bjh guidelines

Guidelines on the use of irradiated blood components

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Methodology

This guideline was compiled according to the British Society for Haematology (BSH) process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

The last guideline covering this topic was published in 2012.

Publications were searched systematically in English between 2008 and August 2019 covering the period since the last publication (Appendices 2 and 3).

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee Transfusion Task Force, the BSH Guidelines Committee and the Transfusion and Malignant Haematology sounding board of BSH, and relevant specialists including paediatric cardiac anaesthetists and haematologists specialising in malignant diseases. It was also on the members section of the BSH website for comment.

Purpose

To provide healthcare professionals with clear guidance on situations when the use of irradiated blood components is indicated. The term 'blood component' means the therapeutic constituents of human blood (red cells, white cells, platelets and plasma) that can be prepared by various methods (JPAC https://www.transfusionguidelines.org/red-book/definitions). The multidisciplinary writing group developed evidence-based clarification and practical guidance in clinical areas of ambiguity. Publications relating to patients of all age groups have been assessed. The guidance may not be appropriate in all patient situations and assessment of individual circumstances with the appropriate risk assessments and patient involvement may lead to alternative decisions.

Introduction

Transfusion-associated graft-*versus*-host disease (TA-GvHD) is a rare, usually fatal, complication of transfusion of blood components containing lymphocytes. There are no published clinical trials, and evidence for the prevention mostly relies on case reports, haemovigilance data and laboratory methods aiming to inactivate or eliminate lymphocytes in the transfused components. Attempts have been made in the literature to understand recipient susceptibility based on retrospective epidemiological data and information about the level of immunosuppression, not specific for the pathophysiology of TA-GvHD.

The clinical and laboratory features of TA-GvHD and the relative contribution of recipient and component factors remain poorly understood.

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[Following technical errors at the editorial office and publisher's office, this Guideline has been updated on 8 October 2020 after its first online publication. If you downloaded a version of this Guideline before this date, we ask you to refer to this updated version]

First published online 18 August 2020
doi: 10.1111/bjh.17015

The condition was first recognised in immunocompromised recipients transfused with cellular blood components containing viable lymphocytes.[1,2,3] Subsequently it was evident that non-immunosuppressed patients could also develop the condition, particularly if the blood components transfused derived from a human leucocyte antigen (HLA)-haploidentical unrelated donor or family member.[4,5,6,7]

The current hypothesis is that 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 setting.

A systematic review[8] of the world literature relating to TA-GvHD examined some of the features of TA-GvHD. The sharing of HLA antigens between donor and recipient was the strongest risk factor for development of the condition (71% of reported cases with available HLA data) among recipients without other typical indications for component irradiation. The review included 348 cases and suggested that the incidence in recipients is very much in keeping with transfusion rates rather than with patient characteristics. The authors concluded that immune incompetence as a risk for TA-GvHD is less significant than previously thought.

Components were typically whole blood and red cells. Component storage time was reported in the same review in 158 cases (45·4%) reviewed. In these, the implicated component was either described as fresh or as ≤10 days old in 148 cases (93·7%). Ten cases (6·3%) reported a storage time of 11–14 days, with no cases implicating components stored for > 2 weeks. Similar findings were reported by the Japanese Red Cross in two series of TA-GvHD with no case reported with components stored for >14 days.[9,10]

Leucocyte depletion has been considered as a protective intervention.[11] However, TA-GvHD continues to be reported within the era of leucocyte depletion, with 66 out of the 348 (18·9%) cases being reported between 2000 and 2013.[8] In some instances patients were transfused with leucocyte-depleted (LD) blood components with no full details available for the quality of leucocyte depletion.

Features of TA-GvHD noted in the Kopolovic *et al.*[8] review include: rash (80·2%), fever (67·5%), elevated liver enzymes (66·4%), pancytopenia (65·2%), diarrhoea (43·1%), bone marrow aplasia (22·7%) or hypocellularity (17·2%) and hepatomegaly (13·5%). Relevant abnormalities occur 1–6 weeks after transfusion, with the median time from transfusion to first symptom being 11 days. The majority of reported cases (61·6%) occured in men. Overall survival rate is reported to be 8·4%.[12]

As part of the literature search for this guideline, the authors reviewed all cases of TA-GvHD reported in the literature from 2008 to 2018 and these are summarised in Table I. Although the information and exact specification are limited, note that three cases occurred in patients despite use of LD components.

Diagnosis

Diagnosis is usually made by biopsy of skin, gut or liver. The presence of donor cells can be demonstrated by DNA amplification in peripheral blood[35] 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.[36] Fluorescence *in situ* hybridisation (FISH) can be used for the diagnosis of TA-GvHD in sex mis-matched cases with rapid turnaround of results.[37]

Serious Hazards of Transfusion (SHOT) incidents relevant to the irradiation guidelines

The SHOT scheme collects data on adverse events related to transfusion of all labile blood components. A retrospective analysis of 21 years of SHOT reporting (April 1996 to December 2019) found 14 cases of TA-GvHD, 12 prior to the introduction of pre-storage LD that was achieved by November 1999, none of which have been reported in the literature other than in the annual SHOT Reports. These data are included in the Kopolovic *et al.*[8] review. Only two cases have been reported since then, one of which received non-LD blood. One of the cases reported during the period of introduction of universal LD did receive LD red cells; however, it is not clear if the LD was undertaken pre-storage. Symptoms generally occurred rapidly following the transfusion, reported in most cases to be between 5 and 20 days.

Summary of cases reported to SHOT

Apart from the case of intrauterine transfusion (IUT), none of the cases occurred in patients considered at high risk of TA-GvHD at the time of transfusion, and so these individuals would not normally have received irradiated components, although two may have been immunodeficient.

In the 21 years following the introduction of LD, only two cases of TA-GvHD were reported to SHOT: the first was a patient with B-cell acute lymphoblastic leukaemia (B-ALL) in 2000 and the second was in a baby following an emergency IUT of non-irradiated maternal blood in 2012.[25] This is despite reported omission of irradiation in 1478 patients identified as being at risk.[38] It is important to recognise that many of these patients are exposed to non-irradiated blood components on more than one occasion.

A detailed retrospective analysis was undertaken to review SHOT cases where the specific requirement for irradiation was not met between 2010 and 2016,[39] updated by P.H.B. Bolton-Maggs to include 2017 data. This included 637 reports. The three largest cohorts of patients were those having received purine analogue chemotherapy (n = 290, 46%),

those with a history of Hodgkin lymphoma (HL; $n = 132$, 21%) and those treated with alemtuzumab ($n = 53$, 8%). For 43 patients the indication for irradiation was haematopoietic stem cell transplantation (HSCT). The number of components received by an individual was variable (not reported in 66, 10%) and ranged from 1 to 486. Overall, 477 (84%) patients received between 1 and 4 components. Where the patient received 486 non-irradiated blood components this was due to a failure to identify a historical diagnosis of HL.

Overall, from the SHOT data, given the dramatic reduction of reported cases in the UK since the introduction of universal LD, compared with 12 cases reported in immunocompetent recipients in the prior 3 years (1996–1999), it appears that standardised pre-storage LD is sufficient to prevent or markedly reduce TA-GvHD at least in the immune-competent non-HLA-matched recipients (Table II).

