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Preventing Transfusion-Associated Graft-Versus-Host Disease with Blood Component Irradiation: Indispensable Guidance for a Deadly Disorder

Sorcha Ní Loingsigh[1], **Willy A. Flegel**[2], **Jeanne E. Hendrickson**[3,4], **Christopher A. Tormey**[3]

[1]Department of Haematology, University Hospital Galway, Newcastle Road, Galway, Ireland

[2]Department of Transfusion Medicine, NIH Clinical Center, National Institutes of Health, Bethesda, MD USA

[3]Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT USA

[4]Department of Pediatrics, Yale University School of Medicine, New Haven, CT USA

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A European Viewpoint (SN)

Transfusion associated graft versus host disease (TAGVHD) is a rare but largely fatal complication of transfusion characterised by fever, rash, diarrhoea, hepatitis and pancytopenia two to 30 days after transfusion. Diagnosis is confirmed detecting persistent donor lymphocytes from a transfused component in affected tissue biopsy or peripheral blood of recipients (CDC, 2018) (Jawa *et al.*, 2015) (Sage *et al.*, 2005). Diagnosis can be challenging due to competing differentials and lack of leucocytes.

TAGVHD pathophysiology is extrapolated from case reports/case series and experimental mouse models. Current thinking is that transfused lymphocytes which are not eliminated by the recipient immune system, proliferate and attack recipient organs which are recognised as foreign, including recipient bone marrow (Bahar and Tormey, 2018) (Kleinman and Stassinopoulos, 2018). Three main factors appear to influence risk – the lymphocyte load in the product (reduced by leukoreduction (LR)), immune competence (specifically impaired cellular mediated immunity) and shared human leucocyte antigen (HLA) type between recipient and donor (related or unrelated). Components implicated have largely been (fresh) red cells, historically fresh whole blood, platelets, and fresh (never frozen) plasma (Kopolovic *et al.*, 2015). However, cases continue to be described in patients with without

Correspondence: Christopher A. Tormey, MD, Department of Laboratory Medicine, Yale University School of Medicine, 55 Park Street, PS329-D, New Haven, CT USA 06520, 1-203-688-2441 (phone) 1-203-688-2748 (fax) christopher.tormey@yale.edu.

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these risk factors, demonstrating how our ability to predict this complication remains limited (Kopolovic *et al.*, 2015).

Universal pre-storage leucoreduction of blood was introduced in the United Kingdom (UK) in 1999 (Bennett and Daraktchiev, 2013) and has become standard in Western Europe over the past twenty years (European Committee on Blood Transfusion, 2014). This policy change is credited with reducing the number of cases reported to haemovigilance systems in recent years by reducing the lymphocyte load in the product (Kleinman and Stassinopoulos, 2018). Approaches to further reduce harm currently rely on identifying *patients* at risk due to underlying immunocompromise or *products* known or suspected (e.g. family donations) to be HLA matched. In these circumstances, irradiation of blood components is recommended in the previous British Committee for Standards in Haematology (BCSH) guidelines (Treleaven *et al.*, 2011).

Irradiation of blood components using gamma or X rays has been shown to prevent proliferation of transfused lymphocytes in the recipient by inactivating lymphocytes via cross-linking DNA (Kleinman and Stassinopoulos, 2018). Universal irradiation of blood components could avoid the need to differentiate between recipients and simplify stock management. However, irradiation affects the quality of red cell concentrates, (particularly) with rises in potassium concentration and haemolysis over time (Serrano *et al.*, 2014) (Qadri *et al.*, 2017) (de Korte *et al.*, 2018). By limiting the shelf life. universal irradiation of red cells would be both wasteful (due to the reduction in lifespan) and risks a potentially inferior product avoidably being transfused. Irradiation to order is performed commonly in the US where transfusion services are very differently organised, with many academic centres having the ability to secondarily process blood components (Bahar and Tormey, 2018) – further comments on the applicability of this guidance to US transfusion practice can be found later in this Commentary.

