Australian and New Zealand Society of Blood Transfusion

2nd Edition, January 2024

GUIDELINES FOR THE PREVENTION OF TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE (TA-GVHD)

Australian & New Zealand Society of Blood Transfusion Ltd

Published in Australia by:

Australian & New Zealand Society of Blood Transfusion Ltd
145 Macquarie Street
Sydney
NSW 2000
AUSTRALIA

ISBN No: 978-0-6452251-3-6

1st edition, January 2011
2nd edition, November 2023

Guidelines for prevention of transfusion-associated graft-versus-host disease (TA-GVHD)

Prepared by the Clinical Practice Improvement Committee
Australian & New Zealand Society of Blood Transfusion Ltd
145 Macquarie Street
Sydney
NSW 2000
AUSTRALIA

ANZSBT Clinical Practice Improvement Committee

Clin. A/Prof. Philip Crispin	Australian Capital Territory (Chair)
Ms Christine Akers	Victoria
Ms Kristen Brown	New South Wales
Ms Alana Delaforce	Queensland
Ms Joanne Goodwin	South Australia
Dr Anastazia Keegan	Western Australia
Ms Fiona King	New Zealand
Dr Amanda Ormerod	Victoria
Dr Bryony Ross	New South Wales

Foreword

Transfusion associated graft versus host disease (TA-GVHD) is a devastating and fortunately rare complication of transfusion. Research into low frequency transfusion events is difficult, however, the field has evolved and our understanding of TA-GVHD pathogenesis, risk and risk mitigation has expanded.

Partial HLA matching has emerged from the previous focus on host immunodeficiency, although both remain important risk factors. Leucodepletion, longer storage of red cells and platelet pathogen reduction appear to reduce the reduce the risk of TA-GVHD.

Thankfully, the risk of TA-GVHD in Australia and New Zealand remains low, though difficult to quantify, due to the universal leucodepletion of fresh components and selective irradiation for "high-risk" patient cohorts.

The challenge of incorporating new technologies and understanding of factors already embedded in our transfusion practice has been addressed in these Guidelines using a risk matrix approach. Our usual quality of evidence assessments underpinning many modern guidelines fall short when event frequency is rare.

At the outset, the Clinical Practice Improvement Committee (CPIC) was determined to follow the evidence. This has led to wider recognition of the importance of the age of red cells in TA-GVHD. As such, leucodepleted "older" red cells are now recognised as being very low risk and after 21 days storage, indistinguishable in terms of TA-GVHD risk from irradiated units. This recommendation provides an evidence-based strategy to minimise the risk of TA-GVHD through the transfusion of red cells closer to expiry if irradiated units are not available. Conversely, the Guidelines highlight the need for clinicians to recognise that the transfusion of "fresher" red cells are associated with a higher risk of TA-GVHD.

Finally, the Guidelines consider the universal irradiation of red cells, as we do for platelets in Australia and New Zealand, recognising the impacts on supply and the potential harm associated with red cell storage lesions, of a similar whole of inventory approach. The complexity of our health care environments allows for different approaches to risk mitigation and although the expectation is that most services will target irradiation to at-risk recipients, alternative strategies need to be recognised.

I would like to congratulate the Society on the development of these guidelines. CPIC led their revision and must be recognised for the huge commitment in bringing these together. But they were not alone, and I would like to thank the many Society members who provided feedback and input to update the Guidelines and contribute to optimising blood safety.

Primum non nocere!

Dr Philip Crispin
Vice President, Chair CPIC

Dr Anastazia Keegan
President, CPIC member
January 2024

Summary of amendments to the 2011 guidelines

This edition has undergone a major revision. These changes include:

- Options for implementation of TA-GVHD prophylaxis through universal irradiation immediately prior to red cell issue (section 4.2) or using traditional risk assessment based approach (section 4.3).
- Inclusion of guideline development method (section 1.3)
- Inclusion / update on the treatments of cellular products to reduce the risk of TA-GVHD, including:
    - X-ray irradiation (section 3.3),
    - pathogen reduction technologies (section 3.4),
    - leucocycte depletion (section 3.5),
    - cold storage duration of red cells (section 3.6).
- Inclusion of older cold stored red cells as irradiation equivalent or irradiation safe based on storage duration and minimal to no ability to cause TA-GVHD (section 4.4).
- More specific advice on patient selection in neonates and children (section 5.2)
- Additional advice on assessment for severe immunodeficiency in children (section 5.2)
- Specific advice for emergency transfusions (section 5.9), including in paediatric practice (section 5.2)
- Inclusion of new indications:
    - Chemotherapy equivalent to acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML) induction (section 5.3)
    - Irradiation of blood products to extend to six months post infusion for chimeric antigen receptor (CAR)-T cell or autologous stem cell recipients or (section 5.3)
    - Acute radiation injury
- Removal of indications:
    - Lower dose alemtuzumab (used for solid organ transplantation, multiple sclerosis or similar indications)
- Possible indications have been removed from the guidelines. Clinicians are encouraged to use a risk based assessment when the risk of irradiation is uncertain. Non-Hodgkin lymphoma (including T and B cell malignancies), acute leukaemia (section 5.3), term neonates (section 5.2), long term steroid therapy (section 5.5) and aplastic anaemia (section 5.3) have been discussed in relevant sections as many patients in these groups will require irradiation, although the conditions are not in themselves indications. Patient receiving chemotherapy has been modified to therapy of similar intensity to acute leukaemia induction. Massive transfusion for trauma is no longer considered a possible indication, based on new data (section 6.1).

Contents

Abbreviations and definitions

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ANZSBT	Australian and New Zealand Society of Blood Transfusion
ATG	Antithymocyte globulin
Blood Service	The organisation (or part thereof) that collects, manufactures and distributes fresh blood components. Australian Red Cross Lifeblood and the New Zealand Blood Service fulfil these roles in Australia and New Zealand, respectively.
BSH	British Society for Haematology
CAR	Chimeric antigen receptor
CHD	Congenital heart disease
CPB	Cardiopulmonary bypass
CPIC	Clinical Practice Improvement Committee, a standing committee of ANZSBT
DNA	Deoxyribonucleic acid
ECLS	Extra corporeal life support
ECMO	Extracorporeal membrane oxygenation
ELBW	Extremely low birth weight; weight <1000gm
GVHD	Graft versus host disease
HLA	Human leucocyte antigen
HLH	Haemophagocytic lymphohistiocytosis
IST	Immunosuppressive therapy
IUT	intrauterine transfusion
Neonatal small volume transfusion	10-20ml/kg, given over 4 hours
Neonatal large volume transfusion	At least equivalent to a single circulating blood volume (approximately 80 ml/kg for neonates) over 24 h or 50% of the circulating volume (approximately 40ml/kg for neonates) within 3 h [1]
NHL	Non-Hodgkins lymphoma
NICU	neonatal intensive care unit
TA-GVHD	Transfusion-associated graft-versus-host disease
VLBW	Very low birth weight; weight <1500gm

Tabulated recommendations

Table 1: Recommendations for TA-GVHD prevention practice

Practice	Recommendation	Section Reference
General transfusion practices	R 1: Cellular blood products should be transfused in accordance with evidence-based recommendations to prevent complications of unnecessary transfusions.	3.1
X-ray irradiation	R2: Gamma-rays and x-rays are considered equivalent for TA-GVHD prevention.	3.3
Pathogen inactivation technologies	R3: Pathogen inactivation technologies are a suitable alternative to irradiation.	3.4
Storage duration of red cells	R4: Cold-stored red cells in storage for 21 days or more are irradiation equivalent.	3.6
Practical implementation of TA-GVHD prevention strategies	R5: Both universal irradiation and selective risk-based irradiation strategies are acceptable practice.	4..2 & 4.3
Irradiation practice	R6: Cellular components including red cells, platelets and granulocytes must be irradiated, where there are appropriate indications.	4.4
Irradiation practice	R7: Stem cells, donor T lymphocytes and chimeric antigen receptor T lymphocytes must NOT be irradiated.	4.4
Irradiation practice	R8: Cryoprecipitate, fresh frozen plasma and manufactured plasma components do not require irradiation.	4.4
Irradiation practice	R9: The minimum radiation dose is 25Gy to all parts of the unit, with no part of the unit receiving more than 50Gy.	4.4
Irradiation practice	R10: Irradiator installation, safety and security must be under the supervision of suitably qualified personnel.	4.4
Irradiation practice	R11: Irradiators must be installed, calibrated, validated and maintained to deliver doses outlined above.	4.4
Irradiation practice	R12: Where an irradiation equivalent or TA-GVHD safe component is issued where an irradiated component was otherwise indicated, the unit must be tagged accordingly.	4.4
Inventory management	R13: Inventory management of irradiated blood components must prioritise ABO identical transfusion and avoid increased wastage.	4.5

Table 2: Clinical Indications for Irradiation (or equivalent TA-GVHD prevention strategy)

