Received: 27 August 2020 | Revised: 14 October 2020 | Accepted: 16 October 2020

DOI: 10.1111/trf.16189

TRANSFUSION MEDICINE

TRANSFUSION

Missed irradiation of cellular blood components for vulnerable patients: Insights from 10 years of SHOT data

Johnathon Elliot[1] | **Shruthi Narayan**[1] | **Debbi Poles**[1] | **Victoria Tuckley**[1] | **Paula H. B. Bolton-Maggs**[1,2]

[1]Serious Hazards of Transfusion Office, Manchester Blood Center, UK

[2]Faculty of Biology, Medicine and Health, University of Manchester, UK

Correspondence
Paula H. B. Bolton-Maggs, Serious Hazards of Transfusion Office, Manchester Blood Center, Plymouth Grovie, Manchester M13 9LL, UK.
Email: paula.bolton-maggs@manchester.ac.uk

Abstract

Background: Irradiation of cellular blood components is recommended for patients at risk of transfusion-associated graft-vs-host disease (TA-GvHD). Prestorage leucodepletion (LD) of blood components is standard in the UK since 1999.

Study Design and Methods: Analysis of 10 years' reports from UK national hemovigilance scheme, Serious Hazards of Transfusion (2010-2019), where patients failed to receive irradiated components when indicated according to British Society for Haematology guidelines (2011).

Results: There were 956 incidents of failure to receive irradiated components all due to errors. One hundred and seventy two incidents were excluded from analysis, 125 of 172 (72.7%) because of missing essential information. No cases of TA-GvHD were reported in this cohort. The 784 patients received 2809 components (number unknown for 67 incidents). Most failures occurred in patients treated with purine analogues (365) or alemtuzumab (69), or with a history of Hodgkin lymphoma (HL) (192). Together these make up 626 of 784 (79.9%). Poor communication is an important cause of errors.

Conclusion: Leucodepletion appears to reduce the risk for TA-GvHD. None of 12 cases of TA-GvHD reported to SHOT prior to introduction of LD occurred in patients with conditions recommended for irradiated components by current guidelines. Irradiation indefinitely for all stages of HL is not based on good evidence and is a difficult guideline to follow. Further research on long-term immune function in HL is required. Variation between different national guidelines reflects the very limited evidence.

1 | INTRODUCTION

Transfusion-associated graft vs host disease (TA-GvHD) is a very rare and usually fatal complication of cellular blood component transfusion. Since its recognition in 1965,[1] measures were introduced to prevent it.[2] TA-GvHD is caused by donor lymphocytes engrafting in the recipient and irradiation of cellular components to eradicate lymphocytes is recommended for specific groups of patients in British Society for Hematology (BSH) guidelines since 1996.[3,4]

The Serious Hazards of Transfusion (SHOT) scheme is the United Kingdom (UK) national hemovigilance organization since 1996. Hemovigilance reporting includes errors when specific patient requirements are not met, such as missed component irradiation, and serious clinical outcomes including cases of confirmed TA-GvHD.

Since the implementation of universal prestorage leucodepletion (LD) in UK (United Kingdom) Blood Services from August 1999 only three cases of TA-GvHD have been reported to SHOT compared to four in each of the preceding 3 years. Irradiated components were not indicated for these 12 (immunocompetent) patients transfused prior to universal LD.[5] One occurred in the period of transition to universal LD in 1999. This was a patient with myeloma who received fresh red cells (<7 days old), not irradiated as there was no indication, and it was not clear whether the LD components were LD at the bedside (which may be less effective) or prestorage at a blood center. The second case occurring after introduction of LD followed treatment for relapsed acute lymphoblastic leukemia (ALL) in 2001, and the patient received non-irradiated LD components. The third case resulted from an intrauterine transfusion (IUT) with maternal blood which was not LD or irradiated. The infant died at 3 months of age. This confirms the high risk associated with HLA-related fresh blood in the absence of irradiation and LD.[3,6]

Here we review the data reported to SHOT from January 2010 to December 2019 where patients did not receive irradiated components when indicated according to BSH guidelines.[3]