In the recent 'Recommendations For the Use of Irradiated Blood Components in Canada' by the National Advisory Committee on Blood and Blood Products (https://nacblood.ca/resources/guidelines/downloads/Recommendations_Irradiated_Blood_Components.pdf), storage time of cellular blood components was recognised as a significant factor, with no cases of TA-GvHD reported in the literature involving components stored for >14 days.[8,9,10]

Recommendations. **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 (1/C).**

In emergency situations where irradiated components are unavailable, blood banks should consider preferentially issuing older red cells where possible (>14 days) (2/C). For neonates and infants, see BSH guidelines for transfusion of fetuses, neonates and older children[40] for a suggested hierarchy of blood component characteristics to use in emergency.

Prevention of TA-GvHD

Prevention of TA-GvHD requires a strategy to address risk factors for the development of the condition. It involves selection of an effective method for inactivation of lymphocytes in the transfused components, management of transfusions where HLA haplotypes are likely to be shared between donor and recipient, and identification of susceptible individuals where the intervention is necessary. It is likely that different interventions work in synergy to provide the best protection. Identification of susceptible individuals might vary in different countries, as it can be influenced by the overall characteristics of the population in terms of HLA typing. Specifications of cellular blood components and more specifically implementation and effectiveness of universal leucodepletion should be taken into consideration.

TA-GvHD is a rare condition with significant mortality and no randomised control trials available. It should be noted that the literature is scant and levels of evidence are low. In addition, local practices and processes for the development of blood components vary among countries. For these reasons there is considerable variation in recommendations between different national guidelines.

The writing group aims to offer guidance on selection of the effective method for inactivation of lymphocytes on the transfused component, identification of components requiring irradiation (either universally or selectively for susceptible individuals) and identification of susceptible individual. The guideline is based on information from the literature, data from the UK (where universal LD is standard practice since 1999) and cases reported to SHOT.

The authors aim to offer guidance for reduction rather than elimination of the risk of TA-GvHD acknowledging that exceptionally rarely the condition might be a complication of blood transfusion that cannot be predicted when there are no identifiable risk factors.

Inactivation or elimination of lymphocytes in the transfused components

Irradiation remains the main method of inactivating lymphocytes in the transfused component. Washing red cells using standard methods employed in the UK does not appreciably reduce the leucocyte content[41] and therefore these need to be irradiated for susceptible patients. The authors, as part of the literature review, assessed LD and pathogen inactivation as alternative strategies to prevent 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. There is international interest in moving away from using radioactive sources for gamma irradiation due to concerns with respect to biosecurity. Dedicated X-ray blood irradiators are now available, have been widely used in North America and are also used within the UK Transfusion Services. Published data indicate that the small differences in red cell permeability found between X- and gamma-irradiated components are not clinically significant.[42] Further work, commissioned by the Joint United Kingdom Blood Transfusion Services Professional Advisory Committee (JPAC) on blood components irradiated using the Radsource irradiator, concluded that gamma- and X-irradiation can be regarded as equivalent and both are suitable and safe for clinical use (JPAC Guidelines for the Blood Transfusion Services in the UK https://www.transfusionguidelines.org/document-library/position-statements).

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

Year	Case summary and reference	Component	LD	Irr	HLA*	Immunosuppression	Preventable by previous UK guidelines and practice
2008	4-year-old child with SCID[13]	Red cells	NR	N	Y	Y	Y
2009	Family-directed transfusion during CABG[14]	Red cells	NR	N	Y	N	Y
2010	Goodpasture's syndrome[15]	Red cells	Y	N	Y	Y	Y
2010	Whole blood transfusion[16]	Red cells	NR	NR	NR	N	Y
2010	2 cases of TA-GvHD following non-irradiated blood given to SCID patients[17]	Red cells	NR	N	NR	Y	Y
2010	7-month-old admitted to Paediatric Intensive Care Unit with infective complications of what was later confirmed to be combined immunodeficiency[18]	Red cells	Y	N	N	Y	U†
2010	Patient who received transfusion abroad, presumed family directed[19]	Red cells	NR	NR	Y	N	Y
2010	56-year-old man given non-irradiated granulocyte transfusion[20]	Granulocytes	N	N	N	Y	Y
2012	Family-directed transfusion[21]	Red cells	NR	NR	NR	N	Y
2012	Afghanistan trauma resuscitation[22]	Red cells and whole blood	N	N	Y	N	Y
2012	Family-directed transfusion for anaemia due to malaria[23]	Red cells	NR	N	Y	N	Y
2012	52-year-old man given blood during CABG 11 years after treatment for HL[24]	Red cells	NR	N	N	Y	Y
2013	IUT[25]	Whole blood	N	N	Y	Y	Y
2013	59-year-old following family-directed transfusion[26]	Red cells	NR	N	Y	N	Y
2013	Family-directed transfusion for post-operative bleeding[27]	Red cells	NR	N	Y	N	Y
2013	Delayed TA-GvHD in patient who received blood prior to liver transplant, and treated with anakinra[28]	Red cells	N	N	Y	Y	Y
2013	66-year-old given family-directed transfusion post-CABG[29]	Red cells	NR	N	Y	N	Y
2013	70-year-old male post liver transplant – convincing evidence of TA-GvHD responded to IL2 blockade[30]	Red cells	NR	N	N	Y	U†
2013	55-year-old male patient with acute lymphoblastic leukaemia previously treated with purine analogue (fludarabine)[31]	Red cells	Y	N	NR	Y	Y
2016	5-year old with unexplained pancytopenia – TA-GvHD diagnosis not confirmed[32]	Red cells	N	N	Not done	Y	Y
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]	Red cells	NR	NR	Y	N	Y
2017†	Neonate with haemophagocytic lymphohistiocytosis; TA-GVHD diagnosis based on skin biopsy[34]	Red cells	NR	N	Not done	Y	U

CABG, coronary artery bypass graft; IL2, interleukin 2; Irr, irradiated; LD, leucocyte depleted; N, no; NR, not reported; SCID, severe combined immunodeficiency; U, unclear; Y, yes.
*Evidence of HLA relatedness, either by genotyping or for family-directed transfusion where the mechanism is presumed to be HLA mediated.
†It is not clear from the publications whether immunodeficiency could have been suspected prior to transfusion.

Table II. All SHOT cases 1996–2017

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

Recommendation. **Gamma- or X-irradiation of blood components, by validated systems, is the recommended procedure to prevent TA-GvHD (1/B).**

Effective dose—Studies indicate that a dose of 25 Gy, measured at the mid-plane of a component, completely abolishes mixed lymphocyte responses.[43] The American Association of Blood Banks (AABB) *Standards for Blood Banks and Transfusion Services*, 32nd Edition,[44] recommends a dose of 25 Gy to the central area of the component with no portion receiving <15 Gy, but sets no upper limit. The Japanese Society of Blood Transfusion's Guidelines recommend a similar dose.[45] 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, as is validation and regular monitoring of dosimetry in accordance with relevant standards.[46,47] JPAC Guidelines for the Blood Transfusion Services in the UK are available at: https://www.transfusionguidelines.org/red-book/chapter-7-specifications-for-blood-components. Data substantiating the effect of irradiation in excess of 50 Gy on cell quality are lacking.

