An update on the irradiation guidelines

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BSH

bjh guidelines

Guidelines on the use of irradiated blood components

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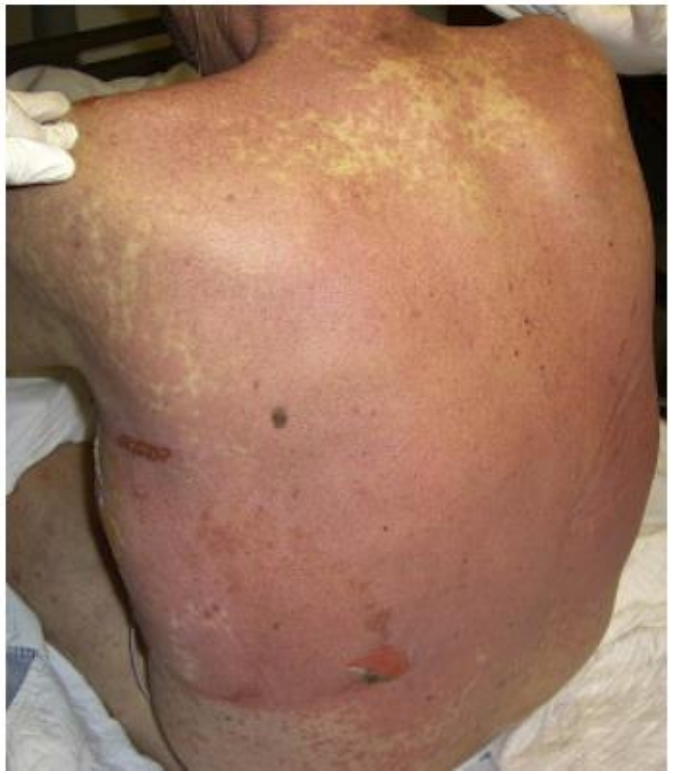
Recognising irradiated blood components

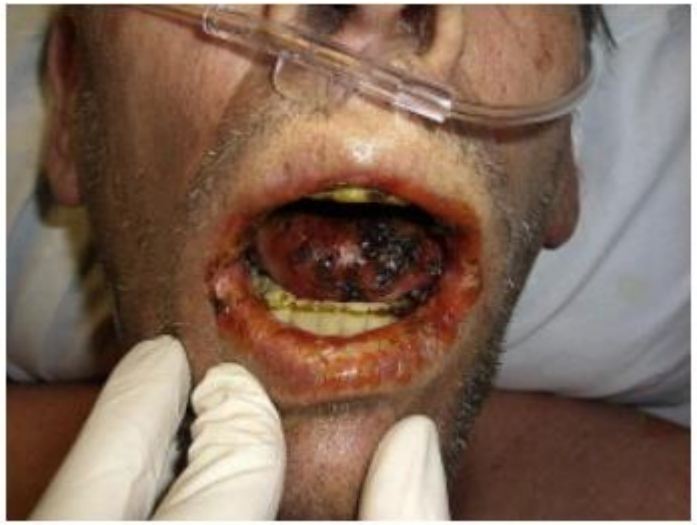
There are two types of RADTAG label for irradiated components

Gamma irradiated and X-Ray irradiated

Why do we irradiate cellular blood components?