2 | METHODS

In the UK transfusion-related serious adverse events (SAE) and reactions (SAR) are reportable by law to the Medicines and Healthcare products Regulatory Agency (MHRA)[7] and also professionally mandated to be reported to SHOT. From 2010, reports were made through a purpose-built online database (Dendrite). Repeat episodes (not duplicates) for the same patient are reported as separate incidents or in some cases are summarized in a single report. Data are submitted through the MHRA "Serious Adverse Blood Reactions and Events" (SABRE) online portal by registered transfusion personnel in each Trust or Health Board, and additional details are sought by SHOT through the linked questionnaire summarized in Figure 1. SHOT incident specialists review the information provided and confirm the classification. Incidents in each category are reviewed by designated experts (SHOT working expert group). Annual reports are published each July. Reporting is confidential and anonymous with no identifiable patient data. Duplicate reports are identified by source, date of

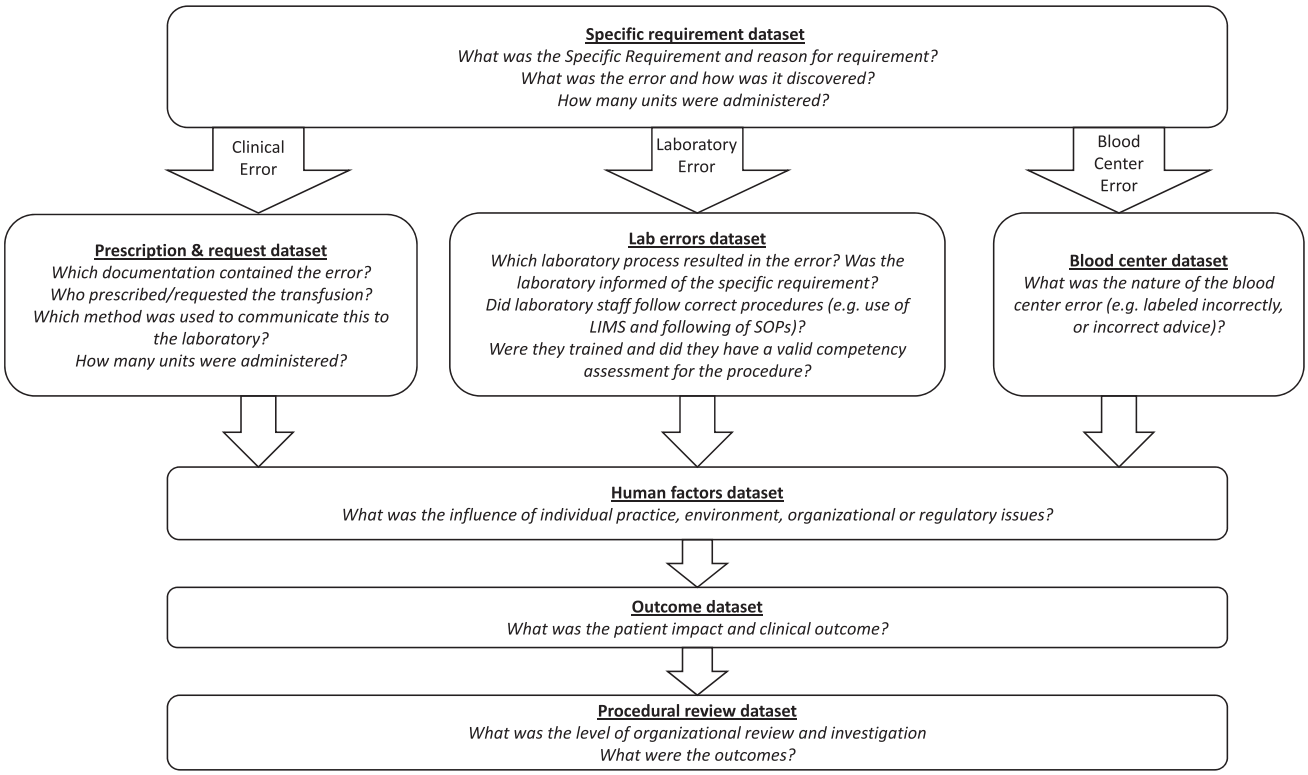

FIGURE 1 Flow diagram summarizing the SHOT questionnaire for cases where the specific requirements are not met

TABLE 1 Indications for irradiation of cellular components defined by UK guidelines[3]

