

Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force

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Background and methods

The following were searched systematically for publications in English, until June, 2009:

PubMed – from 1950
 Medline – from 1950
 EMBASE – from 1980
 CINAHL (Cumulative Index to Nursing and Allied Health Literature) – from 1982
 The Cochrane Library 2008, Issue 3
 DARE CRD Website (Centre for Reviews and Dissemination)
 SRI (Systematic Review Initiative) Handsearch Databases

Search terms included: Transfusion-associated graft-versus-host disease, Transfusion-associated graft-versus-host, TA-GvHD. The last guideline covering this topic was published in 1996 (British Committee for Standards in Haematology (BCSH) Blood Transfusion Task Force, 1996). The writing group produced the new draft guideline, which was subsequently revised by consensus by members of the Haemato-oncology and Blood Transfusion Task Forces of the BCSH. The guideline was then reviewed by a sounding board of approximately 100 UK haematologists, the BCSH and the committee

of the British Society for Haematology and amended, again by consensus.

Criteria used to quote levels and grades of evidence are according to the GRADE system (Guyatt *et al*, 2006). Strong recommendations (grade 1, 'recommended') are made when there is confidence that the benefits either do or do not outweigh the harm and burden and costs of treatment. Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation ('suggested') is made. Grade 1 recommendations can be applied uniformly to most patients whereas grade 2 recommendations require judicious application. The quality of evidence is graded as A (high quality randomized clinical trials), moderate (B) or low (C).

This publication reports the key recommendations of the Writing Group. It is also accessible at <http://www.bcsguide lines.com>.

Purpose and objectives

To provide healthcare professionals with clear guidance on situations when the use of irradiated blood components is appropriate, and to document any recognized advantages and disadvantages of their use. The guidance may not be appropriate in all patient situations, and individual circumstances may dictate an alternative approach. Studies of patients in all age groups have been considered.

Major changes since the last Guideline

- Use of X-irradiation as an alternative to gamma irradiation.
- All cases of transfusion-associated graft-versus host disease and all episodes where non-irradiated components are transfused to *high risk* patients should be reported to national haemovigilance systems [in the UK, the Serious Hazards of Transfusion (SHOT) initiative].
- Irradiated components are recommended for aplastic anaemia patients receiving immunosuppressive therapy with anti-thymocyte globulin (ATG).

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- Indication for irradiated components extended to newer purine analogues and related drugs until evidence of their safety is forthcoming (e.g. bendamustine and clofarabine).
- Irradiated components indicated for patients receiving the biological immunosuppressive agent *alemtuzumab* (anti-CD52), but not *rituximab* (anti-CD20) – regular review will be needed as new biological agents enter clinical practice.

Summary of key recommendations

- All cases of transfusion-associated graft-versus-host disease (TA-GvHD) should be reported to the national haemovigilance system, as should all ‘near misses’ where non-irradiated components are transfused to high-risk patients without incident (1B).
- Gamma or X-irradiation of blood components, by validated systems, is the recommended procedure to prevent TA-GvHD (1B).
- The minimum dose achieved in the irradiated volume should be 25 Gy, with no part receiving more than 50 Gy (1B).
- For at-risk patients, all red cell, platelet and granulocyte concentrates should be irradiated except cryopreserved red cells after deglycerolization. It is not necessary to irradiate fresh frozen plasma, cryoprecipitate or fractionated plasma products (1B).
- All donations from first- or second-degree relatives should be irradiated, even if the patient is immunocompetent (1B).
- All human leucocyte antigen (HLA)-selected components should be irradiated, even if the patient is immunocompetent (2C).
- Red cells may be irradiated at any time up to 14 d after collection, and thereafter may be stored for a further 14 d. 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 (1A).
- Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection (1A).
- All granulocyte components should be irradiated before issue and transfused with minimum delay (1C).
- Irradiated components not used for the intended recipient can safely be returned to stock to be used for recipients who do not require irradiated components. The reduction in shelf life must be observed (1B).
- All irradiated components should be labelled as such, using an approved bar code label. Each unit should be monitored using a radiation-sensitive device, and the result permanently recorded, manually or by computer (1C).
- All blood for intrauterine transfusion (IUT) should be irradiated (1B). It is essential to irradiate blood for neonatal exchange transfusion (ET) if there has been a previous IUT or if the donation comes from a first- or second-degree relative (1B). For other neonatal ET cases, irradiation is recommended provided this does not unduly delay transfusion (1C). For IUT and ET, blood should be transfused within 24 h of irradiation and, in any case, by 5 d or less from collection (1A).
- It is not necessary to irradiate red cells for routine ‘top-up’ transfusions of premature or term infants unless either 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), or the donation has come from a first- or second-degree relative (2C).
- Platelets transfused in utero to treat alloimmune thrombocytopenia should be irradiated and any subsequent red cell or platelet transfusions irradiated until 6 months after the expected date of delivery (40 weeks gestation). There is no need to irradiate other platelet transfusions for pre-term or term infants, unless they have been donated by first- or second-degree relatives (1C).
- All severe T lymphocyte immunodeficiency syndromes should be considered as indications for irradiation of cellular blood components. Once a diagnosis of immunodeficiency has been suspected, irradiated components should be given while further diagnostic tests are being undertaken. A clinical immunologist should be consulted for advice in cases where there is uncertainty (1A).
- There is no indication for routine irradiation of cellular blood components for infants or children who are suffering from a common viral infection, who are human immunodeficiency virus (HIV) antibody positive, or who have acquired immunodeficiency syndrome (AIDS). However, this should be kept under review. There is also no indication for routine irradiation of cellular blood components for adults who are HIV antibody positive or who have AIDS (2B).
- There is no need to irradiate red cells or platelets for infants undergoing cardiac surgery unless clinical or laboratory features suggest a coexisting T lymphocyte immunodeficiency syndrome (2B).
- It is not necessary to irradiate red cells or platelets for adults or children with acute leukaemia, except for HLA-selected platelets or donations from first- or second-degree relatives (1B).
- All recipients of allogeneic haemopoietic stem cell transplantation (SCT) must receive irradiated blood components from the time of initiation of conditioning chemoradiotherapy (1B). This should be continued while the patient continues to receive graft-versus-host disease (GvHD) prophylaxis, i.e. usually for 6 months post-transplant, or until lymphocytes are $>1 \times 10^9/l$. If chronic GvHD is present or if continued immunosuppressive treatment is required, irradiated blood

components should be given indefinitely (2C). Allogeneic blood transfused to bone marrow and peripheral blood stem cell donors 7 d prior to or during the harvest should also be irradiated (2C).