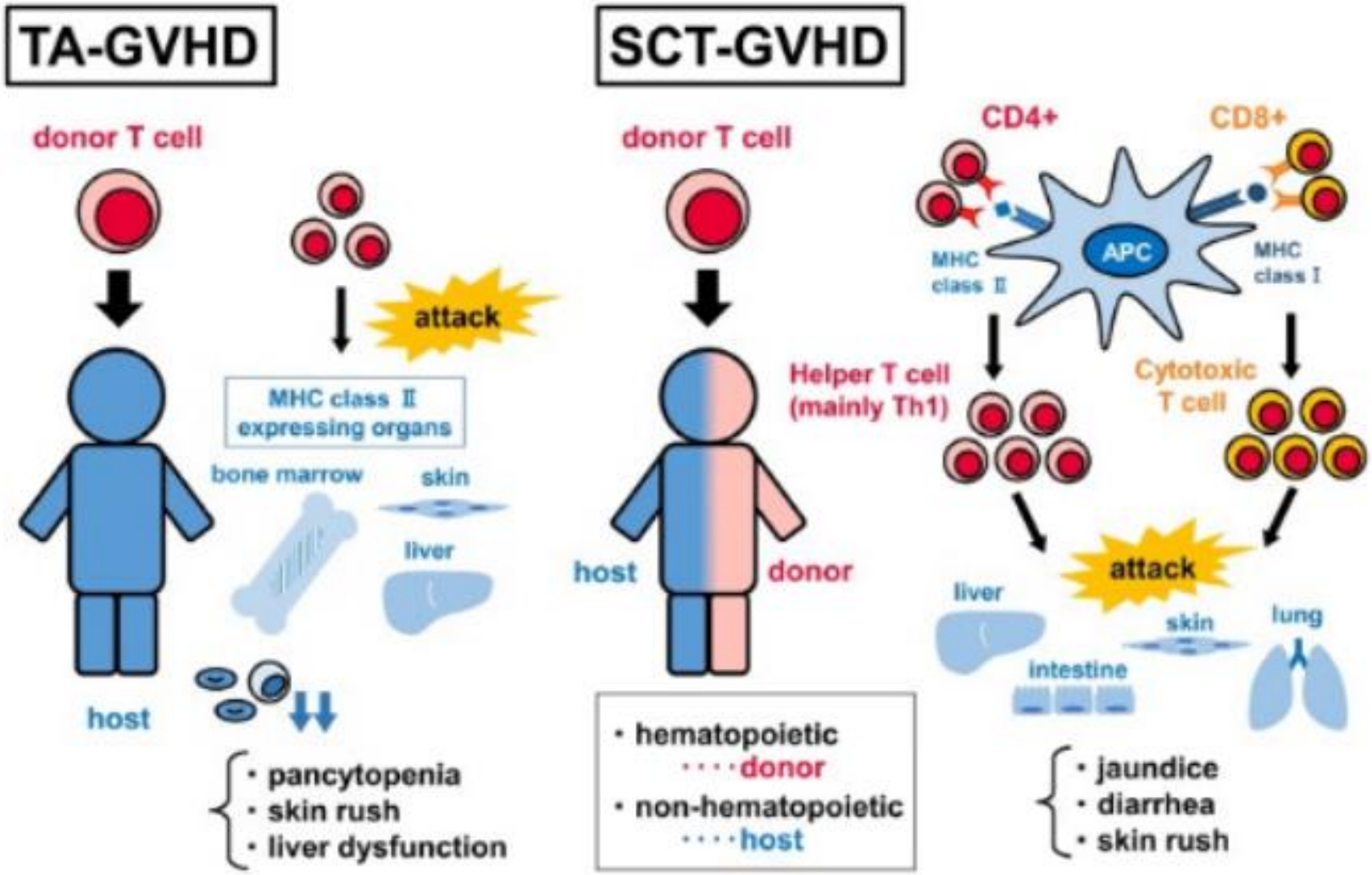
Transfusion associated graft versus host disease