1. All HLA-selected components
2. Granulocytes
3. Infants
   a. Red cells or platelets for intrauterine transfusion (IUT)
   b. Red cells for neonatal exchange transfusion (ET) following previous IUT and other neonatal ET as long as this would not cause a delay
   c. Top-up red cell transfusions after previous IUT for 6 mo after the expected date of delivery[a]
   d. Platelet transfusions for neonatal alloimmune thrombocytopenia and then red cell or platelet transfusions for 6 mo after the expected date of delivery[a]
4. Severe T-cell immune deficiency syndromes
5. Hodgkin lymphoma at any stage of disease for life
6. Treatment with purine analogues and alemtuzumab (anti-CD52) indefinitely
7. Patients with aplastic anemia treated with antithymocyte globulin or alemtuzumab
8. Solid organ transplants if alemtuzumab was used in the conditioning regimen
9. Stem cell transplants
   a. During autologous harvest and harvest from stem cell donors and for 7 days prior
   b. Autograft from initiation of conditioning until 3 mo post-transplant or 6 mo post-transplant if conditioning included total body irradiation
   c. Allograft from initiation of conditioning chemoradiotherapy until 6 mo post-transplant or until lymphocyte count $>1 \times 10^9$/L; give indefinitely with ongoing chronic graft vs host disease or continued immunosuppressive treatment is required

[a]This recommendation was based on two cases of TA-GvHD reported in immunocompetent infants (1974) after IUT and ET for Rh hemolytic disease[24].

incident, patient date of birth, and are excluded from this analysis.

Reports where non-irradiated components were transfused against guidelines were analyzed from January 2010 to December 2019. Participation in SHOT reporting by UK National Health Service Trusts/Health Boards is close to 100%, however there are wide variations in reporting levels between different reporting organizations.[8] This suggests that there may be an element of under-reporting, and it is likely that not all cases of missed irradiation have been reported to SHOT. However, TA-GvHD is a severe and usually fatal disease and missed reporting is very unlikely.

The guidelines for use of irradiated components over this period in the UK are summarized in Table 1.[3] Reports were excluded if key data were missing; also, those where irradiated components were no longer required, and those where the reason given was not part of national guidelines. Incomplete reports with some data missing are included where we considered that there was sufficient evidence in the case report to confirm that irradiated components were required (Figure 2).

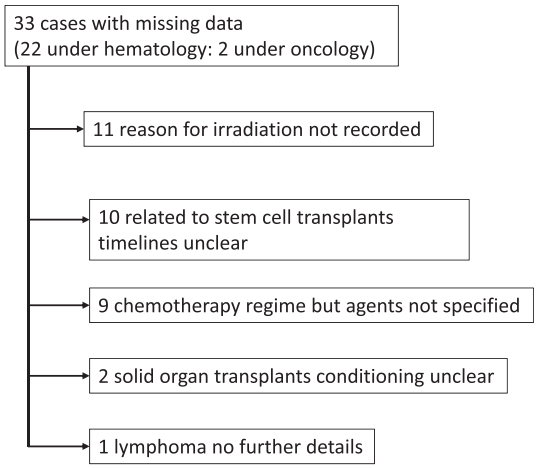

FIGURE 2 Further details of 33 reports included with missing data

3 | RESULTS

In this 10-year period, SHOT received 956 reports where patients had received non-irradiated blood components when indicated (Figure 3). No cases of TA-GvHD were reported in relation to these incidents.

3.1 | Cases excluded

A total of 172 cases were excluded. There was insufficient information provided for 125 of 172 (72.7%) particularly missing diagnosis and indication for irradiated components, or unclear timelines in relation to stem cell transplants (SCT). In 32 of 172 (18.6%) irradiated components were not indicated according to the guidelines,[3] for example cases of non-Hodgkin lymphoma (NHL), renal transplants conditioned with anti-thymocyte globulin (ATG) or where there was a hospital-wide irradiation policy. Seven excluded incidents were near misses: administration of non-irradiated red cells avoided by intervention of a patient, relative, or ward staff, or where irradiated red cells were issued by chance. (Incidents reported to SHOT primarily as near misses are not included in this analysis.) In eight others a previously appropriate indication had expired, for example, years following an autologous SCT.