In the UK, where irradiators are usually located in the blood service, irradiated units must be specifically ordered and risks maintaining a dual inventory to avoid delays. As inventory management is not the focus of this guideline and this aspect is not addressed. Fortunately, blanket irradiation is practical for platelets as quality of the product and shelf life is unaffected (Cid, 2017) (Bahar and Tormey, 2018) (Tynngård *et al.*, 2008). This is performed by a number of blood services though not universally throughout the UK.

Decision making and formulating recommendations in this area is difficult. The feared adverse event is rare (making data collection challenging) and has a high fatality rate. Randomised controlled trials are neither feasible nor ethical and the evidence that exists is observational or based on laboratory data. The British Society of Haematology (BSH) have updated their guidance on indications for use of irradiated blood components based on recent and historic publications and relevant UK Serious Hazards of Transfusion (SHOT) reports (Foukaneli et al., 2020). The authors emphasise that their guideline aims for risk reduction or mitigation rather than elimination - as previously noted, TAGvHD has been observed in the absence of standard risk factors.

TAGvHD has been linked with fresh blood components in reported cases – possibly due to a reduction in T cell viability or antigen expression (Jawa *et al.*, 2015). The new guidance recommends red cell units >14 days post collection (if irradiated units unavailable in urgent situations) and similar advice was recently incorporated into Canadian guidelines also (Morrison et al, 2018).

Modern medicine now includes an array of treatments that induce immune defects raising the question regarding whether irradiation of blood components is indicated for recipients. These clinical practice changes include the expansion of indication of pharmaceutical agents already in use (e.g. Alemtuzumab in Multiple sclerosis, as immunosuppressive therapies post solid organ transplantation), and novel therapies (Chimeric antigen T cell therapy – CAR-T). A strength of this guideline is that it examines these situations in this update and attempts to provide guidance for these complex patients, based on the degree of immune competence expected in the recipient. The recommendation that irradiation is not required even if anti-lymphocyte globulin or alemtuzumab are used in solid organ transplantation may make inventory management easier for hospital transfusion laboratories and simplify shared care arrangements.

Immune incompetence in foetuses and neonates is well described. Historic cases of TAGvHD were described in the past following intrauterine transfusion and neonatal exchange blood transfusion (Parkman *et al.*, 1974). The recommendation for irradiation of components in these circumstances has not changed although the recommendation for small volume “top-up” transfusions for post-natal transfusions following IUT has been removed. The authors’ rationale is that this is less likely with the advent of modern processing methods plus the absence of affected cases of TAGvHD in those patients in this category who did not received irradiated components. Irradiation of blood components for neonates or infants in other circumstances without a known or suspected defect of cellular immunity is still not recommended. Helpfully, in this latest revision, the authors define cellular immunity defects. The rise in plasma potassium in red cell components following irradiation is a potential risk for neonatal recipients, given their vulnerability to hyperkalaemia. This is exacerbated by a large volume transfusion such as exchange red cell transfusion hence, the recommendation to transfuse as close to time of irradiation as possible (24 hours) remains.

Shared donor and recipient HLA alleles (especially where the donor are homozygous for the shared allele) is a longstanding known TAGvHD risk factor (Bahar and Tormey, 2018). Therefore, the recommendation to irradiate cellular blood components donated by close family members or from volunteer HLA matched donations (e.g. HLA matched platelet donations) remains unchanged.

Any policy which requires prescribers to order a specific product carries the dual risks of omission (not ordering when indicated) and commission (ordering when not required). Unsurprisingly, the former is common. SHOT data on omissions reassuringly shows no cases have been associated with TAGvHD, in line with the assumption that this is an uncommon phenomenon and the incidence fell following universal leucoreduction which mitigates risk further that leucocyte reduction does mitigate the risk – given that the incidence fell after the introduction of universal leucoreduction in the UK. However, given

the rarity of TAGvHD, overall evidence is insufficient to remove the need for irradiation for most indications.

What feasible alternatives to irradiation does the future hold? Filtering to decrease the number of leucocytes mitigate the risk of TAGvHD may be one approach. An intriguing study by Chun et al. (Chun *et al.*, 2020) demonstrated a reduction in the residual leucocyte count in the product, although not sufficient to confirm a reduction in TAGvHD and came at the expense of approximately 20% of the red cell content.