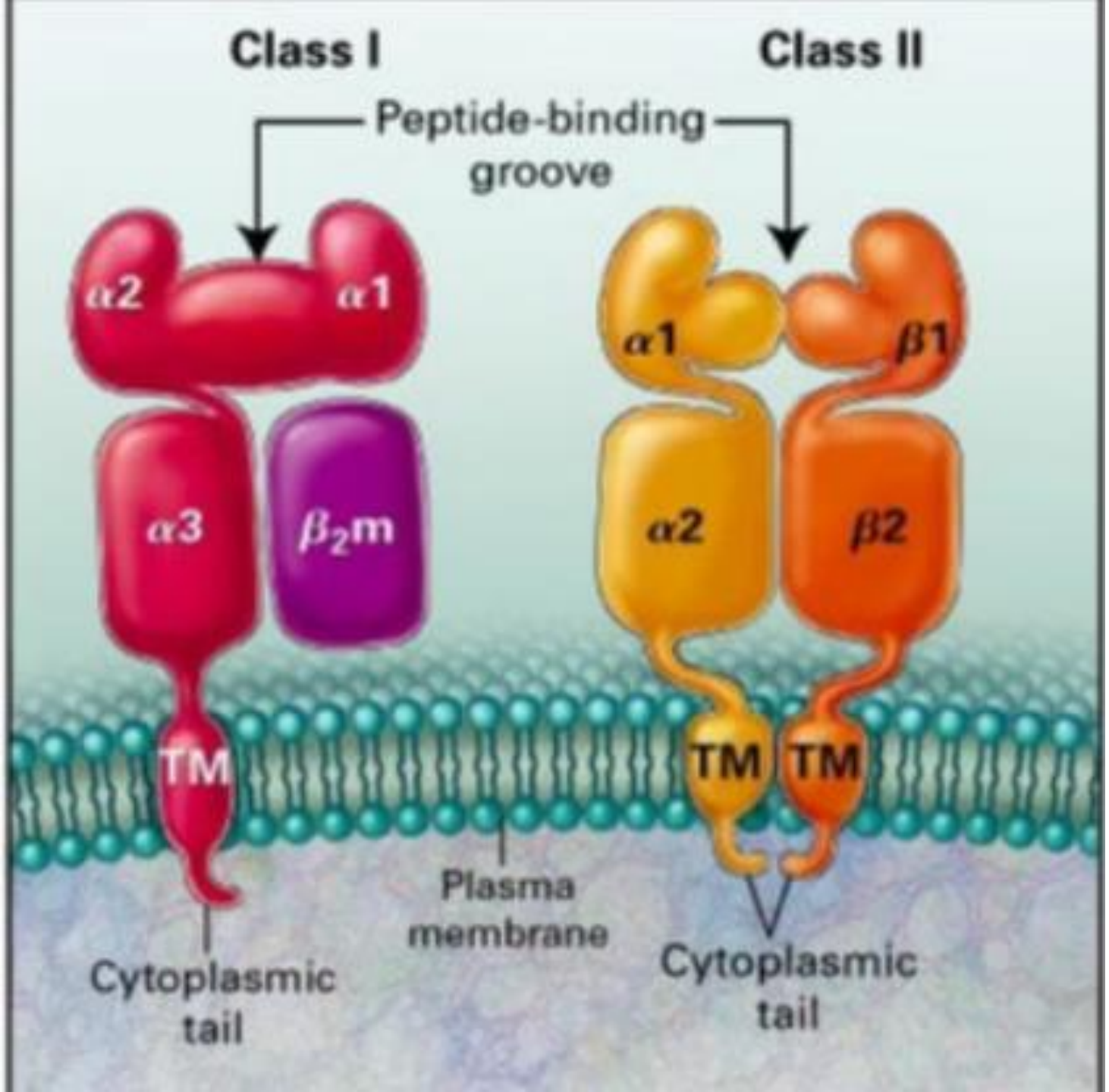




Today's presentation

- Pathophysiology of the condition
- Components requiring irradiation
- Patients at risk requiring irradiated blood components
- Transfusion in an emergency
- Areas for further research


TA-GVHD
donor T cell
attack
MHC class Ⅱ
expressing organs
bone marrow
skin
liver
host
・pancytopenia
・skin rush
・liver dysfunction
SCT-GVHD
donor T cell
host
donor
・hematopoietic
····donor
・non-hematopoietic
····host
CD4+
CD8+
APC
MHC
class Ⅱ
MHC
class Ⅰ
Helper T cell
(mainly Th1)
Cytotoxic
T cell
attack
liver
skin
lung
intestine
・jaundice
・diarrhea
・skin rush

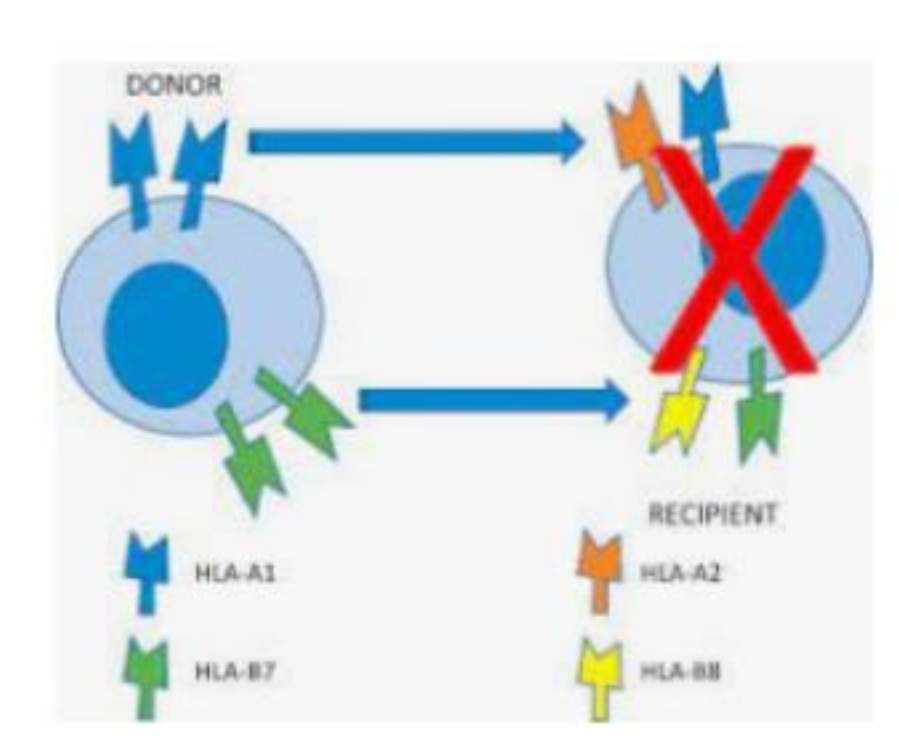


Graft and host interaction

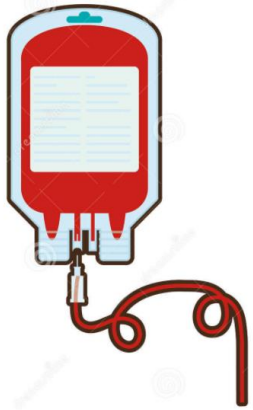
- Any cell displaying some other HLA type is "non-self" and is seen as an invader by the body's immune system, resulting in the rejection