- Patients undergoing bone marrow or peripheral blood stem cell 'harvesting' for future autologous re-infusion should receive irradiated cellular blood components during and for 7 d before the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes which can potentially withstand cryopreservation (2C).
- All patients undergoing autologous bone marrow transplant or peripheral blood stem cell transplant 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) (2C).
- All adults and children with Hodgkin lymphoma at any stage of the disease should have irradiated red cells and platelets for life (1B).
- Patients treated with purine analogue drugs (fludarabine, cladribine and deoxycoformycin) should receive irradiated blood components indefinitely (1B). The situation with other purine antagonists and new and related agents, such as bendamustine and clofarabine, is unclear, but use of irradiated blood components is recommended as these agents have a similar mode of action. Irradiated blood components should be used after alemtuzumab (anti-CD52) therapy. Their use after rituximab (anti-CD20) is not recommended at this time. As new potent immunosuppressive drugs and biological agents are introduced into practice there is a need for regular review of these recommendations (2C).
- It is not necessary to irradiate blood components for patients undergoing routine surgery, those with solid tumours HIV infection, autoimmune diseases or after solid organ transplantation (unless alemtuzumab (anti-CD52) has been used in the conditioning regimen). The effects of new regimens of chemo- and immunotherapy entering clinical practice must continue to be monitored (2C).
- In view of the recent switch from horse anti-thymocyte globulin (ATG) to the more immunosuppressive rabbit ATG, we now recommend use of irradiated blood components for aplastic anaemia patients receiving immunosuppressive therapy with ATG (and/or alemtuzumab) (2C). We cannot make a firm recommendation as to how long irradiated components should continue to be used after ATG administration.
- Patients at risk of TA-GvHD should be made aware of their need for irradiated blood components and provided with appropriate written information and an alert-card for clinical staff. We endorse the recommendations from SHOT (<http://www.shotuk.org>) relating to improved clinical and laboratory awareness, documentation and communication of special requirements for

transfusion, including irradiated components. Initiatives to improve laboratory and clinical information management systems (including IT links with Pharmacy and diagnostic services to highlight 'at risk' patients) should be incorporated into local policies and regularly audited. Poor communication between centres involved in 'shared care' of patients is a well-reported hazard and the development of a standardized national system for recording and transferring details of special transfusion requirements is an urgent requirement to improve patient safety. (2C).

More detailed recommendations on ensuring special transfusion requirements are met are given in the BCSH Administration of Blood Components Guideline 2009 (<http://www.bcsghguidelines.com>). Information leaflets for patients and healthcare staff are available from the UK Blood Services. Table I depicts a summary of the key recommendations.

Introduction

TA-GvHD is a very rare but usually fatal complication following transfusion of lymphocyte-containing blood components. Although the first reports concerned cases where viable allogeneic lymphocytes had been transfused into immunosuppressed recipients (von Fliedner *et al*, 1982; Burns *et al*, 1984; Anderson & Weinstein, 1990), it became apparent that non-immunosuppressed patients could also experience this problem, particularly if the blood components they received came from an HLA haploidentical unrelated donor or family member (Ohto *et al*, 1992; Aoun *et al*, 2003; Serefhanoglu *et al*, 2005; Triulzi *et al*, 2006; Agbaht *et al*, 2007).

The risk associated with an individual transfusion depends on the number and viability of contaminating lymphocytes, susceptibility of the recipient's immune system to their engraftment and degree of immunological (HLA) disparity between donor and patient. The minimum number of transfused lymphocytes necessary to provoke a GvHD reaction is unknown and may vary by clinical settings. Until recently, gamma irradiation of cellular blood components has been the mainstay of TA-GvHD prevention and practice was standardized in the UK following publication of the 1996 version of this BCSH Guideline (BCSH Blood Transfusion Task Force, 1996).

Pathogenesis, clinical features and diagnosis of TA-GvHD

Pathogenesis

TA-GvHD is a potential complication of transfusion of any blood component containing viable T lymphocytes when there is disparity in the histocompatibility antigens between donor and recipient. As well as the classical skin, gut and liver involvement seen in GvHD occurring after allogeneic stem cell transplantation, TA-GvHD is characterized by profound marrow hypoplasia and mortality in excess of 90% (Aoun

Table I. Summary of key recommendations.

Irradiation	Products requiring irradiation	National haemovigilance reporting	When to irradiate	Fetal/neonatal irradiation requirements	Infant/child irradiation requirements	Situations/disorders mandating irradiated components	Awareness issues
Dose: 25-50 Gy	All cellular components: red cells, white cells platelets	All cases of TA-GvHD	Red cells: up to 14 d after collection. May then be stored for a further 14 d except where patient is at particular risk from hyperkalaemia	All red cells for intrauterine transfusion	All severe T-lymphocyte immunodeficiency syndromes	All allogeneic HSCT recipients from time of conditioning therapy, continued while patient is receiving GvHD prophylaxis. If chronic GvHD present or taking immunosuppressants irradiated components required indefinitely	'At-risk' patients should be aware of their need for irradiated components and given written information and an alert-card
Source: Gamma or X	Donations from first- or second-degree relatives	All 'near misses'	Platelets: at any stage during storage. May then be stored for normal shelf life.	Red cells for neonatal exchange if prior IUT or if donation from first- or second-degree relative	Unnecessary for infants or children with a viral infection, who are HIV antibody positive, or who have AIDS	Allogeneic blood transfused to stem cell donors 7 d prior to or during harvest should also be irradiated	Initiatives to improve laboratory and clinical information management systems should be put in place in pharmacy and diagnostic services and policies regularly audited
Unused irradiated components can be returned to stock for general use	HLA-selected components	Granulocytes should be transfused ASAP after irradiation	For other neonatal ET cases, irradiation recommended if transfusion will not be unduly delayed	Patients undergoing autologous stem cell transplantation from start of conditioning therapy until 3 months post-transplant (6 months if total body irradiation was used)	Standardized national system for recording/transferring details of special transfusion requirements urgently required		

Table I. Continued.