Indication	Recommendation	Section Reference
Intrauterine transfusion	R14: Cellular products used for IUT should be irradiated.	5.1
Intrauterine transfusion	R15: Red cells for IUT should be as fresh as possible and must be transfused within 24 hours of irradiation.	5.1
Neonatal exchange transfusions	R16: Red cells for neonatal exchange transfusion should be irradiated.	5.2.1
Neonatal exchange transfusions	R17: Red cells for neonatal exchange transfusion should be as fresh as possible and must be transfused within 24 hours of irradiation.	5.2.1
Neonatal small volume ("top-up") transfusions	R18: In neonates who have received prior IUT irradiation is required for small volume transfusions.	5.2.2
Paediatric emergency and large volume transfusions	R19: For emergency transfusions in the setting of neonatal resuscitation, irradiated cellular components are not required, even in neonates otherwise considered at higher risk of TA-GVHD.	5.2.3
Congenital and acquired immunodeficiencies in infants and children.	R20: In patients with severe congenital T-lymphocyte immunodeficiency syndromes with significant qualitative or quantitative T-lymphocyte deficiency are it is recommended that cellular blood products are irradiated.	5.2.4
Remission induction and consolidation therapy for acute leukaemia and chemotherapy of similar intensity for other malignancies	R21: Irradiation of cellular products is recommended for patients undergoing chemotherapy equivalent to AML or ALL intensive remission induction and consolidation therapy, to continue for a period of 6 months following intensive therapy. Irradiation is not required when supportive care only or lower intensity chemotherapy is offered.	5.3.1
Allogeneic stem cell transplantation	R22: Patients undergoing allogeneic stem cell transplant should receive irradiated cellular blood components from the time of conditioning and for a minimum of 12 months post-transplant, but to continue while there is active GVHD or immunosuppression for GVHD	5.3.2
Autologous stem cell transplant	R23: Autologous stem cell transplant recipients should receive irradiated cellular blood components from the time of initiation of conditioning, with this to be reviewed 6 months post-transplant.	5.3.3
Haematopoietic stem cell donors (including autologous and T cell donors)	R24: Haemopoietic cell donors (including autologous stem cell and T lymphocyte donors) should receive irradiated cellular blood components from seven days prior to the planned collection.	5.3.4
Chimeric antigen receptor T cells	R25: CAR-T cell recipients should receive irradiated cellular products for a period of six months following CAR T cell infusion. Longer or shorter	5.3.5

	periods of may be applied based on conditioning regimens and cellular targets.	
Hodgkin Lymphoma	R26: For patients with Hodgkin lymphoma, irradiated blood components are recommended.	5.3.6
Non-Hodgkin Lymphoma	R27: For people with Non-Hodgkin lymphoma irradiation is not recommended, unless indicated due to specific therapies received.	5.3.7
Aplastic anaemia	R28: For patients with aplastic anaemia, cellular components should be irradiated during and following treatment with immunosuppressive therapy including anti-thymocyte globulin or similar T lymphocyte depleting therapy (e.g., alemtuzumab) and to continue until all immunosuppression has been ceased (including ciclosporin).	5.3.8
Cytotoxic therapies	R29: For patients treated with purine analogues, for malignant or non-malignant indications, cellular components should be irradiated during and following treatment.	5.4
Cytotoxic therapies	R30: For patients with haematological neoplasms treated with alemtuzumab, cellular components should be irradiated during and following treatment.	5.4
HLA-matched donors	R31: Cellular components from HLA matched (HLA compatible) donors must be irradiated.	5.6
Related donors	R32: Cellular components from related donors must be irradiated.	5.7
Radiation exposure / acute radiation injury	R33: Patients requiring cellular blood components due to radiation injury should receive irradiated products.	5.8
Massive transfusion / critical bleeding	R34: Irradiation is not required for critical bleeding or trauma.	6.1

Table 3: Practice Points for irradiation practice and clinical applications

Indication	Recommendation	Section reference
General transfusion practices	PP1: Blood components should be transfused from related or HLA-matched donors only when specifically indicated.	3.1
Leucocyte depletion	PP2: Pre-storage leucocyte depletion reduces the risk of TA GVHD but is not recommended as an alternative to irradiation.	3.5
Leucocyte depletion	PP3: Double leucocyte filtration may further reduce the risk of TA-GVHD however there is insufficient data to recommend its use	3.5
Storage duration of red cells	PP4: Cold-stored red cells in storage for 14 days or more may be considered TA-GVHD safe and utilised for patients at risk of TA-GVHD when irradiation equivalent red cells are not available.	3.6
Practical implementation of TA-GVHD prevention strategies	PP5: Irradiation of all cellular components issued fresh irrespective of recipient risk factors, is the most effective strategy to prevent TA-GVHD. However, it is acknowledged that this approach will not be suitable for most laboratories.	4..2 & 4.3
Practical implementation of TA-GVHD prevention strategies	PP6: Where irradiated inventories are stocked, these should be tailored to minimise stock wastage due to expiry and promote ABO identical red cell transfusion.	4.3 & 4.5
Practical implementation of TA-GVHD prevention strategies	PP7: Processes are required to ensure irradiation requirements are identified and communicated across clinical and laboratory services involved in the care of at-risk patients.	4.3
Irradiation practice	PP8: Red cells should be no more than 14 days of storage at the time of irradiation.	4.4
Irradiation practice	PP9: Red cells should be expired no more than 14 days after irradiation.	4.4
Irradiation practice	PP10: Where irradiated inventories are stocked, these should be tailored to minimise stock wastage due to expiry and promote ABO identical red cell transfusion.	4.4
Irradiation practice	PP11: Fresh (never frozen) plasma should be irradiated for at-risk recipients.	4.4
Irradiation practice	PP12: Deglycerolised thawed red cells may be irradiated if clinically indicated and time permits.	4.4
Neonates and infants with congenital heart disease (CHD) requiring cardiopulmonary bypass (CPB) surgery or extracorporeal life support (ECLS); and those undergoing cardiothoracic surgery.	PP13: Consider evaluation of neonates and infants undergoing cardiac surgery for an undiagnosed T-cell immunodeficiency, and where this is not possible/feasible consider irradiation of cellular components until risk of relevant immunodeficiency has been excluded.	5.2.1.1
Neonates and infants with congenital heart disease (CHD)	PP14: Consider irradiation of red blood cells in suspected T cell immunodeficiency. As a guide, a	5.2.1.1

requiring cardiopulmonary bypass (CPB) surgery or extracorporeal life support (ECLS); and those undergoing cardiothoracic surgery.	CD4+ T-lymphocyte count >400 cells/µl, of which 30% are naive T lymphocytes, largely excludes severe T cell immunodeficiency and in this case, there is no need to irradiate red cell. Discussion with a paediatric immunologist is suggested if there are concerns of a possible T- lymphocyte immunodeficiency.	
Neonates and infants with congenital heart disease (CHD) requiring cardiopulmonary bypass (CPB) surgery or extracorporeal life support (ECLS); and those undergoing cardiothoracic surgery.	PP15: To reduce the risk of hyperkalaemia to patients undergoing CPB, ECMO and cardiac surgery requiring large volume transfusion; IF irradiated red cells are used, transfusion should ideally be as soon as possible post- irradiation and should be within 24 hours of irradiation.	5.2.1.1
Neonatal small volume ("top-up") transfusions	PP16: Term neonates and pre-term (>28 weeks) infants receiving small volume transfusions do not require irradiated blood components.	5.2.2
Neonatal small volume ("top-up") transfusions	PP17: In extremely pre-term (<28 weeks) and extremely low birthweight (<1000g) infants, the decision for irradiated components should be based on additional features rather than only gestational age and weight.	5.2.2
Neonatal small volume ("top-up") transfusions	PP18: Blood banks should have a mechanism for capturing and recording neonates who have received an IUT antenatally and should receive post-natal irradiated top up red cell transfusion.	5.2.2
Neonatal small volume ("top-up") transfusions	PP19: Where irradiated red cells are indicated for small volume neonatal transfusion, then consideration should be given to minimizing the shelf-life following irradiation.	5.2.2
Neonatal small volume ("top-up") transfusions	PP20: Where irradiated red cells are used for small volume neonatal transfusion, it is recommended that inventory be managed so that freshest irradiated products are prioritised for neonatal transfusion wherever possible; that modified components (including paediatric leucodepleted red cell units) be transfused within 48 hours of irradiation as per their manufacturing recommendations; and centrifuged, supernatant removed products (including adult leucodepleted red cell units) be transfused within 14 days of irradiation.	5.2.2
Emergency transfusions and large volume transfusions	PP21: For large volume neonatal transfusion where it has been determined that irradiation is required, red cells should be transfused as soon as possible after irradiation, and preferably within 24 hours of irradiation.	5.2.3
Congenital and acquired immunodeficiencies in infants and children.	PP22: If a severe T-lymphocyte immunodeficiency disorder is suspected, irradiated components should be given while diagnostic testing is undertaken.	5.2.4

Congenital and acquired immunodeficiencies in infants and children.	PP23: Transfusion laboratories should have a mechanism for capturing and recording patients with a severe T lymphocyte immunodeficiency who required irradiated products.	5.2.4
Congenital and acquired immunodeficiencies in infants and children.	PP24: Irradiation of cellular blood components is not indicated for infants or children with temporary defects of T-lymphocyte function, including following viral infections, acquired T-lymphocyte deficiencies, those who are HIV-antibody positive or with acquired immune deficiency syndrome (AIDS)	5.2.4
Hodgkin Lymphoma	PP25: Provision of irradiated products indefinitely for people who have had Hodgkin lymphoma has been recommended, however the evidence for a particular duration following completion of therapy and confirmation of remission is limited and no firm recommendation can be made. An indefinite requirement is advised, with a very low level of certainty. Where cases of non-irradiated transfusions are identified, there should be consideration of reporting to haemovigilance systems to assist is future risk assessments.	5.3.6
Emergency transfusion for patients at risk of TA-GVHD	PP26: In patients at risk of TA-GVHD who need emergency transfusion, the use of the shortest expiry suitable red cells is acceptable if irradiated (or equivalent) units are not available.	5.9

1. Introduction

1.1 Scope

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare iatrogenic complication of transfusion. TA-GVHD has a high mortality rate so the focus must be on prevention.