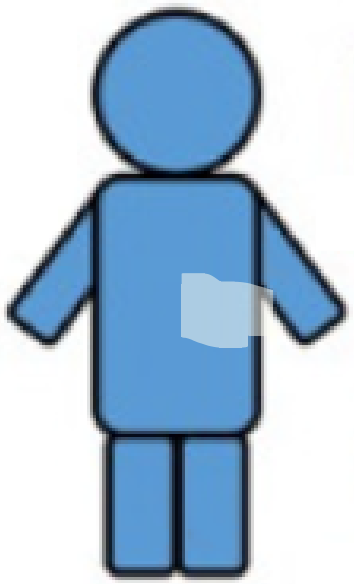
TA-GvHD

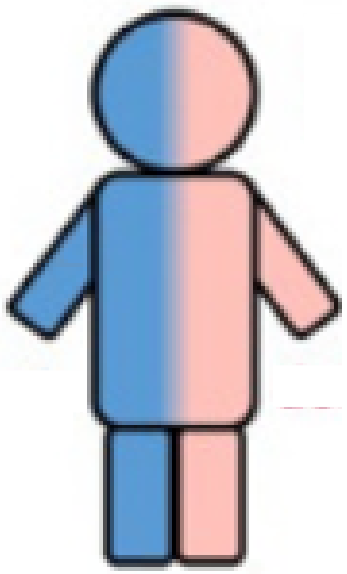
- Transfused cells recognized as foreign and destroyed by the recipient immune system. However, if there is partial HLA matching between the host and donor, the host immune system is less likely to destroy transfused donor T cells
- Partial HLA matching is more common in ethnically homogenous populations, such as the Japanese, or transfusion from family members. This typically occurs when the HLA haplotype of the transfused T cells is homozygous.
- Similarly, patients with primary or secondary immune deficiencies are also less likely to reject transfused donor T cells.



- TA-GVHD, T cells from the transfused blood product proliferate and expand in the recipient and attack tissues, such as the bone marrow and skin, expressing mismatched human leukocyte antigens (HLA). Tissue damage in TA-GVHD is caused by the Fas-mediated killing mechanism of CD4+ helper T cells and CD8+ cytotoxic T cells .
- In addition to Fas-mediated cytotoxicity, inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), and other immune cells, such as natural killer (NK) cells and macrophages, contribute to the pathogenesis of TA-GVHD. However, their contribution is less critical than in HCT-GVHD.