Recommendation. **The minimum dose achieved in the irradiation volume should be 25 Gy, with no part receiving >50 Gy (1/B). The irradiation procedure must be validated and there must be regular monitoring of dosimetry.**

Leucocyte depletion. In the UK all cellular components except granulocytes are LD. This raises the question of whether irradiation, in addition to LD, is necessary to prevent TA-GvHD. It is not possible to sample and test all blood components for residual leucocytes, and therefore the specification for LD is based on statistical confidence from testing a sample of those produced, typically 1%. The current specification is that >99% of components should contain $<5 \times 10^6$ leucocytes per unit and >90% $<1 \times 10^6$ per unit with 95% confidence. The process of LD fails occasionally and the UK calculate figures for the residual risk of issuing a unit above these specified levels. At the time of writing, the likelihood of a unit of red cells containing more than 1×10^6 leucocytes is 1:230, and $>5 \times 10^6$ leucocytes is 1:1881. For apheresis platelets these values are 1:321 and 1:8154 respectively, and for pooled platelets 1:75 and 1:3205 (personal communication, Simon Procter Head of Quality Monitoring NHS Blood and Transplant, June 2020).

Therefore, in considering the effectiveness of LD alone in preventing TA-GvHD, one must consider the risk of issuing a non-LD component and its potential clinical consequences, that is, that TA-GvHD is usually fatal when it does occur. In a recent international systematic review of 348 cases of TA-GvHD,[8] LD components were implicated in 17% of cases where LD status was reported (6·6% overall cases). However, in about half of these cases the level of leucocyte depletion achieved was below current standards in the UK. We are not

aware of any country that relies on leucocyte depletion alone for effective prevention of TA-GvHD.

Recommendation. **There is insufficient evidence to recommend leucocyte depletion alone to prevent TA-GvHD in susceptible patients (1/C).**

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.[48,49] 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.[50] Although these systems are considered by some authors as potential future solutions for prevention of TA-GvHD,[51,52] they are not yet used in the UK, and similar systems in development for red cells are not yet licensed with limited data available.[53,54]

Manufacturing aspects for irradiated components

Irradiation of blood components constitutes a manufacturing process. The responsible institution is therefore expected to comply with relevant aspects of the European Commission Guide to Good Manufacturing Practice[55] and hold the appropriate licence as a Blood Establishment according to the Blood Safety and Quality Regulations 2005.[56]

Red cells

Irradiation of red cells results in significant changes in some markers of red cell quality, most notably increased haemolysis and potassium leakage. Irradiation has no clinically significant effect on red cell pH, glucose consumption, ATP or 2,3-diphosphoglycerate (DPG) levels,[57] but can increase levels of microparticles[58] with no adverse effects reported. The magnitude of this effect of irradiation on red cells is dependent upon the age of red cells prior to irradiation, dose of irradiation and length of storage once irradiated. Irradiation of red cells in the last few weeks of their normal shelf life, currently permitted by AABB standards (*Standards for Blood Banks and Transfusion Services*, 32nd Edition),[44] and Council of Europe guide (*Guide to the Preparation, Use and Quality Assurance of Blood Components*, 20th Edition, 2020)[59], results in increased haemolysis of red cells[60,61] and reduced post-transfusion red cell recovery, although recovery is still above the minimum defined as acceptable by the United States Food and Drug Administration (75%).[62,63] As red cells can be irradiated up to 14 days after collection and stored for a maximum of a further 14 days without significant loss of viability[64] or haemolysis,[61] and there is little operational gain in enabling irradiation later in shelf life in the UK, it is recommended that red cells are irradiated within 14 days from collection, and stored for a maximum of 14 days after irradiation.

Both gamma- and X-irradiation of red cells result in significantly accelerated leakage of potassium and an increase in the level of extracellular potassium.[42,65,66] Small volume 'top-up' transfusions given at standard flow rates do not constitute a risk of hyperkalaemia, even when given to premature neonates.[67] Potassium load may be clinically important in rapid large-volume transfusions, such as neonatal exchange blood transfusion (EBT) or IUT,[68,69] and therefore the shelf life of the latter components is restricted to 24 h following irradiation and by the end of Day 5 from collection to reduce the risk of hyperkalaemia.[40] These restrictions are also recommended for infants receiving other large volume transfusions such as for cardiac bypass or extracorporeal membrane oxygenation (ECMO): small infants are particularly susceptible to risks of hyperkalaemia due to their small size compared to extracorporeal circuits and the potential for high transfusion rates relative to weight. Routine removal of supernatant plasma and washing of irradiated red cells is not considered necessary. Rapid infusion of irradiated red cells for patients with massive haemorrhage could potentially contribute to the development of hyperkalaemia. With only limited data available,[70] it is probably safer to avoid transfusion of irradiated blood for patients with massive haemorrhage, unless irradiated blood is otherwise indicated.

For patients requiring washed and irradiated red cells, red cells can be irradiated at any time up to 14 days after collection. Due to the effect of the combination of washing and irradiation on red cell quality, the shelf life of these red cells is shorter than standard red cells (JPAC Guidelines for the Blood Transfusion Services in the UK https://www.transfusionguidelines.org/).

In a recently published retrospective study,[71] prolonged storage of irradiated red cells was associated with a significant increase in non-allergic transfusion reactions. Overall, the irradiated red cells appeared to cause more non-allergic reactions compared with non-irradiated red cells with the leading type of reaction being febrile non-haemolytic transfusion reaction. Red cells units included in this study could be irradiated at any time before the expiry date and subsequently could be stored for up to 28 days or up to expiry date (whichever comes first). This finding has not been recorded in the UK haemovigilance system, where manufacturing practice is different with <15% of the reported febrile non-haemolytic transfusion reactions involving irradiated components (Bolton-Maggs, P, personal communication from SHOT data).

Recommendations. **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, it**

is recommended that red cells are transfused within 24 h of irradiation (1/C).

If washed red cells are irradiated, they should be transfused as soon as possible and according to UK Blood Transfusion Services Guidelines (1/B).

Irradiated components not used for the intended recipient can be returned to stock to be used for recipients who do not require irradiated components (1/C).

Platelets

Although recent laboratory studies suggest that irradiation may result in proteomic/metabolomic changes in platelets, irradiation <50 Gy has not been shown to produce significant clinical changes in platelet function.[58,72,73,74]

Recommendation. **Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection (1/A).**

Granulocytes

The evidence for irradiation damage to granulocyte function is conflicting, but in any case, granulocytes should be transfused as soon as possible after production and irradiation, as granulocyte function declines rapidly with time.[75,76]

Recommendation. **All granulocytes should be irradiated before issue. They should be transfused with minimum delay (1/C).**

Labelling and documentation requirements

Irradiated components must be identified by the applied labelling and include any reduction in shelf life.

Labels that are sensitive to irradiation and undergo a visual change to indicate their irradiated status are available and are considered a useful indicator of exposure to irradiation. The dose at which the label changes to indicate irradiated status must be marked on the label. It must be remembered that such labels simply reflect that the unit has been exposed to radiation and their use does not replace the need for regular and precise dosimetry nor for carefully controlled working procedures.

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 (1/C).**

Blood components that should be irradiated

TA-GvHD has been reported after transfusion of whole blood, red cells, platelets and granulocytes.[77] Scotland, Wales and Northern Ireland use universal irradiation of platelets, whereas England irradiates blood components on request. Internationally there is also variation. In the USA, a survey of irradiation practices at College of American Pathologists member institutions (>2000) showed considerable variation in practice for different conditions. Some institutions irradiated by specialty or service, and 75 institutions used universal irradiation.[78]

Japan uses universal irradiation of all labile blood components,[45] as a higher rate of TA-GvHD has been reported due to common HLA tissue types.[79]

Blood components that do not require irradiation

TA-GvHD has not been described following transfusion of frozen deglycerolised red cells, which are thoroughly washed free of leucocytes after thawing.[80]

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. Liquid (never frozen) plasma is not currently produced in the UK. In contrast to frozen plasma components, any contaminating lymphocytes can remain viable in the component during storage and the component has been implicated in cases of TA-GvHD.[81] Therefore, this component, where produced, should be irradiated.