3.2 | Cases included

Figure 3 shows 784 included incidents. The majority were patients receiving purine analogues (365/784, 46.6%), or

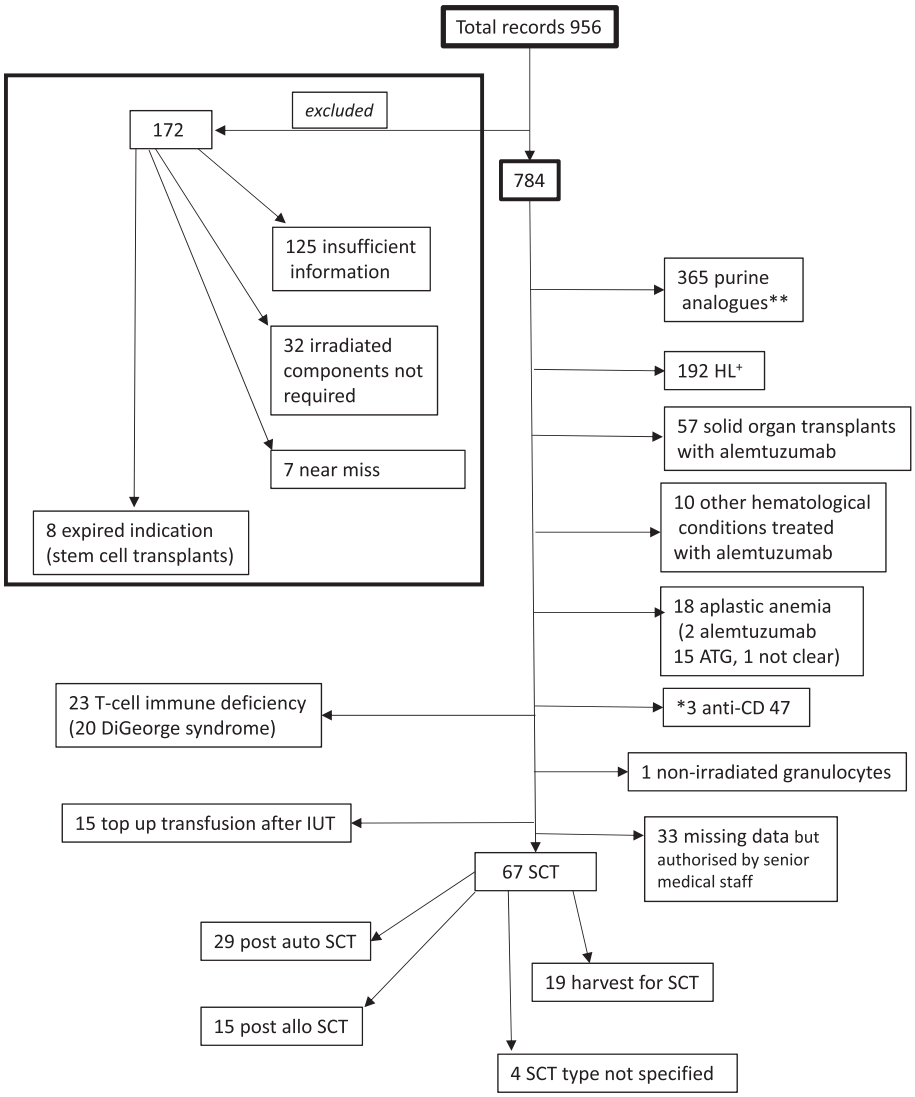

FIGURE 3 Classification of reports where irradiation was missed 2010-2019. AA, aplastic anemia; ATG, antithymocyte globulin; HL, Hodgkin lymphoma; SCT, stem cell transplant. *Irradiation not part of national guidelines but indicated as part of a clinical trial. **One patient received both a purine analogue and alemtuzumab; three patients also had allograft stem cell transplants. +One patient had also received autograft SCT

alemtuzumab (69/784, 8.8%) and those with previous or current Hodgkin lymphoma (HL) (192/784, 24.5%), these three indications together account for 626 of 784 (79.9%). All are indications for provision of irradiated cellular components indefinitely.