These guidelines cover the pathophysiology of TA-GVHD, equipment dosimetry and maintenance, clinical indications for irradiated blood components, alternatives to irradiation and risk-management approaches to patient identification, component selection and modification and inventory management to prevent TA-GVHD.

1.2 Background

TA-GVHD results from the engraftment of T lymphocytes into a susceptible recipient, with the risk associated with an individual transfusion depending on the interplay of several factors, including:

1) the number and viability of contaminating lymphocytes in the transfused cellular component;
2) the susceptibility of the recipient's immune system to the engraftment of donor lymphocytes; and
3) the degree of immunological (human leucocyte antigen, HLA) homology between the donor and the recipient.

TA-GVHD can be prevented by reducing or eliminating viable T lymphocytes capable of mounting an immune response in cellular blood components prior to transfusion. Traditionally, this has been achieved through the transfusion of gamma irradiated cellular blood components to recipients perceived to be at risk due to immunodeficiency. While this is an effective strategy, TA-GVHD in immunocompetent individuals is also recognised and, due to the high case-fatality rate, universal gamma irradiation has been applied to some blood components, by some clinical departments or jurisdictions.

Universal irradiation prior to transfusion has been adopted in Australia and New Zealand for platelet concentrates. A large proportion of platelets are transfused to recipients with haematological malignancies who may be at risk and platelet concentrates are always given “fresh” (shelf life of 7 days) due to room temperature storage. The universal irradiation approach aims to prevent transfusion of components with viable T lymphocytes to at risk patients. The same approach has not been adopted for red cells, where irradiation impacts the red cell membrane, causing an increased loss of potassium into the supernatant and affecting the duration of storage.

Since the first edition of these guidelines, there has been increasing evidence that pre-storage leuco-depletion has reduced, but has not eliminated, the risk of TA-GVHD. There is also increasing evidence that cold-stored red cells result in significant loss of T lymphocytes and that TA-GVHD is usually due to transfusion of fresh cellular components. Considering both the population data and *in vitro* evidence, irradiation of all components less than 14 days of storage as close as possible to the time of administration, would be the most efficacious preventative strategy, eliminating TA-GVHD from immune competent and immune deficient recipients alike. This approach eliminates the risk of transfusion of non-irradiated components to susceptible recipients,[2] does not require the consideration of whether new immunosuppressive therapy carry an increased risk of TA-GVHD and protects people otherwise considered not at risk of TA-GVHD, who have made up the majority of cases over recent years.[2] However, this approach requires on-site irradiators and associated infrastructure, including adequate staff, and an irradiation time to enable rapid processing at the time of issue for all non-emergent red cells as they are being issued. This is not practical in most centres.

The ability of T lymphocytes from cold-stored red cells at 21 days to be activated is equivalent to that seen in irradiated red cells;[3,4] and therefore, red cells at or beyond 21 days of storage are "irradiation equivalent." The decline in T-lymphocyte function is not linear; there is an exponential decline in T lymphocyte proliferative capacity earlier in red cell storage. Furthermore, the absence of known cases of TA-GVHD beyond 14 days storage indicates that prolonged storage of red cell components is an efficacious intervention for TA-GVHD prevention.[5] Therefore, leucodepleted red cells at or beyond 14 days of storage are considered "TA-GVHD safe." Irradiating components for a planned transfusion beyond this timeframe is unlikely to increase patient safety and introduces added risk of complications due to red cell membrane changes.

Local practice needs to consider the availability of local resources, such as blood irradiators, stock management practices and implementation strategies. Clinical practice may vary between jurisdictions and over time, such as the use of related donors, which is actively discouraged within Australia and New Zealand. Therefore, while these guidelines have considered international guidelines, they may differ to account for local factors.

1.3 Methods

These Guidelines have been developed by the Clinical Practice Improvement Committee (CPIC) of Australian and New Zealand Society of Blood Transfusion (ANZSBT). International guidelines and previous ANZSBT guidelines were reviewed. A literature search was performed for any articles related to TA-GVHD from 2018 to August 2021 to capture new cases, recommendations or mechanistic studies since the most recent update of the British Society for Haematology (BSH) guidelines.[6] This search was updated in May 2023. The committee accepted that there is adequate evidence that irradiation eliminates the risk of TA-GVHD and that this is not dependent on the clinical patient population. An assessment of the *efficacy* of irradiation was therefore not required for individual clinical indications. Guidance for clinical conditions was therefore decided based on a risk assessment. This included assessing recipient factors (immunodeficiency), the volume of immune competent lymphocytes transfused (component processing to remove or impair T cells, cold storage duration) and the likelihood of HLA partial matching. The occurrence of TA-GVHD was rated as a severe to catastrophic outcome. With the exception of HLA-matched or related donors, the absolute baseline risk (where no other risk factors exist) in the New Zealand and Australian populations was considered to be low. A risk assessment was conducted for each clinical indication (Appendix 3).

The role of radiation induced red cell injury has been considered in these guidelines, and advice provided to minimise the clinical impact. However, the degree of risk is highly variable depending red cell storage time before and after irradiation and therefore the risk assessment table (Appendix 3) does not specifically consider radiation induced red cell injury, unless specifically addressed in the accompanying text.

In patients at risk of both hyperkalaemia and TA-GVHD, if blood is irradiated, it should be transfused within 24 hours of irradiation if large volumes are expected. Such circumstances may arise with major neonatal surgery or sub-galeal haemorrhage. It is acknowledged however, that the risk of hyperkalaemia might outweigh benefit if there are longer storage times for irradiated red cell inventories.

1.4 Terminology

These guidelines are primarily informative. The evidence in support of most of the clinical indications is weak. Guidance is provided in the form of recommendations, where the evidence warrants them, and practice points based on examination of the current literature. The strength of recommendations is indicated by the following (modal) terms:

Must Indicates a strongly recommended practice where compliance would be expected.

Should Indicates a recommended practice where compliance would be expected but alternative practices may be acceptable.

May Indicates a practice that is permitted within the context of the guidelines.

2. Essential features of TA-GVHD

2.1 Pathogenesis and clinical features

There are three essential features required for TA-GVHD. Firstly, the graft must contain immunologically competent cells. Secondly, the recipient must possess antigens capable of stimulating a response in the donor. Thirdly, the recipient must not be able to mount an effective immune response to the donor T lymphocytes.[7] This latter condition can be met either by recipient immunodeficiency or by similarity of donor and recipient HLA antigens, for example where the donor is homozygous for an antigen present in the recipient.

Survival of lymphocytes following transfusion does not in itself constitute TA-GVHD. Microchimerism following pregnancy or transfusion for trauma is of uncertain clinical significance.[8,9] TA-GVHD requires the T lymphocytes to mount an immune response to the host with replication of T lymphocytes and inflammation, and this does not always arise.

Pathologically, TA-GVHD is characterised by lymphocytic infiltrates in multiple organs.[10] In the skin, mononuclear epidermal infiltrates with bullae formation and vacuolisation of basal cells are typical, but not specific.[10,11] Polymorphs and eosinophils are not seen, the latter more suggestive of a drug eruption. Bone marrow is typically hypoplastic and may have a lymphocytic infiltrate or haemophagocytosis. The liver shows lymphocytic infiltrates within the portal tracts. Confirmation of the allogeneic nature of the infiltrate should be confirmed, such as by disparate HLA typing, sex mismatch or molecular evidence of chimerism.[11,12]

The clinical features of TA-GVHD include fever (67.5%) followed by multisystem inflammation with rash (80.2%), liver dysfunction (66.4%), pancytopenia (65.2%) and diarrhoea (43.1%).[5] The median time of onset was 11 days following transfusion, although it may occur later in infants. The rash is typically maculopapular and can become erythrodermic. Lymphocytic infiltrates within the liver cause cholestatic hepatitis and the pancytopenia is largely attributed to marrow hypoplasia.

The mortality rate is approximately 90% and no reported treatments are associated with improved outcomes, highlighting the critical importance of prevention strategies.[5]

2.2 Incidence

The rate of TA-GVHD is uncertain. It varies between populations due to the likelihood of HLA similarity amongst different ethnic groups and blood banking practices, including the use of leucodepletion, irradiation and inventory management practices that influence the age of blood at transfusion. One estimate predicted approximately 1 in 8.3 million transfusions of leucodepleted non-irradiated cells, in countries where irradiation was routine practice for high-risk patients.[13] Incidence rates would be expected to be higher were irradiation not implemented at all. However, approximately half of the reported cases occurred in patients without recognized risk factors.[5]

2.3 Risk factors

Specific interventions to reduce T lymphocyte functionality, such as irradiation and ultraviolet pathogen inactivation processes, both of which interfere with DNA replication, can sufficiently damage T lymphocytes to prevent TA-GVHD.