Pathogen inactivation systems for platelets may obviate the need for irradiation based on the capability of these systems to inactivate lymphocytes. Data and claims from the manufacturers of these systems should be reviewed to determine the effectiveness of lymphocyte inactivation and prevention of TA-GvHD.

Recommendation. **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 (1/B).**

Donations from family members and HLA-selected donors

Because of the sharing of HLA haplotypes, donations from family members pose a risk of TA-GvHD. Red cells, granulocytes, platelets and fresh plasma (not previously frozen) have all been implicated in TA-GvHD after transfusion from family members,[4] 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.[82]

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).

Transfusion of donor lymphocytes whose HLA antigens are all shared by the recipient was recognised as the strongest risk factor for the development of TA-GvHD in the recent review[8] of the world literature.

There are no reports of TA-GvHD following transfusion of HLA-matched red cells. However, it is likely for the risk to be similar to the transfusion of HLA-matched platelets.

Recommendations. **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 (1/B).**

Clinical indications for use of irradiated components

Paediatric practice

The risk of TA-GvHD in the fetus and neonate, especially if preterm, is thought to be higher than in older recipients. Contributing factors are the immunological immaturity,[83] the use of fresher blood[8] and transfusion of relatively large volumes in situations such as neonatal EBT. Donor lymphocytes have been found in the neonatal circulation up to 6–8 weeks after EBT,[84] and cases of TA-GvHD have been described in neonates and young infants.[82,85,86] These cases were almost exclusively in the presence of additional risk factors: EBT with or without preceding IUT, congenital immunodeficiency syndromes, and transfusion from blood relatives. Moreover, many publications on TA-GvHD in neonates were prior to the introduction of pre-storage LD, known to have had a major impact on TA-GvHD reduction.[8,11]

International practice for irradiation of components for neonates and children varies,[87] although in the UK the same irradiation recommendations for the perinatal period have been in place since 1996.[88] In some countries and institutions, irradiation is undertaken for blood for older children because of concerns over unrecognised immunodeficiency.[89] However, potential benefits of universal irradiation need to be balanced against the ability to use multiple 'paedipacks' for neonatal top-up transfusions to reduce donor exposure (not practical in the UK if universally irradiated by blood centres) and the potential risk of hyperkalaemia following rapid transfusion of older irradiated blood to a neonate.[40] The combination of irradiation for high-risk patients together with pre-storage LD for all others is considered to be sufficient to prevent virtually all TA-GvHD in the UK.[11] Nonetheless, it is important for neonatologists and paediatricians to retain a high index of suspicion of undiagnosed immunodeficiency in infants and older children (see section on congenital immunodeficiencies in infants and children). It should also be noted that signs of TA-GvHD may present later in neonates than in adults.[82]

Intrauterine and neonatal exchange red cell transfusions. A fatal case of TA-GvHD occurred following IUT of non-irradiated maternal blood in an emergency.[25] BSH guidelines recommended that maternal blood should not be used for IUT to avoid this risk.[40]

Intrauterine transfusion (IUT)—Red cells for IUT are used by the end of Day 5 of storage. Despite current practice of LD and the few reported cases of TA-GvHD following IUT from unrelated donors,[90] irradiation is recommended given the setting of large-volume transfusion of fresh blood to a very immature recipient. Specific, irradiated, red cells for IUT should be used where possible, and local written protocols should be in place regarding alternatives for use in emergency.[40]

Previous BSH irradiation guidelines[88,91] have recommended that irradiated components continue to be provided for routine 'top-up' neonatal transfusions following IUT, in line with recommendations for EBT following IUT. This recommendation was based on the presumption of transfusion-induced tolerance or immune suppression following IUT and the knowledge of cases of TA-GvHD in the situation of IUT followed by EBT, rather than on specific evidence, and was originally made prior to universal pre-storage LD in the UK. Missed irradiation following IUT appears to be relatively common, in part due to miscommunication between fetal medicine and obstetric delivery centres. Although there have been 18 reports to SHOT from 2007 to 2017 where red cell irradiation was missed for transfusion following IUT (e.g. Bolton-Maggs *et al.*[25]), none resulted in TA-GvHD. However, there is still previous evidence to suggest a degree of adaptive immune paresis following red cell IUT, although the clinical significance is uncertain (e.g. Radder *et al.*[92]). Therefore, although the risk of TA-GvHD is likely to be very low, the recommendation to irradiate transfusions of cellular blood components to infants following IUT remains.

Neonatal exchange blood transfusion (EBT)—Given that there were cases of TA-GvHD in the past reported following EBT, both with and without prior IUT,[85,86] it seems reasonable to continue with previous guidance to irradiate blood for this large-volume indication despite the introduction of LD. Blood issued routinely for EBT by the UK Blood Services is currently universally irradiated.

Recommendations. **Red cells for IUT should be irradiated (1/C).**

Red cells for neonatal EBT should be irradiated (1/C).

As recommended above (Manufacturing), red cells for IUT and EBT should be transfused within 24 h of irradiation.

Intrauterine platelet transfusions—As platelet concentrates may contain small numbers of residual lymphocytes, the relevant recommendations for red cell transfusion should also apply to platelets.

Recommendation. **Platelets for IUT should be irradiated (1/C).**

Neonatal top-up transfusions. Preterm infants are often multiply transfused yet there are few reports of TA-GvHD.[85] With increasing gestational age, the neonatal immune system becomes progressively more mature.[83] Even in the setting of multiple transfusions associated with ECMO there has been only one reported case of TA-GvHD,[93] which could have been associated with a primary immunodeficiency. It is not considered necessary to irradiate components for neonatal/infant top-up transfusions unless a congenital T-cell immunodeficiency is suspected, or if the infant has had a previous IUT.

Recommendations. **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) (2/C).**

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) (2/C).

Congenital immunodeficiencies in infants and children. TA-GvHD has been reported in children with severe primary T-lymphocyte immunodeficiencies characterised by an absence of T lymphocytes or a severe defect of T-cell function.[18,94] In the newborn infant the presenting features of immunodeficiency syndromes (e.g. cardiac disease, hypocalcaemia, thrombocytopenia, eczema) may be unrelated to the immune defect and a high index of suspicion is required, particularly in infants aged <6 months with recurrent or persistent respiratory or gastrointestinal infections. In view of the recent case of possible TA-GvHD in an infant with congenital familial haemophagocytic lymphohistiocytosis (HLH),[34] it is reasonable to give irradiated cellular blood components for patients with suspected congenital HLH and lymphopenia, until T-cell immunodeficiency has been excluded. To date, there have been no reports of TA-GvHD occurring in patients with isolated defects of humoral immunity.

Recommendation. **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 (1/B).**

Once a diagnosis of severe T-lymphocyte 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 (1/C).

Cardiac surgery in neonates and infants (and older patients). There have been occasional published reports of TA-GvHD in apparently immunocompetent neonates and older patients undergoing cardio-pulmonary bypass surgery.[9,11,95] There should be a high index of suspicion concerning co-existing cardiac defects and immunodeficiency. If in doubt, blood should be irradiated until a definitive diagnosis is made. Irradiated components are essential if an immunodeficiency syndrome increasing the risk of TA-GvHD is diagnosed, such as the severe T-lymphocyte immunodeficiency syndrome that may be associated with DiGeorge syndrome or CHARGE syndrome (rare complex genetic disorders).