Twenty-three cases of T-cell immune deficiency were recorded of which 20 had DiGeorge syndrome: ten were aged 2 years or less, five aged 5 to 20 years and five over 20 years of age. Fifteen neonates who had received previous IUT had later top-up transfusions with non-irradiated red cells with no evidence of harm. There were 67 cases relating to SCT subclassified as shown in Figure 3.

3.3 | Distribution of incidents by specialty

More than half these incidents occurred in patients whose transfusions had been authorized by hematologists, 437 of 784 (55.7%). The number of units implicated in each episode was documented in 717 of 784 (91.5%) reports. The 437 hematology cases correspond to 1685 of 2809 (60.0%) blood component units (number of units unknown in 32 hematology cases and 67 overall).

A current or previous diagnosis of HL is frequently missed. In this cohort 6 HL patients received 20 or more components, a total of 702 of 2809 units, 25.0% of recorded components. One patient regularly transfused for Diamond-Blackfan anemia received 486 non-irradiated units from the time HL was diagnosed in 1997 until 2016. More than half the patients with HL were under hematology or oncology: 105 of 192 (54.7%). The others were under many specialties including medicine, surgery, cardiology, and others where the medical staff are unlikely to be familiar with the lifelong specific requirements for HL, and where a historic diagnosis may be overlooked. The total recorded units transfused for patients with HL was 1154 of 2809 (41.1%).

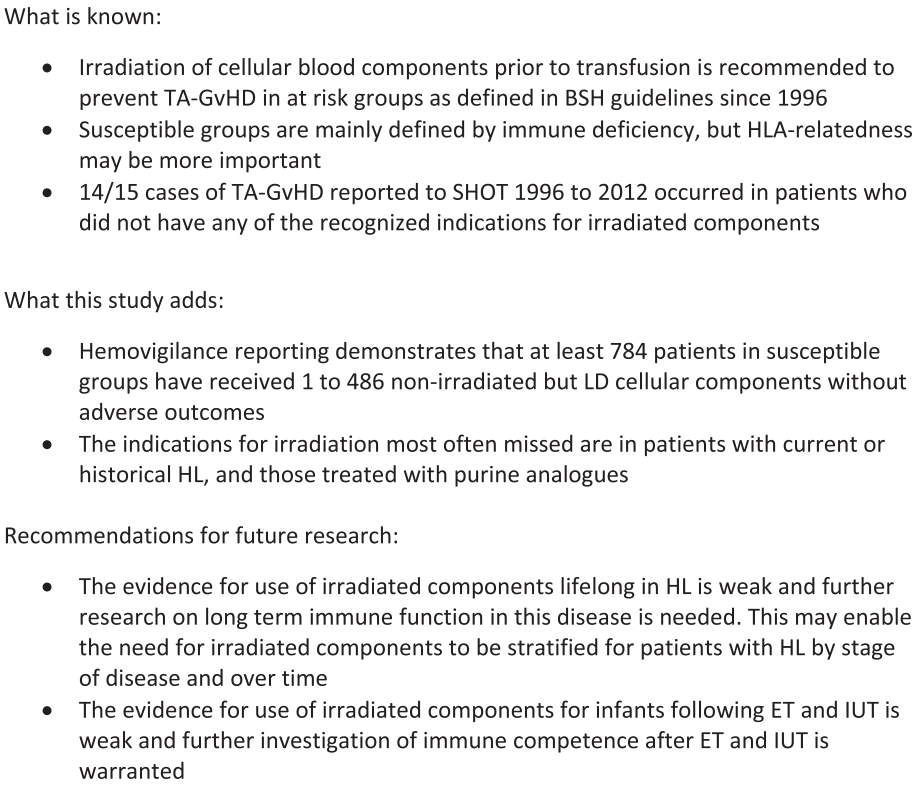

FIGURE 4 What is known and what this study contributes

Most incidents were due to clinical errors, 695 of 784 (88.7%) (one not specified). These were usually failures of communication within a single organization (failure to inform the transfusion laboratory that irradiated components were indicated) or between organizations where patients were under shared care, for example patients who received a SCT in one center and were then followed up at a different hospital (nearer to home) with failure to share relevant information. The remaining 89 of 784 (11.4%) cases were due to errors in the transfusion laboratory.