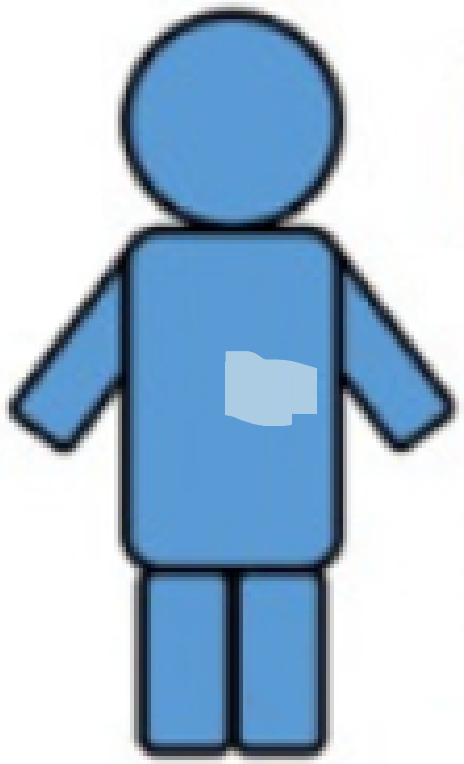




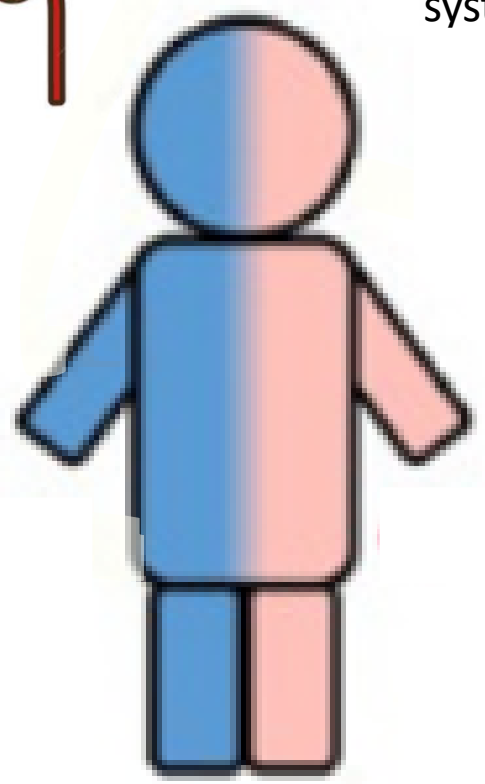


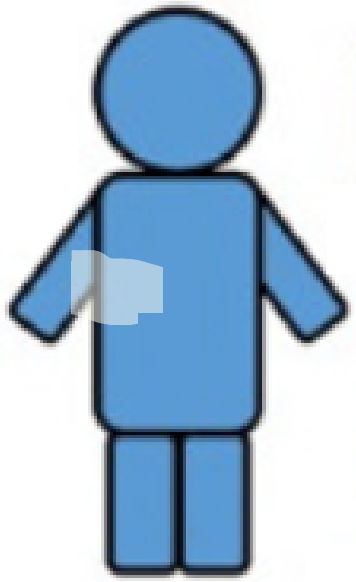
Quality of blood component (effectiveness of leucodepletion)

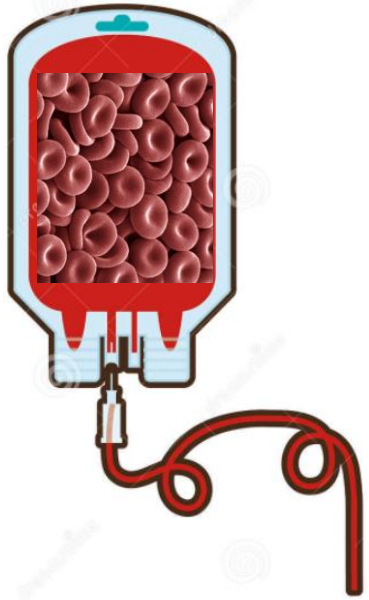
Patient’s immune system

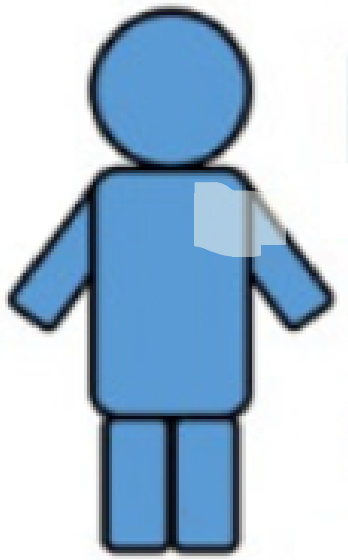


Disparity between the donor and the recipient









Limited literature

Case reports

SHOT data

Kopolovic I, Ostro J, Tsubota H, Lin Y, Cserti-Gazdewich CM, MessnerHA, et al. A systematic review of transfusion-associated graft-versus-hostdisease.Blood. 2015;126:406–14.

Table I. Summary of cases of TA-GvHD reported since 2008

Year	Case summary and reference
2008	4-year-old child with SCID[13]
2009	Family-directed transfusion during CABG[14]
2010	Goodpasture's syndrome[15]
2010	Whole blood transfusion[16]
2010	2 cases of TA-GvHD following non-irradiated blood given to SCID patients[17]
2010	7-month-old admitted to Paediatric Intensive Care Unit with infective complications of what was later confirmed to be combined immunodeficiency[18]
2010	Patient who received transfusion abroad, presumed family directed[19]
2010	56-year-old man given non-irradiated granulocyte transfusion[20]
2012	Family-directed transfusion[21]
2012	Afghanistan trauma resuscitation[22]
2012	Family-directed transfusion for anaemia due to malaria[23]
2012	52-year-old man given blood during CABG 11 years after treatment for HL[24]
2013	IUT[25]
2013	59-year-old following family-directed transfusion[26]
2013	Family-directed transfusion for post-operative bleeding[27]
2013	Delayed TA-GvHD in patient who received blood prior to liver transplant, and treated with anakinra[28]
2013	66-year-old given family-directed transfusion post-CABG[29]
2013	70-year-old male post liver transplant – convincing evidence of TA-GvHD responded to IL2 blockade[30]
2013	55-year-old male patient with acute lymphoblastic leukaemia previously treated with purine analogue (fludarabine)[31]
2016	5-year old with unexplained pancytopenia – TA-GvHD diagnosis not confirmed[32]
2016	45-year-old post hysterectomy received red cells from a sibling donor. A week later developed classical TA-GvHD and died 3 weeks after onset[33]
2017†	Neonate with haemophagocytic lymphohistiocytosis; TA-GVHD diagnosis based on skin biopsy[34]