Pathogen reduction (by amotosalen or riboflavin- based methods), developed to reduce the risk of bacterial and other infectious transfusion transmitted infections presents another strategy. Due to nucleic acid crosslinking, it can result in reduced lymphocytes able to proliferate (Kaiser-Guignard *et al.*, 2014). Data from a manufacturers' laboratory study suggests it may do so more efficaciously (Kleinman and Stassinopoulos, 2018) and pathogen reduced platelets do not need to be irradiated. However, pathogen reduction is still in development for red cells where the greatest disadvantage to irradiation lies.

While frustrating to those tasked with writing guidelines, the lack of recent data in many ways is encouraging as it suggests that the phenomenon of TAGVHD has remained rare and that current risk reduction methods are effective. Changes in this area are more likely to be driven by changes in blood component processing than abandoning the feasible risk reduction methods which have served us well to date.

An USA viewpoint (CAT, WAF, JEH)

As noted and well-described by our colleague Dr. Loingsigh, transfusion-associated graft-versus-host disease (TA-GVHD) is a highly deadly adverse event with limited treatment options (Bahar & Tormey, 2018). As such, there has been much emphasis in the global transfusion medicine community on averting this hazard. From the preventative standpoint, irradiation of cellular blood components has emerged as the most effective means to inactivate residual Tlymphocytes within cellular blood components, thereby halting their engraftment in transfusion recipients. Some institutions (Atreya et al., 2019) and Japan as a country (Asai *et al.*, 2000; Makino *et al.*, 2012) are applying universal irradiation for their cellular blood components. However, given the potentially deleterious side-effects of irradiation on stored blood components (Anand *et al.*, 1997) and the reduction in 'shelf life' of some irradiated units (Bahar & Tormey, 2018), it may not always be practical nor feasible to irradiate every cellular blood component in a blood bank's inventory (Pritchard & Shaz, 2016). Thus, several practical questions regarding irradiation remain, particularly in the US, with those at the forefront being: 1) when should blood banks irradiate products according to available evidence or best clinical practice?; 2) which products qualify for irradiation?; and 3) which patient populations need products to be irradiated?

The answers to many of these questions can be found in the irradiation guidance issued by the British Committee for Standards in Haematology Blood Transfusion Task Force by Foukaneli and colleagues (2020). This document plays a pivotal role in providing the most up-to-date evidence on whether (and when) blood component irradiation is necessary for

transfusion recipients. The updated guideline covers new clinical situations, unknown 10 years ago, such as therapies with novel cell types and monoclonal antibodies, particularly helpful to US institutions which may have irradiation devices on premises and can make decisions for irradiation on a case-bycase basis. Beyond these extraordinarily helpful and detailed clinical recommendations, the document provides other key information, including: a review of TA-GVHD cases/scenarios reported in the worldwide literature and the UK SHOT Hemovigilance database since the prior update; advice regarding logistical issues surrounding irradiation such as effective doses and labeling of products; potential adverse effects of irradiation; and whether there are acceptable alternatives to irradiation. The importance and scope of this document cannot be overstated, as it is the leading and most comprehensive guideline available to the international blood bank, transfusion, hematology/oncology, and transplantation communities on the indications as well as perils/pitfalls for cellular blood component irradiation.

Foukaneli and colleagues (2020) have made a number of updates to the well-cited prior guidance (Treleaven *et al.*, 2011), primarily to account for how the landscapes of blood banking/transfusion medicine, hematology, and cellular therapies have changed over the past decade. Some of the updates, concepts, additions, and/or modifications incorporated into the 2020 guidance, particularly relevant to US and worldwide transfusion practice, include:

- An emphasis on the age of stored components, leukodepletion (LD) status, and risk of TA-GVHD
  - Risks appear highest with fresh (ie, <14-day-old units) non-LD units
    - Older units that have undergone LD may be reasonable to use in urgent situations when there is not time to irradiate
- Removal of recommendations for irradiation of ‘top up’ and other routine transfusions to neonates (term or pre-term), particularly if units used for transfusion have undergone LD
  - Recommendations for irradiation persist for intrauterine transfusions and larger volume neonatal exchange therapies
- Addition of a new recommendation to irradiate cellular blood components for patients with suspected congenital hemophagocytic lymphohistiocytosis (HLH) syndromes associated with lymphopenia, until T-cell immunodeficiency has been excluded
  - T-cell enumeration of mature and naïve T-lymphoid elements is now recommended as a potentially useful marker for irradiation decisions in medical and/or surgical settings
- Addition of a new recommendation to irradiate blood components for patients undergoing chimeric antigen receptor T-cell (CAR-T) therapy
  - Patients undergoing CAR-T therapies should essentially be treated as those undergoing autologous stem cell transplant

- These individuals should receive irradiated cellular components for 7 days prior to, and also during, the CAR-T harvest and for at least 3 months following CAR-T infusion (if not longer, depending on the disease being treated)

- Advising that use of alemtuzumab/anti-CD52 or anti-thymocyte globulin (ATG) for patients with non-hematological conditions (e.g., multiple sclerosis or vasculitis) or solid organ transplanted recipients does not require irradiation of cellular transfusion components during or after treatment with those drugs for these select indications
  - On the other hand, the guidelines recommend continued use of irradiated components for transfusion when alemtuzumab or ATG are used for hematological conditions (eg, hematological malignancies, aplastic anemia) or for immune dysfunction disorders

While Foukaneli and colleagues have done a terrific job scouring the literature and compiling extensive evidence- or experience-based recommendations for blood component irradiation, there remains much that we don't understand regarding the prevention of TA-GVHD. Remaining challenges for the transfusion medicine and hematology communities regarding TA-GVHD include:

- Obtaining more rigorous data on the safety profile of new, highly potent immunosuppressive agents with regard to TA-GVHD risks and need for irradiation of cellular components
  - Until such data are collected, it is likely prudent to consider irradiation of cellular blood components for transfusion in such scenarios unless strongly contraindicated
- Evaluating the safety profile of non-irradiated cellular blood components as a function of the HLA similarity in the donor community
  - Non-directed donations may still pose an increased risk when they derive from smaller communities represented by similar ethnic origin
- Assessing the required duration of irradiation modifications to transfusion, particularly for those disorders in which long term or life-long irradiation is currently recommended
  - Evidence-based shortening of the irradiation 'window' could improve several of the logistical hurdles associated with providing irradiated components on a long-term basis
- Better understanding the risks for TA-GVHD in immunocompetent transfused individuals
  - Previously, such individuals were not thought to be predisposed to this adverse event; however, recent reports suggest that immunocompetent hosts make up more of the described TA-GVHD cases than immunosuppressed patients (Kopolovic *et al.*, 2015)

- Are there immunological defects in these seemingly otherwise healthy individuals that have not yet been discovered that may provide a clue to their risks for TA-GVHD, and could these defects serve as a second “hit” beyond HLA homogeneity in donor/recipient populations?
- Is the risk associated with the concatenation of the HLA genes in distinct haplotypes on one chromosome, a feature not routinely captured by current HLA typing?
- Will the routine or universal implementation of pathogen reduction technologies limit risks for TA-GVHD in general (for both immunosuppressed as well as immunocompetent individuals), particularly as the use of these technologies expands to include components such as red blood cells? The UK may not need such guidance at this time, but the question is imminent and seemingly answered in the affirmative outside the UK.

To cause no harm, we have to balance the limited risk of irradiation for most patients versus the substantial risk of non-irradiated cellular blood components for susceptible patients. Unfortunately, we cannot recognize all such patient by routine clinical methods. T-cell mediated immunosuppression may be harmful, even when subtle and not progressing to clinically apparent TA-GVHD. If in doubt, we should generally decide in favor of irradiation.

In summary, Foukaneli and colleagues, on behalf of the British Committee for Standards in Haematology Blood Transfusion Task Force, have composed a vital and highly practical update on the use of blood component irradiation to prevent TA-GVHD. This document should be of great value to blood banks and transfusion services across the globe, be they small community practices or highly-complex tertiary care centers. The authors should be congratulated for their diligent work and the valuable contribution this guidance offers.

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