A summary of what is known about this topic, what this study adds, and recommendations for further study is provided in Figure 4.

4 | DISCUSSION

These SHOT hemovigilance data show that several patients have received many non-irradiated components when these were indicated, but none developed TA-GvHD. This disease is a rare but usually lethal event and universal prestorage LD appears to have a protective role but is not sufficient to prevent all cases of TA-GvHD. The criteria for LD established by the UK Blood Services are that >99% of components should contain $<5 \times 10^6$ leucocytes per unit and >90% $<1 \times 10^6$ per unit with 95% confidence.[9] However, not every component is checked and there is a small failure rate with the risk that viable lymphocytes may be transfused.[5] It is notable that the 12 cases of TA-GvHD reported prior to LD did not have indications for irradiation at the time of transfusion (three followed cardiac surgery, five had B-cell diseases, one neonate and one adult each had non-specific immune deficiency, and two had no identified risk factors). HLA-relatedness and transfusion of fresh red cells are both recognized as important risk factors.[6] For these 12 SHOT-reported cases, three were HLA-related (nine not recorded), and two received red cells <7 days old.[5]

The most common conditions where irradiation was missed were in patients with hematological malignancy, under hematologists and oncologists. These conditions were treatment with purine analogues or alemtuzumab, and previous or current HL. Many cases (67) were reported in relation to SCT. While more than 60% of red cell transfusions are now given to medical patients, only 28% were under hematology in one regional study.[10] This suggests hematology is overrepresented in these errors, where irradiation is more often a requirement and training needs improvement. Communication errors, especially between clinical and laboratory areas or between shared care hospitals, gaps in knowledge, failure to identify indications for specific requirements, and failure to provide full clinical details on request forms are the reasons for erroneous requests. Staff shortages, distractions, work pressures, and urgency of requests further

compound this. There are additional opportunities to detect omission of irradiation later in the transfusion process if staff complete their part of the process correctly. Hematology and oncology medical and nursing staff should be knowledgeable about specific requirements and have documented treatment pathways. Before administration of blood components, staff should always check that any additional clinical requirements have been met, particularly the need for irradiated components.[11]

The education and training of those responsible for the prescription, ordering, and administration of blood components must be improved, especially in high throughput areas such as hematology. Electronic blood management systems should be considered in all clinical settings where transfusion takes place. An "end-to-end" electronic clinical and laboratory transfusion process with electronic patient records, electronic blood authorization/prescription supporting clinical decision making, interoperability with the laboratory information management systems (LIMS) and use of national databases for historical alloantibodies help improve transfusion decisions and promote patient safety.[8] Inappropriate administration of non-irradiated blood components was avoided in some cases by a patient or relative questioning staff at the time of transfusion. A well-informed patient or relative can be a powerful advocate for transfusion safety. Patient education and provision of an irradiated blood component alert card can provide an additional layer of protection, especially when patients are managed across multiple sites. Patients must be empowered to question medical and nursing staff in all matters regarding blood transfusion and this would help to mitigate risk.

People with a history of HL in remission or cured may be admitted with an unrelated illness to non-hematology departments, as evidenced here, or different hospitals, and a criticism of the 2011 BSH guideline for life long irradiated components in HL was that it may be very difficult or impossible to follow. Nevertheless, this recommendation persists in the updated guideline.[5]

TA-GvHD is reported in NHL as well as HL, but NHL was thought to carry a lower risk.[12,13] The 1996 guideline[4] recommended irradiated components for people with HL "at any stage" of disease, but not those with NHL, and "life-long" was added to the revised guideline[3] based on the same references.[12,13] The caution with HL is based on evidence of long-term immune dysfunction in apparently cured patients reported in the 1980s[14,15] and earlier.[5]

It is notable that no cases of TA-GvHD have been reported in patients with HIV infection despite very severe T-cell immune deficiency in contrast to cases reported in immunocompetent recipients. Unfortunately, once a recommendation is made (irradiated components for HL 1996) and reinforced ("for life," 2011) it becomes dogma because to change it potentially puts patients at risk ("dread factor"), despite the limited evidence.[16]

Reflecting the paucity of evidence, different guidelines vary in their recommendations for HL, NHL and other B-cell diseases.[17] Although irradiation is not recommended in UK guidelines for NHL or ALL (unless there are other indications) both conditions mandate irradiation in the three centers in Canada and the United States (US) contributing to the world-wide review[6] and should be "considered" for NHL and in leukemia when associated with severe lymphopenia according to Australia and New Zealand guidelines[18]; both countries (and Canada) have universal prestorage LD. There is also considerable variation in policies within the US.[19] Previous Netherlands guidelines have recommended irradiation for HL only stages 3 and 4, but in their current revision out for consultation[20] irradiation is not thought necessary for HL at any stage (the Netherlands also have universal prestorage LD).