Year	Diagnoses	Shared haplotype
1996–97	No risk factors – woman in her 80s transfused for epistaxis	NR
	Premature neonate, born at 32 weeks and multiply transfused prior to diagnosis of severe combined immunodeficiency	NR
	Two middle aged men with NHL	NR
		NR
1997–98	Coronary artery bypass surgery followed by transfusion of red cells <5-days-old	Yes
	Autoimmune thrombocytopenia treated only with oral steroids, transfused red cells and platelets	NR
	B-cell NHL in remission, transfused for GI bleeding	NR
	Waldenström's macroglobulinaemia	Yes
1998–99	Myeloma; woman in her 60s, 6 units of red cells 5–7-days-old. These were LD but unclear if pre-storage or at bedside	NR
	Uncharacterised immunodeficiency; 51-year-old man presented with pneumocystis pneumonia, transfused for GI bleeding	NR
	Cardiac surgery, a man in his 60s exposed to 32 donors	NR
	Cardiac surgery, a man in his 60s, 2 units of red cells	Yes
1999–2000	No cases reported	
2000–01	B-ALL, a teenager in the UKALL R2 trial (no fludarabine). Components irradiated in hospital. At relapse she received non-irradiated red cells and platelets (2 units of each)	NR
2001–11	No cases reported	
2012	IUT with maternal blood, therefore fresh, not LD, not irradiated, fully HLA matched with the fetus.[19]	Yes
2013–19	No cases reported	

ALL, acute lymphoblastic leukaemia; GI, gastrointestinal; NHL, non-Hodgkin lymphoma; NR, not recorded

Inactivation or elimination of lymphocytes in the transfused components

Irradiation
Leucocyte depletion
Pathogen inactivation.
Washing

Prevention of TA-GvHD

- **Gamma- or X-irradiation** of blood com-ponents, by validated systems, is the recommended procedure to prevent TA-GvHD
- There is **insufficient** evidence to recommend leucocyte depletion alone to prevent TA-GvHD insusceptible patients
- **Pathogen inactivation**.

Systems to pathogen inactivate platelets are now licensed in Europe. Due to their mechanism of action, as well as inactivating bacteria and viruses, they also inactivate lymphocytes. The manufacturers therefore claim that these systems can be used as an alternative to irradiation for the prevention of TA-GvHD, and many centres 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.

Components requiring irradiation

Red cells

Red cells may be irradiated at any time up to 14 days after collection, and thereafter stored for a further 14 days from irradiation. Where the patient is at risk from hyperkalaemia, e.g. IUT or neonatal EBT, or other large-volume transfusion of neonates and infants, is recommended that red cells are transfused within 24 h of irradiation.

If washed red cells are irradiated, they should be transfused as soon as possible and according to UK Blood Transfusion Services Guidelines.

Irradiated components not used for the intended recipient can be returned to stock to be used for recipients who do not require irradiated blood components

Platelets
Granulocytes

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

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

For all at-risk patients, all **red cell**, **platelet** and **granulocyte** components should be irradiated, except cryopreserved red cells after deglycerolisation. It is not necessary to irradiate fresh frozen plasma, cryoprecipitate or fractionated plasma

First or second degree relatives

All transfusions of cellular components and fresh plasma from first- or second-degree relatives should be irradiated, even if the patient is immunocompetent.

HLA selected compolents

All HLA-selected components should be irradiated even if the patient is immunocompetent

IUT	Red cells for IUT should be irradiated.
EBT	Red cells for neonatal EBT should be irradiated .
	As recommended above, red cells for IUT and EBT should be transfused within 24 h of irradiation

Patients at risk to develop TA-GvHD

All severe congenital T-lymphocyte immunodeficiency syndromes with significant qualitative or quantitative T-lymphocyte deficiency should be considered as indications for irradiation of cellular blood components.

Once a diagnosis of severe T-lymphocyte immunodeficiency has been suspected, irradiated components should be given while further diagnostic tests are being under-taken. A clinical immunologist should be consulted for advice in cases where there is uncertainty

Cardiac surgery in neonates and infants (and older patients)

Neonates and infants with suspected immunodeficiency syndromes

A quantitate approach to identify objectively patients at risk

- Neonates and infants with suspected immunodeficiency syndromes should undergo T-lymphocyte enumeration prior to cardiac surgery wherever possible.