Only around 0·5–1% of infants with suspected DiGeorge or CHARGE syndrome will have a severe co-existing immunodeficiency,[96,97] and most of the severe immunodeficiencies will be diagnosed within the first year of life. Genetic testing (FISH) detects the majority of patients with DiGeorge syndrome, but the presence or absence of a 22q11 chromosomal deletion by FISH does not predict an associated immunodeficiency. Ideally, immunological assessment comprising T-lymphophenotype enumeration, including naïve ($CD45^+$ (+/− $CD27^+$ or $CD31^+$) $CD4^+$) T lymphocytes, and T-lymphocyte proliferation measurement will be performed prior to cardiac surgery for all infants with the suspected syndromes.

For those infants where this is not possible prior to urgent cardiac surgery, irradiated cellular blood components should be given. For infants with a T-lymphocyte count of >400 cells/μl of which ≥30% are naïve T lymphocytes, and no other evidence of immune deficiency, administration of non-irradiated blood is considered safe.[98] For children aged 1 to <2 years without a significant history of infection the risk of TA-GvHD will be extremely low, but for this age group it is reasonable to follow the recommendations for neonates and infants regarding immunological testing and use of irradiated cellular blood components. From 2 years of age without a significant history of infection, it is reasonable to follow the recommendations for adults below, even in the absence of immunological testing.

Sometimes it is discovered during infant cardiac surgery that the patient has no thymus, indicating probable immunodeficiency. In this situation where there is no specific evidence to guide practice it is reasonable to wait for irradiated blood to arrive if this is practical, but not to delay surgery if this would cause a significant detrimental clinical impact given that all blood in the UK is LD.

Recommendations. **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/μl, of which 30% are naive T lymphocytes, there is no need to irradiate red cells or platelets. If it is not possible to undertake T-cell investigations prior to surgery, irradiated cellular blood components should be given until immunological investigations have been undertaken (1/C).**

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 (2/C).

Acquired immunodeficiency states in childhood. Transient defects of T-lymphocyte 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-lymphocyte defect in human immunodeficiency virus (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 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) (1/B).**

Allogeneic haematopoietic stem cell transplantation (HSCT)

Use of irradiated components for patients undergoing allogeneic HSCT is common and widely accepted practice.

Our literature search did not identify any cases of TA-GvHD related to allogeneic HSCT. Furthermore, it is unclear if irradiation of cellular blood components is required for reduced intensity conditioned (RIC) stem cell transplantation and this practice has been questioned in the literature. Jaime-Pérez *et al.* (2015) describe their experience of giving non-irradiated blood components to patients undergoing RIC allogeneic HSCT; 156 patients were exposed to non-irradiated blood with no cases of TA-GvHD, offering some indication that the risk of TA-GvHD is not high in recipients of RIC transplants.[8,99]

Given the severity of TA-GvHD, and the complexity of recognising the diagnosis in this patient population, there is no convincing evidence that the current guidance should be changed.

Recommendations. **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 (1/B).**

Irradiated components should be continued until all of the following criteria are met:

1. **>6 months have elapsed since the transplant date**
2. **The lymphocyte count is $>1{\cdot}0 \times 10^9$/l**
3. **The patient is free of active chronic GvHD**
4. **The patient is off all immunosuppression**

If chronic GvHD is present or continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely (2/C).

Treatment with irradiated blood components should continue indefinitely if this is required based on transplant conditioning, underlying disease or previous treatment, e.g. previous diagnosis of HL or previous purine analogue treatment (1/C).

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 (2/C).

Autologous stem cell transplantation (ASCT)

Despite reports of immune defects persisting for many years following successful ASCT, no cases of TA-GvHD following ASCT were found in our literature review and analysis of reported cases and therefore current recommendations remain unchanged.

Recommendations. **Patients (adult and paediatric) undergoing 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 (1/C).**

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 indefinite duration, for example previous diagnosis of HL or previous purine analogue treatment (1/C).

Hodgkin lymphoma (HL)

Patients with HL are known to be at risk for TA-GvHD unrelated to treatment modality or disease stage or histology.[100,101] Current recommendations for adults and children with HL are to receive irradiated blood components for life. This guidance is often difficult to follow and many reports of failure to offer irradiated components to patients with history of HL have been reported to SHOT with no adverse effects.

The guideline authors attempted to identify evidence from literature to guide optimal duration of the use of irradiated components, acknowledging the challenges and compliance issues with the lifelong recommendations. Literature review and conclusions are summarised as follows:

TA-GvHD has been reported rarely in patients with HL many years after the induction of remission. As patients who are in long-term remission from HL may only rarely need blood component transfusion the relative risk for TA-GvHD in such patients is impossible to determine. In the literature search, one case of TA-GvHD occurred 11 years after successful treatment of HL.[24] However, it should be noted this was in the context of coronary artery bypass surgery; TA-GvHD has been reported in immune-competent patients undergoing such surgery in the past, so that it is not possible to ascertain whether the history of HL was relevant or not.

Individuals with HL exhibit defects in the immune system, including defects in T-cell mediated immunity.[102–111] However, all these studies of immune function in this condition were published up to the 1990s, and the methods used were not as specific as those available today. These included basic enumeration of lymphocyte phenotypes, lymphocyte mitogen responses, mixed lymphocyte responses, and *in vivo* assessment of delayed hypersensitivity. It is quite relevant that allogeneic skin graft rejection was documented to be impaired in patients with HL, indicating that responses to major histocompatibility complex (MHC) antigens were impaired.[112–114]

Humoral responses to bacterial antigens, especially polysaccharide antigens such as the pneumococcal capsular polysaccharides, may be impaired, especially in those treated by splenectomy or lymphoid irradiation.[105,108]

Susceptibility to infections with common opportunistic organisms is a surrogate marker of impaired immunity. Most infections documented in patients with HL are invasive bacterial infections, characteristic of those with antibody deficiency, with the pneumococcus dominating. Splenectomy is often a contributory factor.

Although SHOT surveillance indicates that a considerable number of patients with a history of HL have received non-irradiated blood components with no adverse effects, without detailed analysis of the clinical details of each patient, including the type of HL, staging of disease, therapy received, and time from completion of therapy, it is difficult to provide guidance about risk-assessment for individual patients.

In view of the seriousness of TA-GvHD the recommendation remains unchanged and patients with HL should receive irradiated blood components indefinitely.

Recommendation. **All adults and children with HL at any stage of the disease should have irradiated red cells and platelets indefinitely (2/C).**

Other patient groups

Patients treated with purine analogues (regardless of the underlying condition). The purine analogues fludarabine, cladribine and pentostatin induce profound lymphopenia with low CD4 counts that may persist for several years after treatment.[115] There are case reports of TA-GvHD following treatment of low-grade B-cell malignancies with fludarabine[116,117] and cladribine.[118]

Although no cases of TA-GvHD secondary to purine analogues have been reported in the UK since the introduction of universal LD, there is no adequate evidence in the literature to support modification of current recommendations. It remains a recommendation that cellular blood components should be irradiated for patients receiving purine analogues.