All cases of HL are not the same. Further studies are needed to assess immune function by modern methods in HL at different stages. Perhaps then the requirement for irradiated components could be stratified by severity of disease and over time. The evidence should be gathered and assessed.

4.1 | Other considerations and unanswered questions

HLA-relatedness has been identified as a risk factor for many years, and the contribution of immune deficiency is now questioned. In that review of 348 TA-GvHD cases published from around the world, 227 had no evidence of immune deficiency.[6]

Although DiGeorge syndrome in infancy may be associated with severe T-cell deficiency this does not persist. The revised BSH guidelines[5] recommend that irradiated components will not be required for these patients over 2 years of age or adults unless they have a significant history suggestive of T-cell immunodeficiency as even in neonates with DiGeorge syndrome immune deficiency is rare.[21]

4.2 | What are the disadvantages of component irradiation?

Irradiation results in increased hemolysis and potassium leakage from red cells. As a result of this the shelf-life of red cells for neonatal exchange and for other large

volume transfusions to infants is reduced to 24 hours after irradiation.[22] Standard irradiated red cells in the UK have a shelf life reduced from 35 to 14 days. Sourcing irradiated components may result in delayed transfusion due to availability or limited stock in individual hospitals. It is important to have the right priority: irradiation may add an additional layer of safety, but LD is protective, and patients should not die from anemia or bleeding while waiting for irradiated components. Irradiation also adds cost (approximately an additional 7% to each component). These problems are compounded when irradiation is inappropriate in the first place or continued beyond the indicated duration. All patients with flags for irradiation in 2016 were studied in a large center, 232 of 430 had lifelong indications but 181 had temporary indications (autologous SCT in 166) and flags were not removed in 58; for a further 17 irradiation was not required. Together these two groups received 849 unnecessarily irradiated components, 497 units of red cells and 352 of platelets.[23]

4.3 | This study has some limitations

SHOT data collection relies on hospital transfusion staff to recognize incidents and enter the reports. The rate of reporting is very variable even between organizations of similar size and is almost certainly incomplete.[7,8] It is likely that there are many more instances of missed irradiation than reported here. Many reported cases were excluded from analysis because of incomplete information. Over time SHOT has revised and improved the questionnaires and this study suggests further modifications would be helpful (eg, details of timing in relation to SCT, stage of HL), but there needs to be a balance between the detail requested and the feasibility of completion by busy hospital staff.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

DP provided the SHOT data; Johnathon Elliot, Paula H. B. Bolton-Maggs and Shruthi Narayan designed the study; Johnathon Elliot performed the data analysis and wrote the methods and results sections; Paula H. B. Bolton-Maggs supervised writing the paper; all authors reviewed and revised the paper.