Irradiation	Products requiring irradiation	National haemovigilance reporting	When to irradiate	Fetal/neonatal irradiation requirements	Infant/child irradiation requirements	Situations/disorders mandating irradiated components	Awareness issues
Irradiated components should be labelled. Units should be monitored with a radiation-sensitive device, and result permanently recorded				For IUT and ET, blood should be transfused within 24 h of irradiation and by 5 d or less from collection		Patients undergoing bone marrow or peripheral blood stem cell 'harvesting' for future autologous re-infusion during and for 7 d before harvesting	
				Red cell irradiation unnecessary for routine 'top-ups' of premature or term infants unless prior IUT given, or donation is from first- or second-degree relative		All individuals with Hodgkin lymphoma at any stage	
				Platelets transfused <i>in utero</i> to treat alloimmune thrombocytopenia should be irradiated as should any subsequent red cells or platelets until 6 months after the expected date of delivery. No need to irradiate other platelet transfusions for pre-term or term infants, unless donated by a first- or second-degree relative		Patients with aplastic anaemia receiving ATG (and/or alemtuzumab)	

Table I. Continued.

Irradiation	Products requiring irradiation	National haemovigilance reporting	When to irradiate	Fetal/neonatal irradiation requirements	Infant/child irradiation requirements	Situations/disorders mandating irradiated components	Awareness issues
						<p>Unnecessary for adults or children with acute leukaemia, <u>except</u> for HLA-selected platelets or donations from first- or second-degree relatives</p> <p>After purine analogues (fludarabine, cladribine and deoxycoformicin)</p> <p>Situation with other purine antagonists and new and related agents, such as bendamustine and clofarabine, currently unclear, but use of irradiated components is recommended as mode of action similar.</p> <p>After alemtuzumab (anti-CD52)</p> <p>Unnecessary for patients undergoing routine surgery, those with solid tumours, HIV infection, autoimmune diseases or after solid organ transplantation (unless alemtuzumab was used in conditioning).</p>	

TA-GvHD, transfusion-associated graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; GvHD, graft-versus-host disease; IUT, intrauterine transfusion; ET, exchange transfusion; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HLA, human leucocyte antigen; ASAP, as soon as possible.

et al, 2003; Williamson *et al*, 2007). There is a particular risk of TA-GvHD when the donor and patient share an HLA haplotype, as occurs within families (Petz *et al*, 1993), or in populations with restricted haplotype diversity (Yasuura *et al*, 2000). In the Japanese population, the incidence of TA-GvHD is 10–20 times higher than in the North American Caucasian population. (Shivdasani *et al*, 1993).

Clinical features

The early features are fever, maculopapular skin rash, diarrhoea and hepatitis occurring 1–2 weeks after transfusion. Bone marrow involvement produces severe hypoplasia with profound pancytopenia.

Diagnosis

Diagnosis is usually made by biopsy of skin, gut or liver supported by evidence of persistence of donor lymphocytes. The presence of cells of donor origin may be demonstrated by polymerase chain reaction in peripheral blood (Utter *et al*, 2007) or short tandem repeat analysis using peripheral blood and skin biopsies from affected and non-affected sites in the patient, and peripheral blood samples from the implicated donors (Sage *et al*, 2005).

Haemovigilance

Since its inception in 1996, the UK Serious Hazards of Blood Transfusion (SHOT) scheme has recorded 13 fatal cases of TA-GvHD (Stainsby *et al*, 2006; Taylor *et al*, 2009). Only two cases have been reported since the introduction of universal prestorage leucodepletion in the UK (Williamson *et al*, 2007) and no cases have been reported since 2001. Between 1996 and 2008, SHOT received reports of 405 cases where non-irradiated components had been transfused to high-risk recipients, many of whom had received the purine analogue fludarabine, but none developed TA-GvHD. This implies that prestorage leucodepletion has significantly reduced, if not abolished, the risk of TA-GvHD (Williamson *et al*, 2007).

Recommendation

- **All cases of transfusion-associated graft-versus-host disease (TA-GvHD) should be reported to the national haemovigilance system, as should all 'near misses' where non-irradiated components are transfused to high-risk patients without incident. (Grade 1 recommendation; level B evidence).**

Prevention of TA-GVHD

Irradiation

The major technology for preventing TA-GvHD is irradiation of blood components to inactivate residual lymphocytes.

Gamma rays and X-rays are similar in their ability to inactivate T lymphocytes in blood components at a given absorbed dose. Gamma-irradiators are expensive, and eventual decommissioning and 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. Dedicated X-ray blood irradiators are now available, have been widely used in North America for several years and are being introduced by the UK Transfusion Services. X-ray irradiation machines are less expensive and the absence of a radioactive source results in fewer regulatory requirements (Janatpour *et al*, 2005). Published data indicate that the small differences in red cell permeability found between X- and gamma-irradiated components are not clinically significant (Janatpour *et al*, 2005). Further work, commissioned by the Joint Professional Advisory Committee of the UK Transfusion Services on blood components irradiated using the Raycell X-irradiator, concluded that gamma and X-irradiation can be regarded as equivalent and both are suitable and safe for clinical use.

Recommendation

- **Gamma or X-irradiation of blood components, by validated systems, is the recommended procedure to prevent TA-GvHD. (Grade 1 recommendation; level B evidence).**

Effective dose

Studies using sensitive-limiting dilution assays indicate that a dose of 25 Gy, measured at the mid-plane of a component, completely abolishes mixed lymphocyte response (Pelszynski *et al*, 1994).