Where a patient mounts an effective immune response to the transfused T lymphocytes, TA-GVHD is prevented. Immunodeficient patients therefore appear at greater risk. Patient groups that have been identified to be at risk are discussed in Section 5. There are numerous reports of TA-GVHD in immunocompetent hosts. In these cases, the host's ability to recognise allogeneic T lymphocytes as foreign may be impaired due to shared HLA antigens. In particular, where a donor is homozygous for

an allele present in the recipient, the recipient will not see this antigen as foreign, whereas donor cells will identify one of the host antigens as non-self. This is thought to account for majority of TA-GVHD in non-immunocompromised patients and is likely to also contribute to cases in immunodeficient recipients.[5,11]

3. Principles and techniques of TA-GVHD prevention

3.1 General transfusion practices

There have been many large trials comparing liberal and restrictive transfusion strategies for red cells showing no improvement in mortality at haemoglobin concentrations that were previously commonly accepted transfusion triggers.[14] Randomised studies with platelets have also favoured more conservative transfusion triggers.[15]Avoiding transfusion when it is not clinically beneficial is unequivocally good practice, conserves scarce blood supplies and prevents complications of transfusion, including TA-GVHD.

Potentially harmful T lymphocytes with HLA similarity are more likely to be found in family members and HLA matched transfusions. Family donors may be required at times, for example where a patient has an antibody present to a common blood group, where family members may also be antigen negative. Likewise, HLA matched products may be needed, for example with HLA antibody mediated platelet transfusion refractoriness. However, neither related nor HLA matched transfusions should be routine and specific TA-GVHD prevention measures must be applied when they are required.

Recommendation
R 1: Cellular blood products should be transfused in accordance with evidence-based recommendations to prevent complications of unnecessary transfusions.

Practice point
PP1: Blood components should be transfused from related or HLA-matched donors only when specifically indicated.

3.2 Gamma irradiation

Gamma irradiation has been the mainstay of TA-GVHD by inhibiting T lymphocyte proliferation. Doses need to be adequate to prevent T lymphocyte division while maintaining the integrity of the remaining components within the blood product. Irradiation causes DNA damage, inhibiting the ability of cells to divide. T lymphocytes unable to proliferate cannot cause TA-GVHD.

Gamma irradiation is produced from within nuclei by an isotope source; caesium-137 or cobalt-60 are used in source blood irradiators. Irradiation of blood is achieved by exposing units of blood to the irradiation source, typically on a turntable for an appropriate duration to deliver the required dose of radiation. As the source decays, the time taken to irradiate a unit of blood will increase. This requires that the duration of radiation exposure by reviewed regularly and increased to ensure the blood product receives an adequate dose.[16]

Gamma irradiators with a radioactive source are relatively easy to maintain since they are required only to ensure exposure to the radioactive source for the correct length of time. The path of a unit of blood through the irradiator needs to be mapped so that the dose of radiation to all parts of the unit fall within specifications.

Although relatively easy to maintain, having a radioactive source poses potential logistical and security concerns. With the constant production of gamma rays, radioactive sources need to be well shielded to prevent radiation exposure to people working in the vicinity, even when not in use. This is achieved through lead shielding built into the irradiators, making them heavy and requiring consideration of the location and floor load capacity. Caesium-137 and cobalt-60 are not explosive, however if released from the irradiator, are potentially dispersible, posing a security and health risk. This applies for the life of the irradiator, including transport, installation, and disposal. Laboratories

must be aware of and comply with local radiation safety and security policies and legislation applicable to them. Disposal of radioactive materials is also logistically difficult and costly. While gamma source irradiators have a long lifespan, decommissioning and disposal costs should be factored into whole of life cost assessments.

Irradiation has been shown to effectively inhibit lymphocyte proliferation. Using limiting dilution assays, Pelszynski et al[17] and Luban et al[18] have shown that 25Gy effectively inhibits T cell proliferation in red cells and platelet concentrates, respectively. Lower doses do reduce lymphocyte proliferation, even at doses as low as 5Gy, however there have been cases of TA-GVHD at doses lower than 25Gy.

Irradiation does cause damage to red cells. Increased membrane permeability leads to increased haemolysis accompanied by an increased rate of potassium release following gamma irradiation.[19,20] This is dose dependent, so irradiation dose should not be excessive. Haemolysis in red cell units remains within acceptable limits for up to 14 days post irradiation, even when irradiated at 14 days post-collection. An increase in phosphatidylserine expressing red cell microparticles has been found in irradiated red cells. While this may have a procoagulant and proinflammatory effect, the clinical significance of this finding is yet to be determined.[21] Red cell injury is seen in red cell components as well as irradiated whole blood.[22]

Although some studies used lower doses of radiation than currently recommended, platelet morphology, function and survival do not appear to be impaired with radiation.[23-25]

3.3 X-ray irradiation

X-rays are another form of high energy radiation capable of ionising molecules within tissue and causing DNA damage. They have similar or lower frequencies than gamma irradiation and are produced by changes in the energy states of electrons, external to the nucleus, so they do not rely on radioactive decay for their production. X-rays are produced by the excitation and slowing of electrons within an x-ray tube, so they are only produced when required. While there may be more expensive initial outlays and maintenance for x-ray compared with gamma irradiation, x-ray devices do not require additional security measures and decommissioning does not require long term storage of nuclear waste material.

There have been a number of studies showing the efficacy and suitability of x-rays for prevention of TA-GVHD. They have equivalent efficacy in preventing lymphocyte proliferation in mixed lymphocyte culture and mitogen stimulated culture.[26,27] Supernatant haemoglobin and potassium showed irradiation dose dependent increases overtime with minor, clinically insignificant, or no differences between x-ray and gamma irradiated cells, including high concentration red cells for intrauterine transfusion.[27-29] Meli and colleagues compared the quality of red cells irradiated with x-ray or gamma rays and found no clinically meaningful differences in 2,3 DPG, lactate, ATP, lactate production, haemolysis or potassium levels in the supernatants of matched units.[30]

There are fewer data on the effect of x-ray irradiation on platelets. However, compared with gamma irradiation, platelet morphology, function and surface markers appear unchanged with x-ray treatment.[31]

Internationally, there is consensus that gamma and x-ray irradiation should be considered clinically equivalent for the prevention of TA-GVHD.[6,29,32] Although there may be subtle increases in haemolysis rates with x-ray compared with gamma irradiation of red cells, these are clinically insignificant when red cells are used within a 14 days expiration period after irradiation.[28]

Recommendation
R2: Gamma-rays and x-rays are considered equivalent for TA-GVHD prevention.

3.4 Pathogen inactivation technologies

Processes to inactivate blood borne pathogens in platelets are licensed and in use internationally. Although there may be potential to apply these to red cells, they are not yet licensed. These technologies interfere with nucleic acid and are able to reduce leucocyte proliferation in the same way they do in pathogens. Multiple studies have shown a reduction in T cell viability and activation following ultraviolet / riboflavin or amotosalen pathogen inactivation systems.[33-39] Implementation of these technologies usually includes cessation of irradiation. At present, pathogen reduction technologies have not been implemented in Australia and New Zealand. If pathogen reduction technologies are adopted, it will be the responsibility of regulatory agencies and blood component providers to determine efficacy for TA-GVHD. Based on currently available information, pathogen reduction technologies would appear to be suitable alternative to irradiation.[21,40]
It should be noted on the contrary that while gamma irradiation does also reduce some pathogens, at the doses used in blood component irradiation it has variable effects on organisms and is inadequate to effectively reduce pathogens.[41]

Recommendation
R3: Pathogen inactivation technologies are a suitable alternative to irradiation.

3.5 Leucocyte depletion

As T lymphocytes are responsible for TA-GVHD, removing leucocytes should reduce the potential for TA-GVHD. While there are differences between filters, pre-storage leucocyte depletion typically results in a >4 log reduction in the volume of transfused white cells. There are data suggesting a preferential reduction in T cells with leucodepletion filters although this would need to be validated with each filter.[4] While this is a substantial reduction and in some cases may approach theoretical limits for the number of T cells required, cases of TA-GVHD have been reported following transfusion of leucodepleted blood, even with modern filters and T cell proliferative capacity persists following leucodepletion.[4,5]

Since the introduction of universal leucodepletion in the United Kingdom only 2 cases of TA-GVHD have been reported to the SHOT program, compared with 12 cases in the 3 years prior to implementation.[6] Therefore, both in vitro and surveillance data strongly suggest a highly protective effect of leucodepletion, although it remains inadequate to recommend it as a sufficient strategy for high risk situations.

Double filtration has shown a further reduction in leucocytes. With a second filtration at 72 hours, this significantly further reduces the number of leucocytes below detectable levels and is likely to reduce them to levels where TA-GVHD is highly unlikely.[42] Double depletion could therefore be a possible approach to risk minimisation when irradiated blood is not available. However, it does also further reduce the volume of red cells within the product. As all red cells and platelets within Australia and New Zealand are leucodepleted prior to storage, leucodepletion at the time of transfusion could feasibly improve the safety of non-irradiated blood. However, most institutions will now not stock bedside leucocyte filters, so both filter availability and the reduction in red cells transfused may limit this application. There would also be a need to ensure the individual leucocyte filters used are able to produce results equivalent to those reported in the single study available. For

these reasons, double leucocyte filtration is not currently recommended for routine TA-GVHD prophylaxis.

