An update on the irradiation guidelines

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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.
Why do we irradiate cellular blood components?

Transfusion associated graft versus host disease
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**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
- Helper T cell (mainly Th1)
- CD4+, CD8+
- MHC class II, I
- APC
- Cytotoxic T cell
- liver, intestine, skin, lung
- host
- hematopoietic, non-hematopoietic
- 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)

Disparity between the donor and the recipient

Patient’s immune system
Limited literature

Case reports

SHOT data

<table>
<thead>
<tr>
<th>Year</th>
<th>Case summary and reference</th>
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<tr>
<td>2008</td>
<td>4-year-old child with SCID\textsuperscript{13}</td>
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<td>2009</td>
<td>Family-directed transfusion during CABG\textsuperscript{14}</td>
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<td>2010</td>
<td>Goodpasture’s syndrome\textsuperscript{15}</td>
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<td>2010</td>
<td>Whole blood transfusion\textsuperscript{16}</td>
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<tr>
<td>2010</td>
<td>2 cases of TA-GvHD following non-irradiated blood given to SCID patients\textsuperscript{17}</td>
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<td>2010</td>
<td>7-month-old admitted to Paediatric Intensive Care Unit with infective complications of what was later confirmed to be combined immunodeficiency\textsuperscript{18}</td>
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<td>2010</td>
<td>Patient who received transfusion abroad, presumed family directed\textsuperscript{19}</td>
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<td>2010</td>
<td>56-year-old man given non-irradiated granulocyte transfusion\textsuperscript{20}</td>
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<td>2012</td>
<td>Family-directed transfusion\textsuperscript{21}</td>
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<td>2012</td>
<td>Afghanistan trauma resuscitation\textsuperscript{22}</td>
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<tr>
<td>2012</td>
<td>Family-directed transfusion for anaemia due to malaria\textsuperscript{23}</td>
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<td>2012</td>
<td>52-year-old man given blood during CABG 11 years after treatment for HT\textsuperscript{24}</td>
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<td>2013</td>
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<td>2013</td>
<td>59-year-old following family-directed transfusion\textsuperscript{26}</td>
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<tr>
<td>2013</td>
<td>Family-directed transfusion for post-operative bleeding\textsuperscript{27}</td>
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<tr>
<td>2013</td>
<td>Delayed TA-GvHD in patient who received blood prior to liver transplant, and treated with anakinra\textsuperscript{28}</td>
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<tr>
<td>2013</td>
<td>66-year-old given family-directed transfusion post-CABG\textsuperscript{29}</td>
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<tr>
<td>2013</td>
<td>70-year-old male post liver transplant – convincing evidence of TA-GvHD responded to IL2 blockade\textsuperscript{30}</td>
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<td>2013</td>
<td>55-year-old male patient with acute lymphoblastic leukaemia previously treated with purine analogue (fludarabine)\textsuperscript{31}</td>
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<tr>
<td>2016</td>
<td>5-year old with unexplained pancytopenia – TA-GvHD diagnosis not confirmed\textsuperscript{32}</td>
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<td>2016</td>
<td>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\textsuperscript{33}</td>
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<tr>
<td>2017*</td>
<td>Neonate with haemophagocytic lymphohistiocytosis; TA-GVHD diagnosed based on the biopsy\textsuperscript{34}</td>
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<tr>
<td>Year</td>
<td>Diagnoses</td>
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</table>
| 1996–97  | No risk factors – woman in her 80s transfused for epistaxis  
               Premature neonate, born at 32 weeks and multiply transfused prior to diagnosis of severe combined immunodeficiency  
               Two middle aged men with NHL                                                                                                                  | NR               |
| 1997–98  | Coronary artery bypass surgery followed by transfusion of red cells <5-days-old  
               Autoimmune thrombocytopenia treated only with oral steroids, transfused red cells and platelets  
               B-cell NHL in remission, transfused for GI bleeding  
               Waldenström’s macroglobulinaemia                                                                                                             | Yes NR           |
| 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  
               Uncharacterised immunodeficiency; 51-year-old man presented with pneumocystis pneumonia, transfused for GI bleeding  
               Cardiac surgery, a man in his 60s exposed to 32 donors  
               Cardiac surgery, a man in his 60s, 2 units of red cells                                                                                   | NR               |
| 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.                                                                                                          | 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 components, by validated systems, is the recommended procedure to prevent TA-GvHD

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

HLA selected components

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

All HLA-selected components should be irradiated even if the patient is immunocompetent.
Red cells for IUT should be irradiated.

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-GvHD is extremely low.
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 >1x10⁹ /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 required, irradiated blood components should be given indefinitely.
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.
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 determine indefinite duration, e.g. previous diagnosis of HL or previous purine analogue treatment.
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 components indefinitely.

Patients with CLL or other haematological diagnosis treated with alemtuzumab should receive irradiated components.

Patients with aplastic anaemia undergoing treatment with ATG or alemtuzumab should receive irradiated blood components. Patients receiving ATG or other T-lymphocyte-depletingserotherapy for rare types of immune dysfunction conditions 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 administered 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 routinely recommended, except for HLA-selected platelets, transfusion of granulocytes, donations from first- or second-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.
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

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<th>Where patients require irradiated cellular blood components, components must be requested and clearly prescribed as irradiated.</th>
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<td>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.</td>
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<tr>
<td>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.</td>
</tr>
<tr>
<td>Patients requiring irradiated cellular blood componentsshould receive appropriate information. Where possible patients should carry cards to facilitate provision of appropriate components</td>
</tr>
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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 undertaken 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.