The American Association of Blood Banks (AABB) recommends a dose of 25 Gy to the central area of the component with no portion receiving <15 Gy (AABB 2006). The Japanese Society of Blood Transfusion's Guidelines recommend a similar dose (Asai *et al*, 2000). In the UK, a *minimum* of 25 Gy is recommended, but with the dose to any bag in the container not exceeding 50 Gy. To ensure this dose distribution is achieved, consultation with supporting physicists is mandatory. (Moroff & Luban, 1997; Moroff *et al*, 1997).

Recommendation

- **The minimum dose achieved in the irradiation volume should be 25 Gy, with no part receiving more than 50 Gy. (Grade 1 recommendation; level B evidence).**

Blood components that should be irradiated

Lymphocyte viability is retained in stored red cells for at least 3 weeks and TA-GvHD has been reported after transfusion of whole blood, red cells, platelets and granulocytes (Weiden

et al, 1981). TA-GvHD has not been described following transfusion of frozen deglycerolized red cells, which are thoroughly washed free of leucocytes after thawing.

TA-GvHD has *not* been described following transfusion of cryoprecipitate, fresh frozen plasma or fractionated plasma products, such as clotting factor concentrates, albumin and intravenous immunoglobulin.

Recommendation

- **For at-risk patients, all red cell, platelet and granulocyte components should be irradiated, except cryopreserved red cells after deglycerolization. It is not necessary to irradiate fresh frozen plasma, cryoprecipitate or fractionated plasma. (Grade 1 recommendation; level B evidence).**

Donations from family members and HLA-selected donors

Because of the sharing of HLA haplotypes, donations from family members pose a particular risk of TA-GvHD. Red cells, granulocytes, platelets and fresh plasma have all been implicated in TA-GvHD after transfusion from family members (Agbaht *et al*, 2007), and there is an increased risk with donations from both first- and second-degree relatives.

Several cases of TA-GvHD have been reported from Japan, where limited diversity of HLA haplotypes in the population increases the chance of a transfusion recipient receiving blood from a HLA haploidentical or HLA-identical donor (Ohto & Anderson, 1996). These observations are of relevance for patients receiving HLA-selected platelet concentrates from non-family members because of alloimmune refractoriness to random donor platelets. This would be expected to increase the risk of TA-GvHD, especially if the platelet donor is homozygous for one of the recipient HLA-haplotypes (analogous to donations within families or within racial groups of limited genetic diversity). A case of TA-GvHD in an immunocompetent recipient following transfusion of blood components from an unrelated HLA homozygous donor was recently reported (Triulzi *et al*, 2006), and four more cases were reported from Turkey in immunocompetent recipients who had received non-irradiated blood from relatives (Agbaht *et al*, 2007). The risk from HLA-selected platelets where the donor is *not* homozygous is uncertain. However, many transfusion centres now specifically maintain panels of homozygous donors for refractory patients, and in practice it is probably more reliable to recommend irradiation of *all* HLA-selected platelets, rather than risk the misallocation of some donations.

Recommendation

- **All transfusions from first- or second-degree relatives should be irradiated, even if the patient is immunocompetent (Grade 1 recommendation; level B evidence).**

Recommendation

- **All HLA-selected platelets should be irradiated, even if the patient is immunocompetent. (Grade 2 recommendation; level C evidence).**

Manufacturing aspects of irradiated components

Undertaking irradiation of blood components constitutes a manufacturing process. The responsible department is therefore expected to comply with relevant aspects of the *EC Guide to Good Manufacturing Practice* (EudraLex 2010).

Red 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 (Mintz & Anderson, 1993). Gamma irradiation may result in reduced post-transfusion red cell recovery after more prolonged storage, although recovery is still above the minimum acceptable 75% (Davey *et al*, 1992).

Both gamma and X-irradiation of red cells result in accelerated leakage of potassium and an increase in the level of extracellular potassium (Moroff *et al*, 1999; Janatpour *et al*, 2005; Weiskopf *et al*, 2005). 'Top-up' transfusions given at standard flow rates do *not* constitute a risk of hyperkalaemia, even when given to premature neonates. Potassium load may be clinically important in rapid large-volume transfusions, such as neonatal exchange transfusion or intrauterine transfusion. Routine removal of supernatant plasma and washing of irradiated red cells is not considered necessary but, if this procedure is undertaken, the washed cells should be transfused as soon as possible, ideally within 3–4 h.

Free haemoglobin levels are increased in stored irradiated red cell components (Weiskopf *et al*, 2005) but remain within acceptable limits. Irradiation has no clinically significant effect on red cell pH, glucose consumption, ATP or 2,3 DPG levels (Samuel *et al*, 1997).

Recommendation

- **Red cells may be irradiated at any time up to 14 d after collection, and thereafter stored for a further 14 d from irradiation. 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. (Grade 1 recommendation; level A evidence).**

Platelets

Gamma irradiation below 50 Gy has not been shown to produce significant clinical changes in platelet function (Rock *et al*, 1988; Duguid *et al*, 1991; Sweeney *et al*, 1994).

Recommendation

- **Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection. (Grade 1 recommendation; level A evidence).**

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 (Patrone *et al*, 1979; Haidenberger *et al*, 2003).

Recommendation

- **All granulocytes should be irradiated before issue and transfused with minimum delay. (Grade 1 recommendation; level C evidence).**

Potential hazards of irradiation of blood components

Radiation-induced malignant change. It is likely that the dose of gamma irradiation delivered to blood components significantly exceeds the lethal dose for such cells at high dose rates (3–4 Gy/min), resulting in complete cell death rather than transformation.

Reactivation of latent viruses. Gamma irradiation can activate latent viruses and could theoretically result in transfusion-transmitted infection of the recipient (Ferrieu *et al*, 2003; Chou *et al*, 2007). No cases have been reported and the doses delivered significantly exceed those associated with such activation.

Leakage of plasticizer. Leakage of plasticizer from the transfusion pack is a theoretical risk for recipients of large-volume transfusions of irradiated components (Rock *et al*, 1988), particularly for neonates. The effect of irradiation on the many new plastics and plasticizers potentially used in the manufacture of blood packs requires evaluation and monitoring.