While protective, leucodepletion is not considered equivalent to irradiation and should not be relied upon in circumstances where there are indications for and adequate time to safely source irradiated blood.

Practice Points
PP2: Pre-storage leucocyte depletion reduces the risk of TA GVHD but is not recommended as an alternative to irradiation.
PP3: Double leucocyte filtration may further reduce the risk of TA-GVHD however there is insufficient data to recommend its use.

3.6 Storage duration of red cells

It has been recognised for decades that the majority of cases of TA-GVHD occur following transfusion of blood that is less than 3-4 days old.[43] In their systematic review of all cases of TA-GVHD, Kopolovic et al found that of the 158 cases that reported on the age of the transfused product, 93.7% were described as fresh or <10 days old. The remainder had storage durations of 11-14 days and no cases were reported outside this time frame.[5]

This is supported by in vitro data showing lymphocyte proliferation declines with storage. By day 14, Mykhailova showed a significant reduction in T cell proliferative capacity compared with that seen at day 7 of storage.[4] By day 21 T cell proliferative capacity was below that thought to be required to induce TA-GVHD. Chang and colleagues showed that there was a marked loss of T cell surface antigens required for activation during cold storage and have suggested this causes impairment in T cell activation and proliferation despite maintaining T cell viability.[44] Fiebig and colleagues showed an exponential reduction in the ability for T cells to respond during cold red cell storage but not with room temperature platelet storage, with minimal responses in red cells by day 15.[3]

Recommendation
R4: Cold-stored red cells in storage for 21 days or more are irradiation equivalent.

Practice Point
PP4: Cold-stored red cells in storage for 14 days or more may be considered TA-GVHD safe and utilised for patients at risk of TA-GVHD when irradiation equivalent red cells are not available.

4. Practical implementation of TA-GVHD prevention strategies

4.1 Background

The traditional approach to preventing TA-GVHD is to identify patients at risk and to ensure blood products given to them are irradiated. However, approximately half of all reported cases of TA-GVHD occurred in people with no clearly identifiable risk factors. Universal irradiation would therefore be most efficacious to ensure absolute prevention of TA-GVHD, although this may have a substantial impact on resources, potentially including blood wastage due to reduced shelf-life. It is also apparent that fresh blood carries a much greater risk of TA-GVHD and older blood, particularly if leucodepleted, carries a negligible risk. Therefore, irradiation of all fresh units immediately prior to transfusion, and not irradiating older units, where transfusion services have access to on-site irradiators, is likely to be a highly effective prevention strategy, also eliminating the need to specifically identify patients at perceived higher risk.

These guidelines recognise that services either adopt a policy of local universal irradiation for all appropriate fresh cellular blood products or maintain irradiation only for patients considered at high risk. While the latter will be required for services that do not have an on-site irradiator, the former can be considered, but is not required, for services with access to irradiation immediately prior to transfusion.

In deciding whether to adopt a universal fresh product irradiation policy, institutions with a blood irradiator, or considering on site irradiation, should consider:

- the capacity of the transfusion laboratory to process blood for irradiation in a timely fashion;
- the fate of the blood components, avoiding increased wastage due to irradiated components being issued but not used; and
- the ABO, Rh and Kell composition of red cell inventory, ensuring that irradiation policies do not increase demands for more “universal” blood groups, such as O RhD negative units

4.2 Universal TA-GVHD safe blood for laboratories with on-site irradiators

Most guidelines have suggested that blood irradiation be recommended only for HLA-matched or related donors and for immunocompromised recipients. TA-GVHD however also occurs in immunocompetent recipients and it has been argued that a universal approach to irradiation prior to release from the blood service would eliminate this fatal, otherwise unpredictable complication.[45] While it is not recommended for Australia and New Zealand, this is the strategy currently used in Japan where the risk of receiving HLA-similar blood is greater than in many other populations.[46] Furthermore, there are many institutions or clinical departments within institutions that have adopted universal irradiation policies.

There are difficulties in maintaining a completely irradiated red cell inventory due to the shortened shelf life post irradiation. By contrast, the absence of known TA-GVHD cases after 14 days of storage related to a reduction in viable reactive T cells, especially when combined with leucocyte depletion, suggests that irradiation beyond this time frame might be unnecessary. At 21 days of storage, T cell proliferative capacity is similar to that seen following irradiation.[4]

Most TA-GVHD cases are seen when blood is transfused within the first 4 days of storage.[5] Given the significant impact of storage duration on TA-GVHD risk, irradiation of blood issued fresh to patients, and not older blood (>14-21 days), could effectively achieve a universal TA-GVHD prevention strategy. However, this will only be available in centres with on-site irradiators, and has logistic implications as noted above.

4.3 Recipient risk-based approach

Where irradiation of all fresh cellular products is not policy, irradiation of blood components for at risk recipients is advised. It is expected that this will be the approach in most laboratories. The indications for selecting cellular blood products for irradiation are discussed in Section 5.

Failure to identify at risk patients and transfuse with irradiated blood is a commonly reported error.[2] Institutions should have processes in place to ensure the identification of patients requiring irradiated blood products, the communication of this requirement to the transfusion laboratory, prescribing and administering professionals and the blood supplier. Transfusion of patients at higher risk of TA-GVHD, as identified by these guidelines, with non-irradiated (or equivalent) cellular products should be reported through institutional haemovigilance processes.

Communication of irradiation requirements should include all clinical services and laboratories involved in the care of patients, including when patients are transferred, or care is shared between centres.

Communication regarding irradiation should specify the indication, duration or review date, as appropriate.

Along with other aspects of their treatment plans, patients should be advised of their irradiation requirements, especially when transfusions may occur in more than one institution.

Recommendation
R5: Both universal irradiation and selective risk-based irradiation strategies are acceptable practice.

Practice Point
PP5: Irradiation of all cellular components issued fresh irrespective of recipient risk factors, is the most effective strategy to prevent TA-GVHD. However, it is acknowledged that this approach will not be suitable for most laboratories.
PP6: Where irradiated inventories are stocked, these should be tailored to minimise stock wastage due to expiry and promote ABO identical red cell transfusion.
PP7: Processes are required to ensure irradiation requirements are identified and communicated across clinical and laboratory services involved in the care of at-risk patients.

4.4 Irradiation practice

Where there are appropriate indications, cellular products including red cells, platelets and granulocytes must be irradiated. Stem cells, donor T cells and CAR T cells must NOT be irradiated. Cryoprecipitate, fresh frozen plasma and manufactured plasma products do not contain viable T cells and there is consensus that they do not require irradiation (see table 4).

Fresh (never frozen) plasma may contain some viable T cells. While not in current common use, irradiation should be considered in appropriate clinical circumstances as a single case of TA-GVHD in an immunodeficient infant has been reported.[47]

Glycerolised frozen red cells are washed prior to transfusion. They show a substantial reduction in lymphocyte responsiveness, however lymphocyte responsiveness remains.[48,49] Irradiation has been shown to minimally impact thawed red cell quality.[50,51] While there has been no reported TA-GVHD following transfusion of deglycerolised red cells, these transfusions are few and data are insufficient to establish firm recommendations. However, as the product may be safely irradiated, this may be considered if otherwise clinically indicated and time permits.

Red cells (or whole blood) units should be no more than 14 days old at the time of irradiation.[52]

Room temperature stored platelet and granulocyte units may be irradiated at any time during their standard storage times.

Irradiated units must be expired no later than 14 days following irradiation.[52]

Where patients are at particular risk of hyperkalaemia, transfusion should occur as soon as possible after irradiation, and ideally within 24 hours.

A minimum dose of 25Gy to all parts of the blood product is required to ensure adequate T cell inhibition, with no part of a unit receiving more than 50Gy to avoid excessive cellular damage, in accordance with relevant standards applicable to blood component manufacturers.[52] Irradiation doses are applicable to both gamma and x-ray irradiation.

Irradiators must be compliant with irradiation safety and security regulations within the relevant jurisdiction.

Irradiation installation and safety must be under the supervision of suitably qualified personnel.

All irradiators must ensure adequate radiation shielding. The security of the irradiator and personnel should also be considered for source irradiators.

Irradiators must be installed, calibrated and validated to deliver doses outlined above. Laboratories must maintain valid calibration curves and the duration of irradiation confirmed regularly in accordance with manufacturer specifications.

Validation should be performed after maintenance that may affect radiation dose, for example of the turntable.

Units to be irradiated should have radiosensitive label appropriate to the type (gamma or x-ray) of radiation used affixed prior to irradiation which confirms to the end user that the label / unit has been irradiated as specified.

Irradiated units should be immediately labelled to include the date and time of irradiation and any change in expiry date.

The irradiation status of units must be recorded in the laboratory information system or clinical record.

Products considered radiation equivalent may be used in place of irradiated products wherever indicated in these guidelines.

Where a red cell product is not irradiated, it is considered irradiation equivalent if >21 days of cold storage and TA-GVHD safe at >14 days. When issued in place of an irradiated unit where an irradiated product was otherwise indicated, the unit must be tagged to indicate that it is “Considered irradiation equivalent (or safe) for the prevention of graft versus host disease,” or similar wording.