- If the T-lymphocyte count is>400 cells/l, 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 infections, referred for elective cardiac surgery for problems associated with DiGeorge syndrome, such as aortic arch anomalies and pulmonary artery stenosis, or in whom DiGeorge anomaly is suspected, do not need to receive irradiated cellular blood components, unless there is a significant history consistent with severe T-lymphocyte-associated immunodeficiency, as the risk of TA-GvHDis extremely low

Haemopoietic Stem Cell transplantation

All recipients (adult and paediatric) of allogeneic HSCT should receive irradiated blood components from the time of initiation of conditioning chemo/radiotherapy. The recommendation applies for all conditions where HSCT is indicated regardless of the underlying diagnosis .

- Treatment with irradiated blood components should continue indefinitely if this is required based on transplant conditioning, underlying disease or previous treatment. previous diagnosis of HL or previous purine analogue treatment.

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>$1x10^9$ /L.
- The patient is free of active chronic GvHD4.
- The patient is off all immunosuppression
- If chronic GvHD is present or continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely .
- .

Stem cell and peripheral lymphocyte collection

Patients (adult and paediatric) under-going bone marrow or peripheral blood stem cell collections for future autologous re-infusion should receive irradiated cellular blood components for 7 days prior to and during the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially withstand cryopreservation.

Patients (adult and paediatric) under-going peripheral blood lymphocyte collections for future re-infusion

Allogeneic cellular blood components transfused to bone marrow and peripheral blood stem cell donors of all ages within 7 days prior to or during the harvest should also be irradiated

Autologous HSCT and CAR-T cell treatment

All patients undergoing ASCT irrespective of underlying diagnosis or indication for this treatment 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 conditioning, disease or previous treatment determine definite duration, for example previous diagnosis of HL or previous purine analogue treatment

CAR-T cell re-infusion should receive irradiated cellular blood components for 7 days prior to and during the harvest, to prevent the collection of viable allogeneic T lymphocytes. Irradiated blood components should continue to be used until 3 months following CAR-T cell infusion unless conditioning, disease or previous treatment deter-mine indefinite duration, e.g. previous diagnosis of HL or previous purine analogue treatment

Haematology patients

All adults and children with HL at any stage of the disease should have irradiated red cells and platelets indefinitely

All patients treated with purine analogue drugs (fludarabine, cladribine, bendamustine and pentostatin) should receive irradiated blood componentsindefinitely.

Patients with CLL or other haematological diagnosis treated with alemtuzumab should receive irradiated com-ponents .

Patients with aplastic anaemia undergoing treatment with ATG or alemtuzumab should receive irradiated bloodcomponents .Patients receiving ATG or other T-lymphocyte-depletingserotherapy for rare types of immune dysfunction condi-tions should receive irradiated blood components.

Irradiation is NOT required (paediatric practice)

Routine irradiation of red cells for transfusion to preterm or term infants (other than for EBT) is not required unless there has been a previous IUT, in which case irradiated components should be adminis-tered until 6 months after the expected delivery date(40 weeks gestation).

Routine irradiation of platelet transfusions for preterm or term infants is not required unless there has been a previous IUT, in which case irradiated components should be administered until 6 months after the expected delivery date (40-weeks gestation)

There is 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. There is also no indication for irradiation of cellular blood components for adults or children who are HIV-antibody positive or who have acquired immune deficiency syndrome (AIDS)

Irradiation is not indicated

- For patients with aplastic anaemia, transfusion of irradiated cellular components is not rou-tinely recommended, except for HLA-selected platelets, transfusion of granulocytes, donations from first- or sec-ond-degree relatives, or planned relevant treatment (e.g.ATG, alemtuzumab, HSCT)

- Use of irradiated components for adult patients or children treated for acute leukaemia or NHL(including CLL unless treated with alemtuzumab) is not routinely recommended except for HLA-selected platelets, of granulocytes, donations from first- or second-degree relatives, or due to current or previous treatment.