Haematology patients and patients with rare types of immune dysfunction treated with alemtuzumab (campath 1H-anti-CD 52) or anti-thymocyte globulin (ATG). Use of alemtuzumab (campath 1H; anti-CD 52) has been considered as an indication for irradiation of blood components. This recommendation was based on a reported non-infection-related fatality in a Cancer and Leukaemia Group B (CALGB010101) study, a Phase II study of fludarabine and rituximab induction followed by alemtuzumab in chronic lymphocytic leukaemia (CLL)[119] Treatment schedule varies in different series, with the most common treatment dose to be up to 30 mg three-times a week for 12 weeks.[120]

The risk for development of TA-GvHD for aplastic anaemia patients treated with alemtuzumab remains unclear.

Currently, there is no evidence to discontinue irradiation for patients receiving alemtuzumab for treatment of haematological malignancies or bone marrow failure. It is not possible, based on existing evidence, to make a firm recommendation on how long irradiated blood components should be used for this group of patients.

The risk of development of TA-GvHD for patients with aplastic anaemia following treatment with anti-thymocytic globulin (ATG) is considered to be low. However, it remains unclear if the absence of reported cases is due to the low risk or whether the current guidance for using irradiated blood components is highly effective. In view of the seriousness of TA-GvHD, and unless new evidence emerges, current guidance remains unchanged and irradiated blood components are recommended for bone marrow failure patients receiving ATG (see also solid organ transplant section). This is in line

with the BSH guidelines[121] and European Group for Blood and Marrow Transplantation (EBMT) recommendations.[122,123] It is not known how long the use of irradiated blood components following ATG treatment should be continued, but it is considered reasonable to continue while patients are still taking ciclosporin following ATG therapy.

Rarely, potent immunosuppressive (T-cell depleting) agents are used for treatment of immunology patients. An example is the use of ATG for treatment of familial haemophagocytic lymphohistiocytosis.[124] Most centres treating these rare patients utilise irradiated components. Although there is no evidence from the literature, the authors consider this as a prudent practice. For patients receiving potent T-cell depleting serotherapy (e.g. ATG) for inherited immune dysfunction, irradiation will continue until there is evidence of immune reconstitution (will require immunological review).

Recommendations. **All patients treated with purine analogue drugs (fludarabine, cladribine, bendamustine and pentostatin) should receive irradiated blood components indefinitely (2/C).**

Patients with CLL or other haematological diagnosis treated with alemtuzumab should receive irradiated components (2/C).

Patients with aplastic anaemia undergoing treatment with ATG or alemtuzumab should receive irradiated blood components (2/C).

Patients receiving ATG or other T-lymphocyte-depleting serotherapy for rare types of immune dysfunction conditions should receive irradiated blood components (2/C).

Chimeric antigen receptor T-cell (CAR-T) therapy. CAR-T therapy is a complex and innovative treatment and it is currently approved in the UK for the treatment of some cases of lymphoma and acute leukaemia. A patient's own T cells are collected and genetically altered to recognise target antigens expressed on the cell surface of specific neoplastic cells.[125] CAR-T therapy can lead to significant immunosuppression.

In addition to the immunosuppression associated with CAR-T administration, the process of development of CAR-T therapy involves autologous lymphocyte collection by apheresis; the apheresis product could theoretically contain viable lymphocytes, which could contaminate the final product and lead to TA-GvHD. Therefore, it is recommended that the guidance for autologous stem cells also be followed for CAR-T cells. It has to be noted that no cases of TA-GvHD secondary to CAR-T cells administration have been reported to SHOT, nor were any cases found in the literature review; it is expected that patients receiving CAR-T therapy will already have other indications for blood component irradiation.

Recommendations. **Patients (adult and paediatric) undergoing peripheral blood lymphocyte collections for future 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 (1/C).**

Aplastic anaemia. Adult and paediatric patients following the diagnosis of aplastic anaemia are not known to have increased susceptibility for TA-GvHD and no cases have been identified by the literature search or reported to SHOT.

Recommendation. **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) (1/B).**

Acute leukaemia and non-Hodgkin lymphoma (NHL). Use of irradiated blood components is not routinely recommended for adults or children receiving treatment for acute leukaemia or NHL, except for HLA-selected platelets, granulocytes, donations from first- or second-degree relatives or if patients receive treatment with purine analogues, alemtuzumab or HSCT (1/B).[91] This is consistent with adult and paediatric practice in the UK, with no cases of TA-GvHD reported since 2012. For intermediate forms of lymphoma that show some features of HL, such as grey zone lymphoma, there is no current evidence to suggest that irradiation is required.

Recommendation. **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, transfusion of granulocytes, donations from first- or second-degree relatives, or due to current or previous treatment (2/C).**

Use of irradiated cellular blood components for patients receiving immunosuppressive agents (ATG or alemtuzumab) for non-haematological indication: multiple sclerosis (MS), vasculitis and solid organ transplantation. Potent immunosuppressive agents are used with increasing frequency for patients with autoimmune conditions or in the context of solid organ transplantation. The writing group reviewed the evidence for irradiation when alemtuzumab is used for treatment of patients with MS, vasculitides and solid organ transplantation with the following conclusions and recommendations.

Multiple sclerosis (MS)—Alemtuzumab was licensed as a treatment for active MS in 2013 (EU) and 2014 (USA). Evidence in relation to the level of immunosuppression is based

on the results of Phase III clinical trials[126–128] and subsequent publications[129,130] assessing the incidence of opportunistic and other infections in relation to treatment. Vaccinations are effective at ≥1 month after each treatment cycle.[131] Overall patients are immunocompetent following alemtuzumab treatment when given according to the published regimes and current protocols for MS (alemtuzumab [12 mg/day], infused intravenously on 5 days at baseline and 3 days at 12 months) and therefore they should not be considered at risk of TA-GvHD.

There are currently no reported cases of TA-GvHD following treatment with alemtuzumab for MS. The summary of product characteristics (SPC) for alemtuzumab (now marketed as Lemtrada® for MS) does not include a recommendation for irradiation of cellular blood components.

Vasculitis—Alemtuzumab has been used 'off label' for refractory vasculitides and Behçet's syndrome since 1989 in approximately 250 patients. It is mentioned as a treatment option in the NHS England Behçet's syndrome treatment pathway. No data are available from randomised controlled trials. Mortality, side-effects, development of opportunistic and other infections as well as autoimmune complications have been published.[132–135] A range of opportunistic infections has been observed after alemtuzumab, but these have not differed in type or frequency from those seen with other immunosuppressive treatments. There has been no obvious increased risk of late infection or increased risk of malignancy and no cases of TA-GvHD have been reported.

Solid organ transplantation—GvHD is a rare complication of solid organ transplantation. Most reported cases have been in liver and intestinal transplant recipients, likely reflecting the large lymphoid load within the transplanted organ.

Since 2001 the majority of solid organ transplant recipients have received induction immunosuppression, with either interleukin 2 (IL2) receptor-blocking antibody (basiliximab) or T-cell depleting antibody (ATG or alemtuzumab). The induction dose of ATG is typically 6mg/kg, and a single dose of 30mg of alemtuzumab.

Although the existing recommendation is that alemtuzumab-treated patients should receive irradiated cellular blood components, practice in UK solid organ transplant units is variable. A retrospective review of >600 transfused patients treated with alemtuzumab conditioning for renal transplantation in one centre did not identify any risk of TA-GvHD,[136] despite receiving non-irradiated cellular blood components according to the local practice. Similarly, most USA blood banks do not routinely irradiate blood following treatment with alemtuzumab for solid organ transplantation.[79]

Use of irradiated cellular blood components for solid organ transplanted recipients treated with ATG (either as a pre-transplant conditioning or for treatment of graft rejection) has not been recommended in previous guidelines[91] and it is not included at the licence indications for Atgam®[137] (commonly used preparation of ATG).