Recommendations

R6: Cellular components including red cells, platelets and granulocytes must be irradiated, where there are appropriate indications.

R7: Stem cells, donor T lymphocytes and chimeric antigen receptor T lymphocytes must NOT be irradiated.

R8: Cryoprecipitate, fresh frozen plasma and manufactured plasma components do not require irradiation.

R9: The minimum radiation dose is 25Gy to all parts of the unit, with no part of the unit receiving more than 50Gy.

R10: Irradiator installation, safety and security must be under the supervision of suitably qualified personnel.

R11: Irradiators must be installed, calibrated, validated and maintained to deliver doses outlined above.

R12: Where an irradiation equivalent or TA-GVHD safe component is issued where an irradiated component was otherwise indicated, the unit must be tagged accordingly.

Practice Points

PP8: Red cells should be no more than 14 days of storage at the time of irradiation.

PP9: Red cells should be expired no more than 14 days after irradiation.

PP10: Where irradiated inventories are stocked, these should be tailored to minimise stock wastage due to expiry and promote ABO identical red cell transfusion.

PP11: Fresh (never frozen) plasma should be irradiated for at-risk recipients.

PP12: Deglycerolised thawed red cells may be irradiated if clinically indicated and time permits.

Table 4: Blood components to be irradiated

MUST be irradiated	Irradiation should be considered in clinically susceptible patients	Irradiation not required	MUST NOT be irradiated
Cellular components from HLA-matched or related donors (except as indicated under MUST NOT irradiate): Red cells Platelets Granulocytes Whole blood^ Cryopreserved red cells and platelets*	Red cells Platelets Granulocytes Whole blood^ Cryopreserved red cells and platelets*	Autologous components Fresh frozen plasma Cryo-depleted plasma Cryoprecipitate Cold stored red cells > 21 days of storage Products obtained by plasma fractionation (e,g. Immunoglobulins or clotting factor concentrates)	Stem cells Donor lymphocyte infusions CAR-T cells

^ Whole blood is rarely used in Australia and New Zealand, however will contain viable T lymphocytes with red cells subjected to irradiation showing similar injury to those stored as components

* Cryopreserved platelets are not currently licenced in Australia / New Zealand. They are intended for use in critical bleeding patients, not usually considered at risk of TA-GVHD so irradiation should not be required. The effect of irradiation on cryopreserved platelets is unknown. Specialist advice should be sought where cryopreserved platelets are being considered to patients at higher TA-GVHD risk.

4.5 Inventory management

Due to the reduced storage duration associated with red cell irradiation, there is additional complexity when managing an inventory of irradiated units or mixed inventories of irradiated and non-irradiated units. As platelets have a short expiry, all platelets are irradiated prior to release in Australia and New Zealand, so these additional complexities are not seen with platelets.

Inventory management should consider the impact of irradiation on wastage, the frequency of transfusion for patients requiring irradiation and the available options for transfusion in emergency situations, such as older blood. Wherever possible, inventories should be managed to avoid the need to substitute ABO compatible rather than ABO identical group solely to prevent wastage of ABO compatible units.

Recommendation
R13: Inventory management of irradiated blood components must prioritise ABO identical transfusion and avoid increased wastage.

4.6 Communication

Health services should ensure that patients, treating clinicians and laboratories are aware of the addition and withdrawal of irradiation requirements. If patient care is transferred or shared between centres, procedures should be in place to ensure adequate and timely communication of special transfusion requirements.

Efforts should also be made to educate patients about whether they require blood components with any specific modifications.

To successfully implement the recommendations contained within these guidelines, institutional education programmes and/or protocols should be devised for treating clinicians, nursing staff, pathology and blood bank staff to ensure adherence both to these guidelines and local policies.

4.7 Haemovigilance

There should be mechanisms in place to capture and report any cases of TA-GVHD. Cases should be investigated to ensure any opportunities to prevent future episodes are identified and actioned.

While not mandatory in all haemovigilance systems, the identification and systematic reporting of cases where irradiation was indicated and a suitable product not provided, is encouraged. These may be recorded as near misses or incorrect product administrations. These may also provide opportunities to review and improve practice. In addition, the systematic recording of these cases may help in future risk assessments. Recording product factors known to influence viable T cell numbers may be of value.

5. Clinical indications for TA-GVHD safe components

5.1 Intrauterine transfusions

Red Cells

Intrauterine red cell transfusions (IUT) may be considered in the management of severe fetal anaemia in the second to early third trimester of pregnancy (e.g. haemolytic disease of fetus and newborn).

Haemovigilance surveillance and case reports have identified a number of IUT associated cases of TA-GVHD. While many are associated with related donors, this is not exclusively the case.

IUT delivers a comparatively large volume of blood to the fetus which is administered relatively quickly. Red cells for IUT are used by the end of day 5 of storage therefore increasing the risk of TA-GVHD [6,13,32,43]. Due to the increased number of viable lymphocytes being transfused in fresh units (less than 5 days to reduce the risk of hyperkalaemia) and the fetus' immature immune system, the risk of TA-GVHD is deemed to be high so irradiation is recommended.[6,13,32,43]

To further reduce the risk of hyperkalaemia, red cells for IUT should be transfused as soon as possible following irradiation and must be transfused within 24 hours of irradiation.

Platelets

Despite leucodepletion, as platelet concentrates may contain small numbers of residual lymphocytes, the relevant recommendations for red cell transfusion should also apply to platelets.[6] Currently, all platelets in Australia and New Zealand are leucodepleted and irradiated prior to release from blood services.

Recommendations

R14: Cellular products used for IUT should be irradiated.

R15: Red cells for IUT should be as fresh as possible and must be transfused within 24 hours of irradiation.

5.2 Neonatal and paediatric practice

There remains significant variation in neonatal and paediatric transfusion practice across Australia and New Zealand, and internationally, predominantly due to the lack of high-quality evidence. This section of the guideline (as in similar international guidelines) continues to be one of the most contentious.

5.2.1 Neonatal exchange transfusions

Neonatal exchange transfusions have also been associated with TA-GVHD in otherwise healthy neonates.[53-55] While some cases have occurred when exchange transfusion is performed subsequent to IUT, this is not always the case. Red cells for neonatal exchange transfusion are used by the end of day 5 of storage (to reduce the risk of hyperkalaemia) therefore increasing the risk of TA-GVHD.[6,13,32,43]

Despite the risk mitigation strategy of universal leucodepletion, these guidelines continue to recommend the irradiation of red cells for neonatal exchange transfusion based on the above case reports and the comparatively large volume of fresh blood transfused during the procedure.

To further reduce the risk of hyperkalaemia, red cells for neonatal exchange transfusion should be transfused as soon as possible following irradiation and must be transfused within 24 hours of irradiation.

Recommendations

R16: Red cells for neonatal exchange transfusion should be irradiated.

R17: Red cells for neonatal exchange transfusion should be as fresh as possible and must be transfused within 24 hours of irradiation.

5.2.1.1 Neonates and infants with congenital heart disease (CHD) requiring cardiopulmonary bypass (CPB) surgery or extracorporeal life support (ECLS); and those undergoing cardiothoracic surgery.

There have been numerous case reports of TA-GVHD in paediatric and adult patients undergoing cardiothoracic surgery, however it is not clear if it is the procedure itself that poses the increased risk, underlying immunodeficiency or confounders such as the large volumes of blood transfused or the "freshest" components selected for transfusion.[5,11,56,57]

While CHD does not appear to be an independent risk factor for TA-GVHD, there is an association between congenital heart disease and some primary T-lymphocyte immunodeficiency disorders which may confer an increased risk of TA-GVHD. Many centres have procedures for screening for immunodeficiencies associated with CHD, including the use of lymphocyte subsets, naïve T cell analysis, and 22q FISH or microarray to exclude 22q11 microdeletion/DiGeorge Syndrome.[6]

Due to large volume of fresh components that these recipients may receive, consideration should be given to screening neonates and infants with CHD for an undiagnosed T-lymphocyte immunodeficiency. Screening tests for occult immunodeficiency should be performed as soon as feasible to enable informed decision making regarding ongoing need for irradiated blood products (as well as timely management of immunodeficiency).

Consider irradiation of red blood cells in suspected T cell immunodeficiency. As a guide, a CD4+ T-lymphocyte count >400 cells/µl, of which 30% are naive T lymphocytes, largely excludes severe T cell immunodeficiency and in this case there is no need to irradiate red cells.[6,58,59] Discussion with a paediatric immunologist is suggested if there are concerns of a possible T- lymphocyte immunodeficiency. Where this testing is not possible/feasible consider irradiation of red blood cells in case of an undiagnosed immunodeficiency.[6,60]

Extracorporeal membrane oxygenation (ECMO), CPB and cardiac surgeries are often associated with large volumes of red cell transfusion and increased risk of hyperkalaemia. If irradiated red cells are used, these should be transfused as soon as possible after irradiation and within 24hrs of irradiation. If an infant is found to be athymic during cardiothoracic surgery, they should be assumed to have immunodeficiency.[6] It is reasonable to use irradiated red cells if available, but not to delay surgery if this would have a detrimental clinical outcome.