Recommendation

- **Irradiated components not used for the intended recipient can safely be returned to stock to be used for recipients who do not require irradiated components. The reduction in shelf life must be observed. (Grade 1 recommendation; level B evidence).**

Labelling and documentation requirements

Irradiated components must be identified by an approved overstick label. The label should be permanent and include the

date of irradiation and any reduction in shelf life. Approved bar code labels should be used.

Assurance that components have been adequately irradiated is essential. Labels that are sensitive to irradiation and change from 'NOT IRRADIATED' to 'IRRADIATED' are commercially available. The dose at which the label changes to 'IRRADIATED' must be marked on the label. We recommend using a radiation-sensitive label on *every* pack irradiated. Batch control can also be performed using thermoluminescent dosimeters. The use of radiation-sensitive labels does not replace the need for regular and precise dosimetry.

There should be a permanent record of all units irradiated, including details of irradiation batch and donation numbers, component type, the site of irradiation, when irradiation was performed and by whom.

Recommendation

- **All irradiated units should be labelled as such, using an approved bar code label. Each unit should be monitored using a radiation-sensitive device, and the result should be permanently recorded, manually or by computer. (Grade 1 recommendation; level C evidence).**

Clinical indications for irradiated blood components

Paediatric practice

Neonates at risk of TA-GvHD. The newborn, especially if premature, may be at particular risk of TA-GvHD because of physiological immune incompetence. Donor lymphocytes may be found in the neonatal circulation 6–8 weeks after exchange transfusion (ET) (Hutchinson *et al*, 1971) and allogeneic cells have been detected after intrauterine transfusion (IUT) for haemolytic disease of the newborn and fetus (HDN) 2–4 years after transfusion in otherwise healthy newborns. Most cases of TA-GvHD reported in apparently immune competent infants have occurred in the setting of IUT followed by ET (Parkman *et al*, 1974), suggesting transfusion-induced tolerance or immune suppression.

Intrauterine and exchange transfusions (IUT and ET).

- 1 *IUT alone.* Despite the few reported cases of TA-GvHD following IUT alone from unrelated donors (Naiman *et al*, 1969), it is difficult not to recommend irradiation in the setting of a large-volume transfusion of fresh blood to a very immature recipient.
- 2 *IUT and subsequent exchange transfusion.* Although reports are scarce, the published evidence supports a prudent policy of irradiation of blood for IUT and any subsequent ETs (Parkman *et al*, 1974).

3 *Exchange transfusion alone.* Rare cases of TA-GvHD have been reported after ET alone in pre-term and term infants (Parkman *et al*, 1974; Harte *et al*, 1997). On the balance of current evidence, irradiation of blood for ET in either pre-term or term infants is prudent but not mandatory. The risk of TA-GvHD must be balanced against those of any delay in transfusion while irradiation is performed.

Recommendation

- **All blood for intrauterine transfusion (IUT) should be irradiated. (Grade 1 recommendation; level B evidence).**

Recommendation

- **Blood for neonatal exchange transfusion (ET) must be irradiated if there has been a previous IUT or if the donation comes from a first- or second-degree relative. (Grade 1 recommendation; level B evidence).**

Recommendation

- **For other neonatal ET cases, irradiation is recommended provided this does not unduly delay transfusion. (Grade 1 recommendation; level C evidence).**

Recommendation

- **For IUT and ET, blood should be transfused within 24 h of irradiation and, in any case, by 5 d or less from collection. (Grade 1 recommendation; level A evidence).**

Top-up red cell transfusions in term and pre-term infants

- 1 *Pre-term infants.* Pre-term infants are often multiply transfused yet there are few reports of TA-GvHD (Ohto & Anderson, 1996).
- 2 *Full-Term infants.* With increasing gestational age the ability of transfusions to induce tolerance decreases and the term or near-term infant seems capable of responding appropriately to transfused cells. Even in the setting of multiple transfusions associated with extracorporeal membrane oxygenation (ECMO), there has been only one reported case of TA-GvHD (Hatley *et al*, 1991), and these infants do not appear to be at especial risk. (Berger & Dixon, 1989).

Recommendation

- **It is not necessary to irradiate red cells for routine 'top-up' transfusions of premature or term infants unless either 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), or the**

donation has come from a first- or second-degree relative. (Grade 2 recommendation; level C evidence).

Platelet transfusions in the fetus and infant

There have been no reported cases of TA-GvHD following platelet transfusion alone, but as platelets may contain small numbers of residual lymphocytes, the recommendations for red cell transfusion should also apply to platelets. Irradiation should be performed on platelets transfused *in utero* to treat alloimmune thrombocytopenia and on platelet transfusions given after birth to infants who have received either red cells or platelets *in utero* for 6 months after the expected delivery date.

Recommendation

- **Platelets transfused in utero to treat alloimmune thrombocytopenia should be irradiated and any subsequent red cell or platelet transfusions irradiated until 6 months after the expected date of delivery (40 weeks gestation). There is no need to irradiate other platelet transfusions for pre-term or term infants, unless they have been donated by first- or second-degree relatives. (Grade 1 recommendation; level C evidence).**

Granulocyte transfusions

There have been no cases of TA-GvHD unequivocally attributed to granulocytes. However, because these components are heavily contaminated with lymphocytes and transfused extremely fresh, it is prudent to irradiate all granulocyte transfusions for both children and adults.

Recommendation

- **All granulocyte transfusions should be irradiated for recipients of any age, and they should be transfused as soon as possible after irradiation. (Grade 1 recommendation; level C evidence).**

Congenital immunodeficiencies in infants and children

TA-GvHD has been reported in children with severe primary T lymphocyte immunodeficiencies characterized by an absence of T lymphocytes or a severe defect of T cell function.

In the newborn infant the presenting features of immunodeficiency syndromes may be unrelated to the immune defect (e.g. cardiac disease, hypocalcaemia, thrombocytopenia, eczema) and a high index of suspicion is required, particularly in infants less than 6 months old with recurrent or persistent respiratory or gastro-intestinal infections.