Irradiation is not indicated

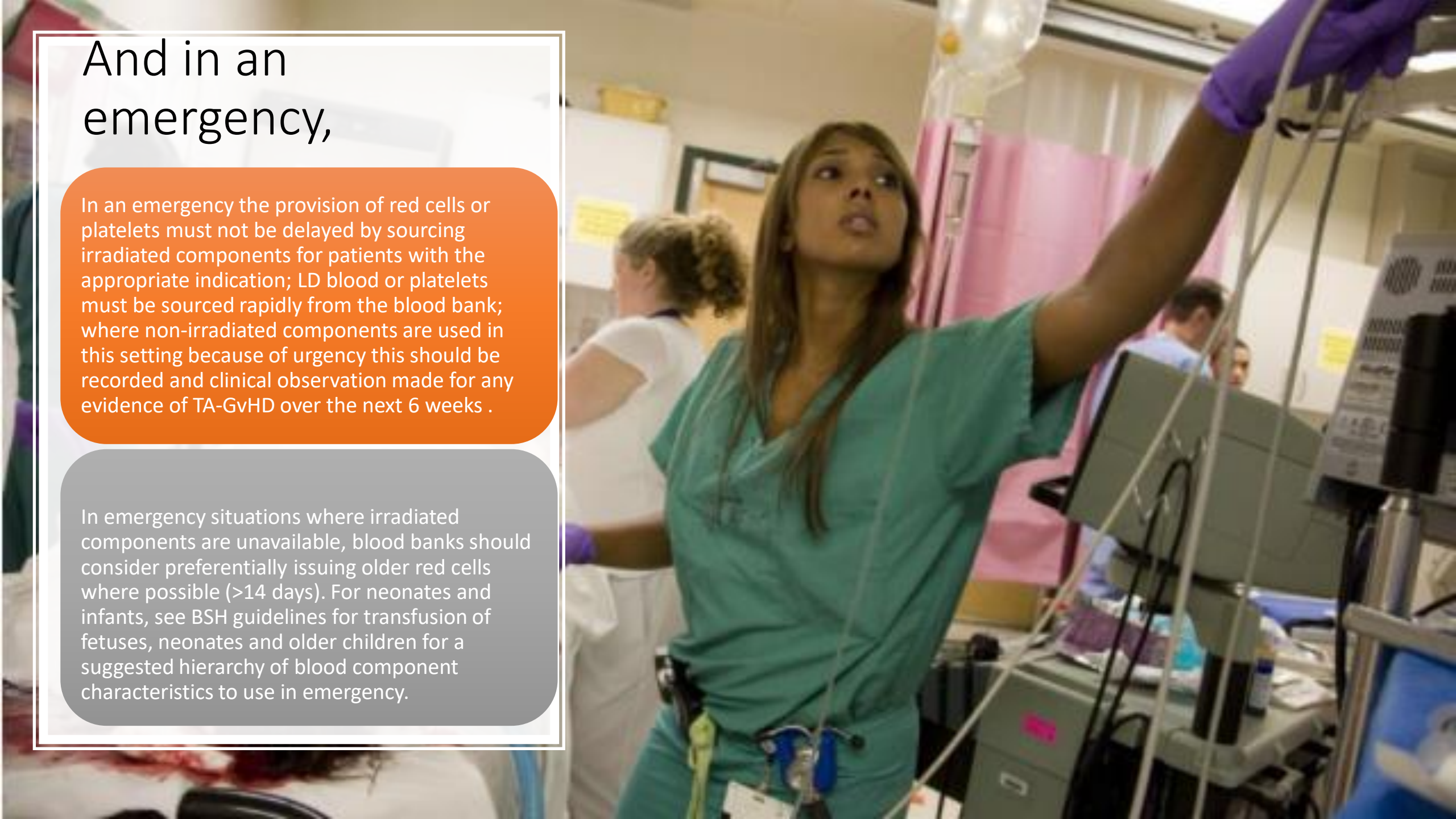
Use of irradiated cellular blood components is not indicated following treatment with alemtuzumab using the schedule currently recommended for MS or vasculitis .

Use of irradiated cellular blood components is not indicated for patients undergoing solid organ transplantation who have received alemtuzumab or ATG as induction therapy or for treatment of graft rejection

And in an emergency,

In an emergency the provision of red cells or platelets must not be delayed by sourcing irradiated components for patients with the appropriate indication; LD blood or platelets must be sourced rapidly from the blood bank; where non-irradiated components are used in this setting because of urgency this should be recorded and clinical observation made for any evidence of TA-GvHD over the next 6 weeks .

In emergency situations where irradiated components are unavailable, blood banks should consider preferentially issuing older red cells where possible (>14 days). For neonates and infants, see BSH guidelines for transfusion of fetuses, neonates and older children for a suggested hierarchy of blood component characteristics to use in emergency.



Responsibilities

Where patients require irradiated cellular blood components, components must be requested and clearly prescribed as irradiated.

Specific requirements, including need for irradiated blood components, must be part of the bedside check prior to administration of all blood components with documentation of checks.

Clinical areas and transfusion laboratories should agree and implement communication processes to ensure specific requirements and provision of irradiated cellular blood components are met for patients under shared care.

Patients requiring irradiated cellular blood componentsshould receive appropriate information. Where possible patients should carry cards to facilitate provision of appropriate components

Recommendations for further research

Is it necessary to provide lifelong irradiated cellular blood components for all patients treated with purine analogues?
Is it necessary to provide lifelong irradiated cellular blood components for all patients with a history of HL regardless of stage or therapy?
Further research should be untaken on the immunological status of neonates and infants following IUT to investigate whether it is necessary to provide irradiated cellular blood components to these recipients.
Research should continue into methods of pathogen inactivation, which may also reduce the risk of TA-GvHD. These technologies will need validation by blood establishment and wider consultation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