> *Practice Points:*
> *PP13: Consider evaluation of neonates and infants undergoing cardiac surgery for an undiagnosed T-cell immunodeficiency, and where this is not possible/feasible consider irradiation of cellular components until risk of relevant immunodeficiency has been excluded.*

PP14: Consider irradiation of red blood cells in suspected T cell immunodeficiency. As a guide, a CD4+ T-lymphocyte count >400 cells/µl, of which 30% are naive T lymphocytes, largely excludes severe T cell immunodeficiency and in this case, there is no need to irradiate red cell. Discussion with a paediatric immunologist is suggested if there are concerns of a possible T-lymphocyte immunodeficiency.

PP15: To reduce the risk of hyperkalaemia to patients undergoing CPB, ECMO and cardiac surgery requiring large volume transfusion; IF irradiated red cells are used, transfusion should ideally be as soon as possible post- irradiation and should be within 24 hours of irradiation.

5.2.2 Neonatal small volume ("top-up") transfusions

Most neonatal red cell transfusions are given to treat anaemia of prematurity due to phlebotomy losses, especially in extremely preterm (<28 week gestation), very low birth weight (VLBW < 1500g) or extremely low birth weight (ELBW < 1000g) infants. These transfusions are usually small volume, 10-20ml/kg, given over 4 hours and were previously referred to as "top-up" transfusions.

There is a paucity of data to convincingly guide transfusion practice and irradiation in neonates undergoing small-volume transfusions, and there is significant variation in practice nationally and internationally. There is however, increasing support to remove absolute irradiation indications for all neonates, including extremely preterm and VLBW infants.[6,32,61,62]

There is evidence that the neonatal immune system is less mature, both from epidemiological data (for example the different susceptibility to infections including group B Streptococci) and from analysis of cell types and cytokines. There is evidence that these changes are dependent on gestational age, but there also appears to be convergence of the preterm and term neonates' immune systems over the first few weeks of life.[58,60] This physiological immunodeficiency has traditionally been suggested as a potential risk factor for TA-GVHD.

There have been no cases of neonatal TA-GVHD associated with "top-up" transfusions in the UK despite the lack of an irradiation requirement in this population, hence the British Society for Haematology (BSH) Guidelines do not recommend the irradiation of red cells for small volume neonatal transfusions[1]. Canadian guidelines also cite insufficient data to support universal irradiation, however do recommend it for very low birthweight infants.[32] A survey of neonatal intensive care units (NICU) during that guideline development showed 18 of 21 units irradiated all neonatal "top-up" transfusions, however there was strong support from directors to remove this indication.[32] In the Australian and New Zealand NICU setting, there remains significant variation in practice, from units that provide irradiated red cells to all neonates, to those that provide non-irradiated red cells for all small volume transfusions to neonates.

There continues to be concern about hyperkalaemia associated with RBC transfusions, particularly in neonates. There have been a number of clinical case reports documenting transfusion associated hyperkalaemia and associated cardiac arrest in patients receiving large volume transfusion, and occasionally following rapid, small volume transfusions of older and/or irradiated blood components. The majority of these have occurred in the surgical setting, when administered via a central venous catheter, not following small volume transfusion.[56] Moreover, recent evidence suggests hyperkalaemia is seldom seen following transfusion in paediatrics.[61] Although hyperkalaemia increases with red cell storage lesion, restoration of ATP-driven ion transport following transfusion is likely to return some lost potassium into the cells such that, provided the rate of transfusion is not rapid, the transfusion of potassium in red cell units should be well tolerated.

Significant variation in neonatal transfusion practice is seen internationally. The BSH Neonatal Transfusion Guidelines suggest that red cells for "top-up" transfusions given at standard infusion rates may be transfused up to 14 days after irradiation;[1] Whilst the Canadian recommendations suggest that in all neonatal small volume transfusion, aliquots must be less than 14 days after irradiation, and no more than 28 days since donation (provided that aliquots that are more than 24 hours from irradiation have undergone centrifugation and supernatant plasma removal as opposed to gravity settling).[32]

In Australia and New Zealand some neonatal units transfuse irradiated red cell units within 24-48 hours of irradiation (in keeping with the ANZSBT guidelines for Transfusion and Immunohaematology Laboratory Practice[63]) particularly in extremely low birth weight (ELBW) and premature infants, although this appears to be based on limited data. This may also be related to the increased use of modified products in some units (which have a 48hr expiry – see paragraph below), or due to inventory management strategies.

In the Australian setting, many paediatric (and in particular neonatal) units use a modified red cell product for transfusion (known as paediatric red cells leucocyte depleted units) to reduce red cell wastage and minimise donor exposure. In the Australian setting, all leucocyte depleted (adult) red cells have undergone centrifugation and supernatant plasma removal; whereas paediatric leucocyte depleted red cell units (whilst having undergone centrifugation and supernatant plasma removal prior to splitting), have undergone post irradiation modification (the splitting and gravity settling of the bags) and therefore are released from Lifeblood with a recommendation that they must be transfused within 48 hours of irradiation.

In Australia and New Zealand, there is also significant variation in the red cell product used in neonatal transfusions, with both paediatric leucocyte-depleted red cell units and standard (adult) leucocyte depleted red cell units being used. In the production of paediatric leucocyte depleted red cell units, an adult red cell unit is split into at least four paediatric red cell units for neonatal transfusion in an attempt to minimise donor exposure following repeated transfusion. However, the shortened shelf-life of irradiated paediatric red cell units may limit the benefit of using a "single donor" strategy, especially where the risk of transfusion transmitted infectious disease in is low. There are very low risks associated either with additional donor exposures or with the transfusion of older (>14 days) non-irradiated leucodepleted paediatric units from the same donor, even in infants with other indications for irradiation. Clinicians should consider and compare these options in discussion with parents, depending on local inventory. All are considered acceptable strategies.

There is also a recent single-centre, double-blinded, proof-of-concept randomized clinical trial by Saito-Benz et al looking at the effect of red cell transfusion on cerebral oxygenation in preterm infants showing that transfusion of freshly irradiated RBCs conferred a small advantage in cerebral oxygenation for at least 5 days after transfusion compared with transfusion of irradiated and stored RBC components.[64] This is a small study, and requires further research, but it supports moving away from universal irradiation, and the recommendation that inventory is managed so that freshest irradiated products are prioritised for neonatal transfusion wherever possible.

Thus, term neonates and pre-term (>28 weeks) infants receiving small volume transfusions do not require irradiated blood components. In extremely pre-term (<28 weeks) and ELBW infants, the decision for irradiated components should be based on additional features rather than only gestational age and weight. Additional risk factors including lymphocyte count, presence of CHD, features to suggest an underlying immunodeficiency, or where repeated infusions of fresh red cells are likely to be required.

Where irradiated red cells are used for neonatal small volume transfusions, it is recommended that inventory is managed so that freshest irradiated components be prioritised for neonates wherever possible; that modified components (including paediatric leucodepleted red cell units) be transfused within 48 hours as per their manufacturing recommendations; and centrifuged, supernatant removed products (including adult leucodepleted red cell units) be transfused within 14 days of irradiation.

Intrauterine transfusion of red cells has been shown to suppress T cell proliferation in neonates.[62] While it is unclear if this leads to an increased risk of TA-GVHD, small volume transfusion following intrauterine transfusion may pose an additional risk hence the recommendation to irradiate red cells in this population remains. The same risk is not seen with high dose maternal immunoglobulin therapy.[62]

Recommendation
R18: In neonates who have received prior IUT irradiation is required for small volume transfusions.

Practice points
PP16: Term neonates and pre-term (>28 weeks) infants receiving small volume transfusions do not require irradiated blood components.
PP17: In extremely pre-term (<28 weeks) and extremely low birthweight (<1000g) infants, the decision for irradiated components should be based on additional features rather than only gestational age and weight.
PP18: Blood banks should have a mechanism for capturing and recording neonates who have received an IUT antenatally and should receive post-natal irradiated top up red cell transfusion.
PP19: Where irradiated red cells are indicated for small volume neonatal transfusion, then consideration should be given to minimizing the shelf-life following irradiation.
PP20: Where irradiated red cells are used for small volume neonatal transfusion, it is recommended that inventory be managed so that freshest irradiated products are prioritised for neonatal transfusion wherever possible; that modified components (including paediatric leucodepleted red cell units) be transfused within 48 hours of irradiation as per their manufacturing recommendations; and centrifuged, supernatant removed products (including adult leucodepleted red cell units) be transfused within 14 days of irradiation.

5.2.3 Emergency transfusions and large volume transfusions

Emergency transfusions for neonatal or paediatric resuscitation or massive transfusion do not require irradiation[6,13,32]. Awaiting irradiated blood components may unnecessarily delay a lifesaving transfusion.

Neonates requiring large volume transfusions (e.g., cardiac surgery, ECLS, sub-galeal haemorrhage, major surgery or vein of Galen malformations) may be at increased risk of both hyperkalaemia and TA-GVHD, therefore it is reasonable to transfuse fresh irradiated red cells if available, but not to delay surgery/treatment if this would have detrimental clinical impact.

For large volume neonatal transfusion where it has been determined that irradiation is required, red cells should be transfused as soon as possible after irradiation, and preferably within 24 hours of irradiation.

Recommendation
R19: For emergency transfusions in the setting of neonatal resuscitation, irradiated cellular components are not required, even in neonates otherwise considered at higher risk of TA-GVHD.

