Hodgkin disease)
  - Components that are crossmatched, HLA matched, or directed donations
  - Fludarabine therapy
  - Granulocyte components

- **Potential indications**
  - Other malignancies, including those treated with cytotoxic agents
  - Donor-recipient pairs from genetically homogenous populations

- **Usually not indicated**
  - Patients with human immunodeficiency virus
  - Term infants
  - Non-immunosuppressed patients

General aspects about Irradiation of Blood components

- Lymphocyte viability is retained in stored red cells for at least 3 weeks
- TA-GvHD has been reported after transfusion of whole blood, red cells, platelets and granulocytes
- TA-GvHD has not been described following transfusion

- **frozen deglycerolized red cells**, which are thoroughly washed free of leucocytes after thawing.

- **cryoprecipitate**

- **fresh frozen plasma** or

- **fractionated plasma products**

Shelf Life of Irradiated Products

Irradiated Red Blood Cells

- Red cells can be irradiated up to 14 d after collection and stored for at least a further 14 d without significant loss of viability
- Shortened to 28 days after irradiation or until original expiration date, whichever comes first
- Where the patient is at particular risk from hyperkalaemia, e.g. intrauterine or neonatal exchange transfusion, it is recommended that red cells be transfused within 24 h of irradiation or that the cells are washed.

Platelets

- No effect of Gamma irradiation below 50 Gy on platelet function
- Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection.

Granulocytes

- The evidence for irradiation damage to granulocyte function is conflicting
- But in any case granulocyte products should be transfused as soon as possible after irradiation
- All granulocytes should be irradiated before issue and transfused with minimum delay.

Methods for Irradiation

- **Gamma Irradiators**
- **X-ray Irradiators**

(Gamma rays and X-rays are similar in their ability to inactivate T lymphocytes in blood components at a given absorbed dose)

Gamma Irradiators

- Both cesium and cobalt irradiators are available
- Expensive
- Disposal present significant difficulties
- These highly radioactive cores may present a security risk in hospital settings
- As the source decays, regular recalibration is required and irradiation time progressively increases
- Strict regulatory requirements are required

Cell Irradiator

X-ray Irradiators

- Less Expensive
- Absence of a radioactive source
- Fewer regulatory requirements

Effective Dose of Radiation

- Dose to the center of the irradiation field must be at least 25 Gy
- Minimum delivered dose delivered to any other portion must be 15 Gy
- No more than 50 Gy should be delivered to the product.
- Special labels (radiochromic film labels which change color upon being irradiated) are affixed to units to confirm irradiation of an adequate dosage
- Process takes 5minutes.

Cons of Irradiated Products

- **Reduced shelf life 35->28 days**
- **Leakage of potassium**
- **Theoretical risks**
  - **–Malignant change? Reactivation of latent virus? Plastic leakage?**
- **Practical issues**
  - **–Cost/upkeep/validation/security of irradiators**

Non-irradiation Prevention Strategies?

- **Leukocyte reduction** has been shown to reduce the risk of TAGVHD, especially in a genetically diverse population, but is not a substitute for irradiation in at-risk populations.
- **Psoralen (S59) + ultra-violet A** – used for pathogen inactivation

Conclusions

- **Prevention** is only the key for this deadly disease.
- All donor blood and blood products for **immuno compromised, suspected or potentially immuno-compromised patients** should be irradiated.
- As new potent immunosupressive drugs and biological agents are introduced into practice, there is a need for regular review of recommendations regarding irradiated blood components.

References

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Thank You