ORCID

Paula H. B. Bolton-Maggs https://orcid.org/0000-0001-6751-7862

REFERENCES

1. Hathaway WE, Githens JH, Blackburn WR, Fulginiti V, Kempe CH. Aplastic anemia, histiocytosis and erythrodermia in immunologically deficient children. Probable human runt disease. N Engl J Med. 1965;273(18):953–958.
2. Anderson KC, Weinstein HJ. Transfusion-associated graft-versus-host disease. N Engl J Med. 1990;323(5):315–321.
3. Treleaven J, Gennery A, Marsh J, et al. Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Hematology blood transfusion task force. Br J Haematol. 2011;152(1):35–51.
4. The BCSH Transfusion Task Force, Voak D, Chapman JD, Finney D, et al. Guidelines on gamma irradiation of blood components for the prevention of transfusion-associated graft-versus-host disease. Transfus Med. 1996;6:261–271.
5. Foukaneli T, Kerr P, Bolton-Maggs P, et al. Guidelines on the use of irradiated blood components. Br J Haematol. 2020. https://doi.org/10.1111/bjh.17015.
6. Kopolovic I, Ostro J, Tsubota H, et al. A systematic review of transfusion-associated graft-versus-host disease. Blood. 2015;126(3):406–414.
7. Blood Safety and Quality Regulations 2005 (as amended). 2005. https://www.health-ni.gov.uk/articles/blood-safety-and-quality-regulations-2005-amended/. Accessed August 23, 2020.
8. Narayan S, Poles D, the SHOT Steering Group. The 2019 Annual SHOT Report (2020). https://www.shotuk.org/shot-reports/report-summary-and-supplement-2019/. Accessed August 23, 2020.
9. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Leucocyte depletion. 2015. https://www.transfusionguidelinesorg/red-book/chapter-7-specifications-for-blood-components/7-1-leucocyte-depletion. Accessed August 20, 2020.
10. Tinegate H, Chattree S, Iqbal A, et al. Ten-year pattern of red blood cell use in the North of England. Transfusion. 2013;53:483–489.
11. Robinson S, Harris A, Atkinson S, et al. The administration of blood components: A British Society for Hematology Guideline. Transfus Med. 2018;28(1):3–21.
12. Anderson KC, Goodnough LT, Sayers M, et al. Variation in blood component irradiation practice: Implications for prevention of transfusion-associated graft-versus-host disease. Blood. 1991;77(10):2096–2102.
13. Spitzer TR, Cahill R, Cottler-Fox M, Treat J, Sacher R, Deeg HJ. Transfusion-induced graft-versus-host disease in patients with malignant lymphoma. A case report and review of the literature. Cancer. 1990;66(11):2346–2349.
14. Fisher RI, DeVita VT Jr, Bostick F, et al. Persistent immunologic abnormalities in long-term survivors of advanced Hodgkin's disease. Ann Intern Med. 1980;92(5):595–599.
15. Twomey JJ, Rice L. Impact of Hodgkin's disease upon the immune system. Semin Oncol. 1980;7(2):114–125.
16. Goldfinger D, Burner JD. You can't get CMV from a blood transfusion: 2017 Emily Cooley award lecture. Transfusion. 2018;58(12):3038–3043.
17. Manduzio P. Transfusion-associated graft-versus-host disease: A concise review. Hematol Rep. 2018;10(4):7724.
18. Australian and New Zealand Society of Blood Transfusion Ltd. Guidelines for prevention of transfusion-associated graft-

versus-host disease 2011. https://anzsbt.org.au/wp-content/uploads/2018/06/PreventionofTA-GVHD.pdf. Accessed August 23, 2020.
19. Pritchard AE, Shaz BH. Survey of irradiation practice for the prevention of transfusion-associated graft-versus-host disease. Arch Pathol Lab Med. 2016;140(10):1092–1097.
20. Richtlijn Bloedtransfusiebeleid – deel 3 Autorisatiefase juli 2020. https://nvbtransfusie.nl/wp-content/uploads/2019/07/Richtlijn-Bloedtransfusiebeleid-deel-3_ter-autorisatie.pdf. Accessed August 23, 2020.
21. Habel A, Herriot R, Kumararatne D, et al. Towards a safety net for management of 22q11.2 deletion syndrome: Guidelines for our times. Eur J Pediatr. 2014;173(6):757–765.
22. New HV, Berryman J, Bolton-Maggs PH, et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol. 2016;175(5):784–828.
23. Booth C, Winter P, Allard S. Challenges in the appropriate use of irradiated blood components at a large UK haemato-oncology centre. Vox Sang. 2017;112(suppl 1): P-627.
24. Parkman R, Mosier D, Umansky I, Cochran W, Carpenter CB, Rosen FS. Graft-versus-host disease after intrauterine and exchange transfusions for hemolytic disease of the newborn. N Engl J Med. 1974;290:359–363.

How to cite this article: Elliot J, Narayan S, Poles D, Tuckley V, Bolton-Maggs PHB. Missed irradiation of cellular blood components for vulnerable patients: Insights from 10 years of SHOT data. *Transfusion*. 2021;61:385–392. https://doi.org/10.1111/trf.16189