There have been no confirmed cases of TA-GvHD in the UK since routine LD of blood components became standard practice in 1999, while >50 000 patients have received an organ transplant since then. Accordingly, there is no indication for irradiation of cellular blood components administered to alemtuzumab or ATG-treated solid organ transplant recipients.

Recommendations. **Use of irradiated cellular blood components is not indicated following treatment with alemtuzumab using the schedule currently recommended for MS or vasculitis (1/B).**

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 (1/B).

Rituximab (anti-CD20)

Use of irradiated components following treatment with rituximab is not recommended[91] and no case of TA-GvHD has been reported in the literature or to SHOT following this treatment (regardless of the patient's underlying diagnosis).

Recommendation. **Treatment of patients with rituximab is not an indication for use of irradiated cellular blood components unless this is indicated for a different reason (underlying diagnosis, type of component or previous treatment) (1/B).**

New immunosuppressive agents

Despite the development and wide usage of new potent immunosuppressive agents, no cases of TA-GvHD have been reported in the literature. The authors are unable to make any recommendation for those agents and advise that manufacturers' recommendations should be followed.

Blood prescription/authorisation and administration issues

It is the responsibility of the clinical team involved with the patient's care to identify patients at risk of TA-GvHD, to inform the transfusion laboratory, and to request and prescribe/authorise cellular blood components as irradiated. This will facilitate appropriate bedside checks and ensure patients' specific requirements are met.[138,139]

Laboratory information management systems (LIMS) should be able to hold information regarding patients' specific requirements and prevent selection of non-irradiated cellular components unless appropriate overrides have been authorised.

For patients under shared care, clinical areas and transfusion laboratories must ensure adequate communication about the requirement for irradiated components.

Patients requiring irradiated components should be informed of the need and the reasons for this.[140] Where possible patients should carry cards to facilitate provision of appropriate components.

Recommendations. **Where patients require irradiated cellular blood components, components must be requested and clearly prescribed as irradiated (1/C).**

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 (1/C).

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 (1/C).

Patients requiring irradiated cellular blood components should receive appropriate information. Where possible patients should carry cards to facilitate provision of appropriate components (1/C).

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 establishments and wider consultation

Acknowledgements

The authors wish to thank Jacky Wilson for help in undertaking the literature review.

The BSH Transfusion task force members at the time of writing this guideline were Susan Robinson, Gavin Cho, Edwin Massey, Sharon Zahra, Paul Kerr, Richard Soutar, Wendy McSporran, Richard Haggas, Chloe George, Katie Hands, Fiona Regan, Shruthi Narayan and Karen Madgwick. The authors would like to thank them, the BSH sounding board, and the BSH guidelines committee for their support in preparing this guideline.

Declaration of interests

The BSH paid the travel expenses incurred during the writing of this guidance.

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. Ania Manson has undertaken advisory boards with CSL and Pharming, received speakers' fees from CSL and had educational grants from CSL, Pharming, Takeda and Shire. Dinakantha Kumararatne has received educational grants from CSL Behring and Shire (now Takeda).

The following members of the writing group Theodora Foukaneli, Paul Kerr, Paula H. B. Bolton-Maggs, Rebecca Cardigan, Alasdair Coles, Andrew Gennery, David Jane, Helen V. New and Nicholas Torpey have no conflicts of interest to declare.

Review process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines/).

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 BSH nor the publishers accept any legal responsibility for the content of the guidelines.

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Appendix 1
Major changes since the last guideline

1. 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 (unlikely) evidence of TA-GvHD over the next few weeks. Where possible, older blood should be used (>14 days) unless there are specific indications for using fresher red cells. For neonates and infants, see BSH guidelines for transfusion of fetuses, neonates and older children[40] for a suggested hierarchy of blood component characteristics to use in emergency.
2. 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/μl, of which ≥30% are naive T lymphocytes, there is no need to irradiate red cells or platelets. If it is not possible to undertake T-cell investigations prior to surgery, irradiated cellular blood components should be given until immunological investigations have been undertaken.
3. Adults, and children aged > 2 years without a significant history of infection, 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.
4. Patients (adult and paediatric) undergoing peripheral blood lymphocyte collections for future CAR-T cell reinfusion 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 (1/C).
5. Use of irradiated cellular blood component is not indicated following treatment with alemtuzumab at the schedule recommended for multiple sclerosis or vasculitis.
6. 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.

Appendix 2
Search strategy and results November 2016

A. The search strategy requested for this guideline:

1. Transfusion associated graft-*versus*-host disease (TA-GvHD)

AND

Contributory factors

Prevention

campath-1h or alemtuzumab

Bendamustine

Anti-thymocytic globulin (ATG)

Brentuximab (or anti-CD30)

solid organ (kidney/ pancreas/ liver/ heart/ lung) transplant

transplantation and Induction/ antibody induction/ T cell depletion/ lymphocyte depletion/ thymoglobulin/ Anti-thymocytic globulin (ATG)/ ATGAM/antilymphocytic globulin (ALG)/campath1H/ alemtuzumab/ muromonab-CD3/Orthoclone OKT3

multiple sclerosis (MS)/ vasculitis/ aplastic anaemia/ DiGeorge/ congenital/primary immunodeficiency

idelalisib/ ibrutinib/ Rituximab/ purine analogues(fludarabine, pentostatin and cladribine)

bone marrow/ peripheral stem cell/allogeneic transplantation/ autologous bone marrow transplantation/ Hodgkin disease, Hodgkin lymphoma

2. T-cell depletion

AND

1. Campath 1H or alemtuzumab
2. Brentuximab
3. Bendamustine
4. Anti-thymocytic globulin (ATG)/ ATGAM/ anti-lymphocytic globulin(ALG)
5. Idelalisib, ibrutinib, rituximab
6. Purine analogues (fludarabine, pentostatin and cladribine)
7. Transplantation and combine immunosuppression

3. Immune reconstitution post-Hodgkin lymphoma/Hodgkin disease

B. Details of the searches

1. Search overview for transfusion-associated graft-*versus*-host disease

Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	21/11/16	6
Issue 10 of 12 2016		0
CDSR (The Cochrane Library)		0
Issue 11 of 12 2016		
DARE (THE Cochrane Library)		
Issue 2 of 4 2015		
(All searched from 2008–)		
MEDLINE (OVID) 2008 to 18/11/16	21/11/16	78
EMBASE (OVID) 2008 to 18/11/16	21/11/16	210
CINAHL (Ebsco) 2008 to Nov 2016	21/11/16	20
Web of Science (SCI-exp & CPCI-S)	21/11/16	91
2008 to Nov 2016		
Total		**405**
After de-duplication		**239**
Further duplicates removed during review (9)		**230**
Exclusions (78)		
Not relevant to clinical question (74)		
No abstract and, from title, not likely to be useful (4)		

Breakdown of remaining results

Articles included	**115**
Alternative methods (40)	
Background/diagnosis (8)	
Clinical indications (8)	
Irradiation techniques/effects (29)	
Practice audit (8)	
Reported cases (22)	
Possible articles	**37**
Possibly of interest (10)	
Possibly relevant based on title only (27)	

Search terms used. TA-GvHD *or* TAGvHD *or* transfusion-associated graft-*versus*-host *or* transfusion-associated graft vs host disease

Searches restricted to English language where available.