To date, there have been no reports of TA-GvHD occurring in patients with isolated defects of humoral immunity.

Recommendation

- All severe T lymphocyte immunodeficiency syndromes should be considered as indications for irradiation of cellular blood components. Once a diagnosis of immunodeficiency has been suspected, irradiated components should be given while further diagnostic tests are being undertaken. A clinical immunologist should be consulted for advice in cases where there is uncertainty. (Grade 1 recommendation; level A evidence).

Acquired immunodeficiency states in childhood

Transient defects of T cell function can occur following common childhood viral infections and in the setting of tuberculosis, leprosy, autoimmune disorders, malnutrition and burns. TA-GvHD has not been reported in these situations and irradiation of blood components is not recommended. Despite the profound T cell defect in HIV infection, no cases of TA-GvHD have been described in children or adults.

Recommendation

- There is no indication for irradiation of cellular blood components for infants or children who are suffering from a common viral infection, who are HIV antibody positive, or who have AIDS. However, this should be kept under review. There is also no indication for irradiation of cellular blood components for adults who are HIV antibody positive or who have AIDS. (Grade 2 recommendation; level B evidence).

Cardiac surgery in neonates and infants

There have been occasional published reports of TA-GvHD in apparently immunocompetent neonates undergoing cardiopulmonary bypass surgery. (Warren *et al*, 1999), and there should be a high index of suspicion concerning coexisting cardiac defects and immunodeficiency. If in doubt, blood should be irradiated until a definitive diagnosis is made. If an immunodeficiency syndrome, such as DiGeorge syndrome or CHARGE syndrome with severe T lymphocyte immunodeficiency, is diagnosed, irradiated components are essential.

Adults 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, should also receive irradiated blood components as the risk of TA-GvHD is uncertain.

Recommendation

- There is no need to irradiate red cells or platelets for infants undergoing cardiac surgery unless clinical or laboratory features suggest a coexisting T lymphocyte immunodeficiency syndrome. (Grade 2 recommendation; level B evidence).

- Acute Leukaemia and Bone Marrow/Peripheral Blood Stem Cell Transplantation in Children and Adults.

Acute leukaemia

There are very few published reports of TA-GvHD in patients receiving intensive chemo-radiotherapy without stem cell transplantation and, since 1988, there has been only one adult case reported in acute myeloid leukaemia (AML) (Mori *et al*, 1995). In children, there have been only eight acute lymphoblastic leukaemia (ALL) and two AML cases reported in the world literature. In surveys of adult and paediatric practice in the UK, no centres routinely irradiate blood components for patients with acute leukaemia without transplantation, and no cases of TA-GvHD have been reported to date.

Recommendation

- It is not necessary to irradiate red cells or platelets for adults or children with acute leukaemia, except for HLA-selected platelets or donations from first- or second-degree relatives. (Grade 1 recommendation; level B evidence).

Allogeneic bone marrow or peripheral blood stem cell transplantation

For the last 30 years it has been common practice to irradiate blood components transfused to allogeneic haemopoietic stem cell transplant (HSCT) recipients. There is no level A evidence to indicate when irradiation of blood components can safely be stopped. In line with the European School of Haematology-European Group for Blood and Marrow Transplantation (ESH-EBMT) Handbook (Apperley *et al*, 2008), we recommend that irradiation should be continued at least until immunosuppressive therapy is withdrawn (at least 6 months in most cases). Should an allogeneic HSCT donor require blood transfusion within 7 d before donating, components should be irradiated. Given that chronic GvHD causes significant immunosuppression, irradiated components should be used for patients with active chronic GvHD.

Recommendation

- All recipients of allogeneic haemopoietic stem cell transplantation (HSCT) must receive irradiated blood components from the time of initiation of conditioning chemoradiotherapy (Grade 1 recommendation; level B evidence).

Recommendation

- Irradiated components should be continued while the patient continues to receive graft-versus-host disease (GvHD) prophylaxis, i.e. usually for 6 months

post-transplant, or until the lymphocyte count is $>1 \times 10^9/l$. If chronic GvHD is present or if continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely. (Grade 2 recommendation; level C evidence).

Recommendation

- **Allogeneic blood transfused to bone marrow and peripheral blood stem cell donors 7 d prior to or during the harvest should also be irradiated.** (Grade 2 recommendation; level C evidence).

Autologous bone marrow or peripheral blood haemopoietic stem cell transplantation

Virtually all UK centres currently irradiate blood components for autologous HSCT recipients and most use irradiated components before and during 'harvesting' of marrow or peripheral blood stem cells. Current evidence does not indicate when irradiation can be safely discontinued. As a minimum, irradiated blood components should be used until there is evidence of haematopoietic engraftment and lymphoid reconstitution (at least 3 months with chemotherapy conditioning alone and 6 months if total body irradiation is given).

Recommendation

- **Patients undergoing bone marrow or peripheral blood stem cell 'harvesting' for future autologous re-infusion should receive irradiated cellular blood components during and for 7 d before the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially withstand cryopreservation.** (Grade 2 recommendation; level C evidence).

Recommendation

- **All patients undergoing autologous bone marrow transplant or peripheral blood stem cell transplant 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).** (Grade 2 recommendation; level C evidence).

Other patient groups

Lymphoma. TA-GvHD has been reported in all forms of lymphoproliferative disease (Spitzer *et al*, 1990; Anderson *et al*, 1991; Munro *et al*, 2002), but especially in patients with Hodgkin lymphoma (HL) where the risk is unrelated to treatment modality and or disease stage. There are relatively few reports of TA-GvHD in non-Hodgkin lymphoma (NHL) and the majority have been in patients with high-grade disease.

Recommendation

- **All adults and children with Hodgkin lymphoma at any stage of the disease should have irradiated red cells and platelets for life.** (Grade 1 recommendation; Level B evidence).