2. Search overview for immune reconstitution in Hodgkin disease

Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	28/11/16	2
Issue 10 of 12 2016		0
CDSR (The Cochrane Library)		0
Issue 11 of 12 2016		
DARE (THE Cochrane Library)		
Issue 2 of 4 2015		
(All searched from 2008–)		
MEDLINE (OVID) 2008 to 25/11/16	28/11/16	18
EMBASE (OVID) 2008 to 23/11/16	28/11/16	118
CINAHL (Ebsco) 2008 to Nov 2016	28/11/16	1
Web of Science (SCI-exp & CPCI-S)	28/11/16	24
2008 to 25 Nov 2016		
Total		**163**
After de-duplication		**129**
Further duplicates removed during review (2)		**127**
Exclusions (85)		
Not relevant to clinical question (83)		
No abstract (2)		

Breakdown of remaining results

Articles included	10
Most relevant (9)	
Rituximab therapy (1)	
Possible articles	32
Allo transplant (23)	
Possibly of interest (9)	

Searches restricted to English language where available.

Search terms used

1. Hodgkin Disease/
2. (hodgkin* not non-hodgkin*).tw.
3. 1 or 2
4. Radiotherapy/
5. radiotherapy.tw.
6. drug therapy/ or chemotherapy, adjuvant/
7. chemotherapy.tw.
8. exp Adrenal Cortex Hormones/
9. (Corticosteroid* or Prednisolone or Methylprednisolone or Dexamethasone).tw.
10. Bone Marrow Transplantation/
11. transplant*.tw.
12. exp Biological Therapy/
13. exp Stem Cell Transplantation/
14. ("biologic* therap*" or therapy or treatment*).tw.
15. or/4-14
16. ·3 and 15
17. ((recovery or reconstitution or regeneration) adj5 immun*).tw.
18. ·16 and 17
19. limit 18 to (english language and yr="2008 -Current")

3. Search overview for T-cell depletion

Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	22/11/16	45
Issue 10 of 12 2016		0
CDSR (The Cochrane Library)		2
Issue 11 of 12 2016		
DARE (THE Cochrane Library)		
Issue 2 of 4 2015		
(All searched from 2008–)		
MEDLINE (OVID) 2008 to 21/11/16	22/11/16	664
EMBASE (OVID) 2008 to 21/11/16	22/11/16	1823
CINAHL (Ebsco) 2008 to Nov 2016	22/11/16	14
Web of Science (SCI-exp & CPCI-S)	22/11/16	384
2008 to 22 Nov 2016		
Total		**2932**
After de-duplication		**2138**
Further duplicates removed during review (34)		**2104**
Exclusions (1980)		
Not relevant to clinical question (1807)		
No abstract (173)		

Breakdown of remaining results

Articles included	54
Most relevant (31)	
Allo transplant (23)	
Possible articles	70
Possibly of interest (67)	
Possibly relevant based on title only (3)	

Searches restricted to English language where available

Search terms used

1. MeSH descriptor: [Lymphocyte Depletion] this term only
2. (T-lymphocytes near/2 deplet*):ti,ab,kw (Word variations have been searched)
3. (T-cell near/2 deplet*):ti,ab,kw (Word variations have been searched)
4. #1 or #2 or #3
5. alemtuzumab:ti,ab,kw (Word variations have been searched)
6. Campath 1H":ti,ab,kw (Word variations have been searched)
7. Brentuximab:ti,ab,kw (Word variations have been searched)
8. MeSH descriptor: [Bendamustine Hydrochloride] this term only
9. Bendamustine:ti,ab,kw (Word variations have been searched)
10. MeSH descriptor: [Antilymphocyte Serum] this term only
11. (Antithymocytic globulin or antithymocytic serum):ti,ab,kw (Word variations have been searched)
12. (antilymphocytic globulin or antilymphocytic serum):ti,ab,kw (Word variations have been searched)
13. (Antilymphocyte near/2 (globulin or serum)):ti,ab,kw (Word variations have been searched)
14. (ATG or ATGAM or ALG):ti,ab,kw (Word variations have been searched)
15. Idelalisib:ti,ab,kw (Word variations have been searched)
16. ibrutinib:ti,ab,kw (Word variations have been searched)
17. MeSH descriptor: [Rituximab] this term only
18. Rituximab:ti,ab,kw (Word variations have been searched)
19. (purine analogue* or purine analog):ti,ab,kw (Word variations have been searched)
20. fludarabine:ti,ab,kw (Word variations have been searched)
21. MeSH descriptor: [Pentostatin] explode all trees
22. pentostatin:ti,ab,kw (Word variations have been searched)
23. MeSH descriptor: [Cladribine] explode all trees
24. cladribine:ti,ab,kw (Word variations have been searched)
25. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. MeSH descriptor: [Bone Marrow Transplantation] explode all trees
27. transplant*:ti,ab,kw (Word variations have been searched)
28. #26 or #27
29. combined immunosuppression:ti,ab,kw (Word variations have been searched)
30. #28 and #29
31. #25 or #30
32. #4 and #31 Publication Year from 2008 to 2016

Appendix 3
Search updates 2019 for irradiated blood components guideline

Overview for transfusion-associated graft-*versus*-host disease

Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library)	30/08/19	11
Issue 8 of 12 2019		4
CDSR (The Cochrane Library)		
Issue 8 of 12 2019		
(Both searched from 2016–)		
MEDLINE (OVID) Nov 2016 to 29/08/19	30/08/19	24
EMBASE (OVID) Nov 2016 to 2019 week 34	30/08/19	67
CINAHL (Ebsco) Nov 2016 to Aug 2019	30/08/19	16
Total		**122**
After de-duplication		**102**
Further duplicates removed during review (4)		**98**
Exclusions (70)		
Not relevant to clinical question (65)		
Too early (4)		
No abstract and, from title, not likely to be useful (1)		

Breakdown of remaining results

Articles included	28
Alternative methods (10)	
Irradiation techniques/effects (4)	
Practice audit (5)	
Reported cases (9)	

Overview for immune reconstitution in Hodgkin disease

Records generated

Database searched	Date searched	Results
CENTRAL (The Cochrane Library) Issue 8 of 12 2019	30/08/19	3 0
CDSR (The Cochrane Library) Issue 8 of 12 2019 (Both searched from Nov 2016–)		
MEDLINE (OVID) Nov 2016 to 29/08/19	30/08/19	4
EMBASE (OVID) Nov 2016 to 2019 week 34	30/08/19	21
CINAHL (Ebsco) Nov 2016 to Aug 2019	30/08/19	5
Total		**33**
After de-duplication		**30**
Exclusions (25)		**5**
Not relevant to clinical question (22)		
Too early (3)		

Breakdown of remaining results

Articles included	**5**
Most relevant (5)	

Overview for T-cell depletion

Records generated

Database searched	**Date searched**	**Results**
CENTRAL (The Cochrane Library) Issue 8 of 12 2019	30/08/19	33
CDSR (The Cochrane Library) Issue 8 of 12 2019 (Both searched from Nov 2016–)		0
MEDLINE (OVID) Nov 2016 to 29/08/19	30/08/19	137
EMBASE (OVID) Nov 2016 to 2019 week 34	30/08/19	332
CINAHL (Ebsco) Nov 2016 to Aug 2019	30/08/19	9
Total		**511**
After de-duplication		**465**
Further duplicates removed during review (2)		**463**
Exclusions (437)		**26**
Not relevant to clinical question (412)		
Too early (8)		
No abstract (17)		

Breakdown of remaining results

Articles included	**26**
Non-transplant treatments (7)	
HSCT (19)	