The purine analogues fludarabine, cladribine (CdA) and deoxycoformycin (DCF) induce profound lymphopenia with low CD4 counts which may persist for several years after treatment (Cheson, 1995). There are case reports of TA-GvHD following treatment of low-grade B cell malignancies with fludarabine (Hutchinson *et al*, 2002; Leitman *et al*, 2003) and cladribine (Zulian *et al*, 1995). The situation with newer purine antagonists and agents with similar activity, such as bendamustine (created to combine the alkylating properties of mechlorethamine and the purine antimetabolite properties of benzimidazole) and clofarabine is unclear. Until evidence of safety emerges, we feel it is prudent to recommend the use of irradiated components in patients receiving clofarabine and other new purine analogues and related agents.

Lymphocyte-depleting antibody therapies, such as alemtuzumab (Campath-1H; anti-CD52) and rituximab (MabThera; anti-CD20), are entering clinical use. One fatal case of TA-GvHD has been reported in the Cancer and Leukaemia Group B (CALGB) 10101 study, a Phase 2 study of fludarabine + rituximab induction followed by alemtuzumab in chronic lymphocytic leukaemia (Lin *et al*, 2010). Originally, six infection-related deaths were reported, but Bayer Health-Care and Genzyme were also informed of an additional non-infection related fatality, believed to be TA-GVHD, which occurred in a non-lymphopenic patient who had received non-irradiated blood products. The US Food and Drug Administration (FDA) recently revised its recommendations for alemtuzumab to include irradiation of blood components 'unless emergent circumstances dictate immediate transfusion' (FDA U.S. Food and Drug Administration, 2009). Irradiation is not currently regarded as necessary with rituximab.

Recommendation

- **Patients treated with purine analogue drugs (fludarabine, cladribine and deoxycoformycin) should receive irradiated blood components indefinitely.** (Grade 1 recommendation; level B evidence).

Recommendation

- **The situation with other purine antagonists and new or related agents, such as bendamustine and clofarabine, is unclear, but use of irradiated blood components is recommended as these agents have a similar mode of action. Irradiated blood components should be used after alemtuzumab (anti-CD52) therapy. Their use after rituximab (anti-CD20) is not recommended at this time. As new potent immunosuppressive drugs and biological**

agents are introduced into practice there is a need for regular review of these recommendations. (Grade 2 recommendation; level C evidence).

Routine surgery

There are a few case reports of TA-GvHD after orthopaedic surgery, cholecystectomy and other routine procedures in apparently immunocompetent individuals. However these are extremely rare given the number of surgical procedures undertaken.

Solid tumours

Occasional cases of TA-GvHD have been reported after treatment of a variety of solid tumours. This is clearly a rare occurrence. However, the effect of dose escalation of chemotherapy regimens in children and young adults is unknown and should be monitored.

Organ transplantation

TA-GvHD following solid organ transplantation is rare (Wisecarver *et al*, 1994; Au *et al*, 2000) and probably due to donor lymphocytes from the transplanted organ. Irradiated blood components are unnecessary. To date, no cases of TA-GvHD have been reported after the use of unirradiated components in solid organ transplant recipients prepared with ATG. If alemtuzumab has been used in conditioning, it is prudent to irradiate blood components in view of the recognized risks associated with this agent in other patient groups.

Autoimmune disorders

Alemtuzumab is being used for the treatment of disorders such as multiple sclerosis and rheumatoid arthritis. Although TA-GvHD is not reported in this setting, it is prudent to irradiate blood components indefinitely in patients receiving this agent until more data emerges.

Acquired immunodeficiency

There are no reports of HIV-infected patients developing TA-GvHD despite the T cell immunodeficiency.

Recommendation

- It is not necessary to irradiate blood components for patients undergoing routine surgery, those with solid tumours, HIV infection, autoimmune diseases or after solid organ transplantation (unless alemtuzumab (anti-CD52) has been used in the conditioning regimen). The effects of new regimens of chemo- and immunotherapy

entering clinical practice must continue to be monitored. (Grade 2 recommendation; level C evidence).

Aplastic anaemia

Animal data show that irradiation of red cell and platelet transfusions *before* allogeneic bone marrow transplantation reduces the risk of sensitization to minor histocompatibility antigens and the risk of graft rejection (Bean *et al*, 1994). An expert committee on aplastic anaemia proposed that irradiated blood components should be used in all patients with aplastic anaemia who are transplant candidates (Schrezenmeier & Bacigalupo, 2000). Although this is common practice in centres in Europe and the USA, there is no clinical evidence to support this intervention and the routine use of prestorage leucodepleted blood components has clearly reduced the risk of alloimmunization in aplastic anaemia patients.

Horse ATG (Lymphoglobuline, Genzyme) has been replaced by the more immunosuppressive rabbit ATG (Thymoglobuline, Genzyme). A recent EBMT Severe Aplastic Anaemia Working Party survey of 12 European and two US centres found that 12 of these exclusively transfuse irradiated blood components after ATG treatment (Marsh *et al* 2009a). There was no consensus on how long to continue this for. The survey identified two cases of TA-GvHD, one in a patient with severe aplastic anaemia treated with ATG 20 years previously and one in a liver allograft recipient who received ATG more than 10 years previously (Marsh *et al*, 2009a).

Studies using alemtuzumab in aplastic anaemia are currently in progress (Risitano *et al*, 2008). Patients in these studies receive irradiated blood components, although the risk of developing TA-GvHD is currently unclear.

In line with the 2009 BCSH Guideline on Diagnosis and Management of Aplastic Anaemia (http://www.bcsghguidelines.com/pdf/AplasticAnaemia_010409.pdf; Marsh *et al*, 2009b) we recommend the use of irradiated blood components in patients with aplastic anaemia treated with immunosuppressive therapy until clearer evidence emerges. There is no evidence to determine the duration of provision of irradiated components, but the 2009 Guideline recommends continuing at least until the lymphocyte count is $>1.0 \times 10^9/l$.

Recommendation

- In view of the recent switch from horse anti-thymocyte globulin (ATG) to the more immunosuppressive rabbit ATG, we now recommend use of irradiated blood components for aplastic anaemia patients receiving immunosuppressive therapy with ATG (and/or alemtuzumab). (Grade 2 recommendation; level C evidence).
- We cannot make a firm recommendation as to how long irradiated components should continue to be used after ATG administration.

Ensuring irradiated components are supplied and transfused

Patients at risk of TA-GvHD should be made aware of their need for irradiated blood components and be provided with clear written information. Patient information leaflets, containing patient cards and stickers for the case notes are available from NHS Blood and Transplant in England and North Wales. (http://hospital.blood.co.uk/library/pdf/english_irradiated_blood.pdf; http://hospital.blood.co.uk/library/pdf/INF_PCS_HL_005_01_Irradiated.pdf), SNBTS in Scotland ([http://www.scotblood.co.uk/site/pubdocs/SNBTS%20Irradiated%20blood%20leaflet%20V7%20lo%20res\[1\].pdf](http://www.scotblood.co.uk/site/pubdocs/SNBTS%20Irradiated%20blood%20leaflet%20V7%20lo%20res[1].pdf)) and are in preparation by the Welsh Blood Service.

Figure 1 shows an example of a currently available alert card, one of which is carried by the patient and the other of which should be attached to the patient's hospital notes.

The annual SHOT Reports (<http://www.shotuk.org>) have identified the urgent need to improve awareness of special transfusion requirements, such as irradiated components, by hospital clinical and laboratory staff and highlighted poor communication between hospitals involved in the shared care of patients as a recurrent cause of incorrect blood component transfused incidents. Many UK centres have developed manual or IT systems with pharmacy and diagnostic services that alert the transfusion laboratory to the prescription of relevant drugs (e.g. purine analogues, anti-lymphocyte globulin) or the diagnosis of high risk conditions, such as HL. The development of a national system, ideally IT-based and part of the

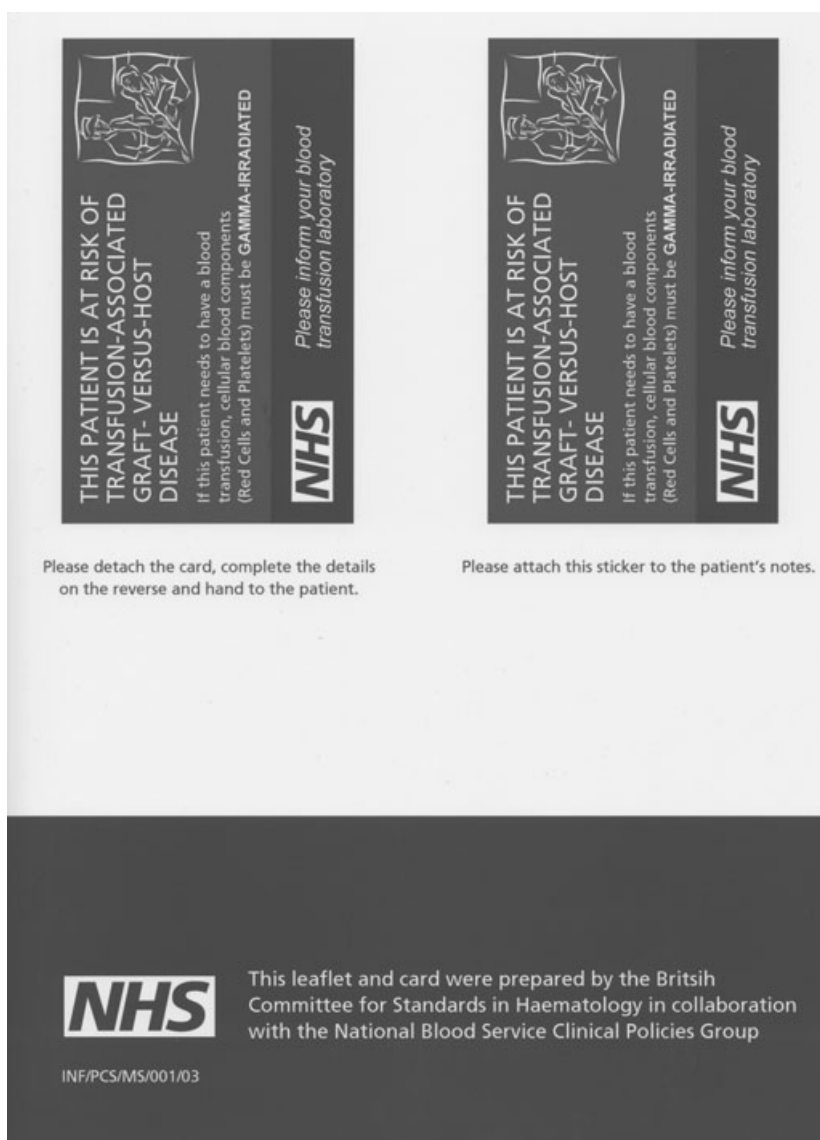


Fig 1. An example of a patient alert card currently in use.

electronic patient record, for recording and transferring special transfusion requirements between healthcare providers would make a significant contribution to patient safety.

Recommendation

• **Patients at risk of TA-GvHD should be made aware of their need for irradiated blood components and be provided with appropriate written information and an alert-card for clinical staff. We endorse the recommendations from SHOT (<http://www.shotuk.org>) relating to improved clinical and laboratory awareness, documentation and communication of special requirements for transfusion, including irradiated components. Initiatives to improve laboratory and clinical information management systems (including IT links with Pharmacy and diagnostic services to highlight 'at risk' patients) should be incorporated into local policies and regularly audited. Poor communication between centres involved in 'shared care' of patients is a well-reported hazard and the development of a standardized national system for recording and transferring details of special transfusion requirements is an urgent requirement to improve patient safety. (Grade 2 recommendation; level C evidence).**

Questions still to be answered

- 1 Is it necessary to irradiate cellular blood components which are leucodepleted? Does leucodepletion alone reduce the number of contaminating lymphocytes sufficiently to avoid any chance of TA-GvHD, rendering irradiation superfluous?
- 2 Which, if any, of the newer purine analogue drugs and other related agents are liable to render recipients susceptible to TA-GvHD?

Disclaimer

While the advice and information in these guidelines are believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of the guidelines.

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