Practice point
PP21: For large volume neonatal transfusion where it has been determined that irradiation is required, red cells should be transfused as soon as possible after irradiation, and preferably within 24 hours of irradiation.

5.2.4 Congenital and acquired immunodeficiencies in infants and children.

Most cases of TA-GHVD occur in neonates with concurrent risk factors. 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-lymphocyte function[6]. Patients with 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.

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. Sanders and Graeber noted that in fact, most cases of immunodeficiency were diagnosed after the diagnosis of TA-GVHD, including at autopsy[55], although these findings were prior to the institution of universal leukodepletion, and as noted above, there have been few cases since. It remains important to note though that in older children and adults, severe immunodeficiency has had the opportunity to be diagnosed, whereas in the neonate this may not be possible unless there are other clinical features of syndromes known to be associated with immunodeficiency[55].

Apart from inherited disorders of T-lymphocyte function, there are few other immunodeficiency states that require irradiated components. The BSH have extended immunodeficiency to include haemophagocytic lymphohistiocytosis (HLH) on the basis of a single case report and an association with secondary HLH and primary immunodeficiency. On the basis of this case, it may be reasonable to give irradiated cellular blood components for patients with suspected congenital HLH and lymphopenia, until T-cell immunodeficiency has been excluded.[6] They likewise also emphasise the importance of recognizing the various ways primary immunodeficiency may present, such as with complex cardiac anomalies, and instituting blood irradiation prior to confirmation of a diagnosis. To date, there have been no reports of TA-GVHD occurring in patients with isolated defects of humoral immunity.

It is relatively common for transient defects in T-lymphocyte function to be seen following common paediatric viral infections and in a range of other conditions (tuberculosis, leprosy, malnutrition and burns). Despite the known T-lymphocyte defects seen in patients with human immunodeficiency virus infection (HIV), there have been no reports TA-GVHD. In all these situations irradiation of blood components is not recommended.

Recommendation

R20: In patients with severe congenital T-lymphocyte immunodeficiency syndromes with significant qualitative or quantitative T-lymphocyte deficiency are it is recommended that cellular blood products are irradiated.

Practice points
PP22: If a severe T-lymphocyte immunodeficiency disorder is suspected, irradiated components should be given while diagnostic testing is undertaken.
PP23: Transfusion laboratories should have a mechanism for capturing and recording patients with a severe T lymphocyte immunodeficiency who required irradiated products.
PP24: Irradiation of cellular blood components is not indicated for infants or children with temporary defects of T-lymphocyte function, including following viral infections, acquired T-lymphocyte deficiencies, those who are HIV-antibody positive or with acquired immune deficiency syndrome (AIDS)

5.3 Haematological disorders

5.3.1 Remission induction and consolidation therapy for acute leukaemia and chemotherapy of similar intensity for other malignancies

It is highly uncertain whether acute leukaemia itself increases the risk of TA-GVHD. Induction chemotherapy for AML is associated with a temporary severe leukopenia. ALL therapy has more prolonged and repeated lymphocyte suppression. There have been cases of TA-GVHD reported with both ALL and AML.[5] The implications of less myelosuppressive therapies, such as hypomethylating agents and BCL2 inhibitors are unknown.

Guidelines vary in their recommendations for TA-GVHD prophylaxis in acute leukaemia.[6,13,43] Based on the severe immunosuppression and prior cases, these guidelines recommend irradiation for patients undergoing intensive cytoreductive remission induction therapy for AML and ALL and for a period of 6 months following completion of therapy. Irradiation may also be considered for patients undergoing immunochemotherapy of similar intensity for other malignancies. Irradiation is not required when supportive care only is offered.

Recommendation
R21: Irradiation of cellular products is recommended for patients undergoing chemotherapy equivalent to AML or ALL intensive remission induction and consolidation therapy, to continue for a period of 6 months following intensive therapy. Irradiation is not required when supportive care only or lower intensity chemotherapy is offered.

5.3.2 Allogeneic stem cell transplantation

Allogeneic stem cell transplant relies on the engraftment of transplanted T cells. Conditioning and immunosuppressive regimens are required to suppress recipient T cells to facilitate donor T cell engraftment. Thus, allogeneic stem cell transplant is an iatrogenic state deliberately designed to induce susceptibility to GVHD.

Chronic GVHD is itself an immunosuppressive condition and where therapy is required, it usually involves T cell suppression.

All allogeneic stem cell recipients should receive irradiated cellular blood products from the time of conditioning for a minimum of 12 months post-transplant and then to continue while there is active GVHD or continuation of immunosuppression for GVHD.

Recommendation

R22: Patients undergoing allogeneic stem cell transplant should receive irradiated cellular blood components from the time of conditioning and for a minimum of 12 months post-transplant, but to continue while there is active GVHD or immunosuppression for GVHD

5.3.3 Autologous stem cell transplant

Autologous stem cell transplantation carries with it a risk of severe immunosuppression, including T cell depletion. Immune recovery is anticipated, however the evidence for a particular duration of irradiation is minimal. International guidelines generally recommend that irradiation continue for at least 6 months.[6,13] These guidelines recommend a pragmatic approach and to align recommendations for cellular therapies internally.

Autologous stem cell transplant recipients requiring transfusion should receive irradiated blood components from the time of initiation of conditioning, with this to be reviewed 6 months post-transplant. These timelines may be personalized based on T cell recovery and longer durations may be required based on other therapies received.

Recommendation

R23: Autologous stem cell transplant recipients should receive irradiated cellular blood components from the time of initiation of conditioning, with this to be reviewed 6 months post-transplant.

5.3.4 Haematopoietic stem cell donors (including autologous and T cell donors)

The theoretical potential to collect transfused viable donor T lymphocytes within a stem cell (or T cell) product should be considered when transfusing prior to anticipated cell collections. International guidelines recommend irradiation of transfusions to donors for durations of up to six weeks prior to cell harvests.[13] Chimerism has been reported post transfusion, and when it occurs there is little difference between the circulating donor T cell levels at day seven compared with timepoints months to years later.[9] Therefore, there appears to be minimal potential benefit from longer periods when compared with seven days, as recommended by other guidelines.[6]

Recommendation

R24: Haemopoietic cell donors (including autologous stem cell and T lymphocyte donors) should receive irradiated cellular blood components from seven days prior to the planned collection.

5.3.5 Chimeric antigen receptor T cells

There is no available evidence on the risk or rate of TA-GVHD following CAR-T cell therapy. It is acknowledged that this therapy is not myelosuppressive and the risks may depend on the antigen targeted and conditioning. Conditioning is designed to suppress T cells adequately to favour the growth of the infused CAR-T cells and this may provide immunosuppression sufficient to allow allogeneic T cell engraftment and TA-GVHD. Therapies prior to CAR-T cells may also be significant in determining the TA-GVHD risk.

While no firm evidence-based practice guideline can therefore be recommended following CAR-T cell therapy, consideration of irradiation requirement for blood products for a duration equivalent to autologous stem cell transplants is advised, allowing a greater consistency in recommendations. Irradiation of blood components transfused in the seven days prior to T lymphocyte collections, as with stem cells collections, is required. Longer durations of irradiation may be indicated based on prior treatment and conditioning regimens.

Recommendation
R25: CAR-T cell recipients should receive irradiated cellular products for a period of six months following CAR T cell infusion. Longer or shorter periods of may be applied based on conditioning regimens and cellular targets.

5.3.6 Hodgkin Lymphoma

The occurrence of TA-GVHD has been noted in Hodgkin lymphoma at all stages of disease.[67] It appears unrelated to treatment modality, stage or timing. Immunodeficiency, including impaired heterologous skin graft rejection, has been associated with Hodgkin lymphoma and other lymphoproliferative disorders.[68,69] There is no clear time point beyond which this risk is reversed following treatment. This has led to advice recommending lifelong irradiation of blood components following a diagnosis of Hodgkin lymphoma.

This lifelong requirement creates difficulties in the identification of patients who have been treated for Hodgkin lymphoma in the distant past and has resulted in a large number of cases where non-irradiated blood has been transfused without incident. Despite SHOT data on 192 patients, these numbers remain substantially less than required to exclude a significant risk of TA-GVHD. British and Canadian guidelines have maintained the indefinite irradiation requirement.[6,32]

By contrast, recent guidelines from the Netherlands have recommended that irradiation for Hodgkin lymphoma is not routinely recommended unless required due to their specific treatment regimen.[13] Acknowledging the need for more data, they also proposed that cases be reported where a patient has received non-irradiated blood despite a recognized indication.

Feedback from haematologists during the development on these guidelines suggests that there is at least a perception that identifying Hodgkin lymphoma patients into the future is impractical and that there are likely to be many unreported cases were transfusion of non-irradiated components has occurred.

Recommendation
R26: For patients with Hodgkin lymphoma, irradiated blood components are recommended.

Practice points
PP25: Provision of irradiated products indefinitely for people who have had Hodgkin lymphoma has been recommended, however the evidence for a particular duration following completion of therapy and confirmation of remission is limited and no firm recommendation can be made. An indefinite requirement is advised, with a very low level of certainty. Where cases of non-irradiated transfusions are identified, there should be consideration of reporting to haemovigilance systems to assist is future risk assessments.

5.3.7 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) may be associated with a degree of immunosuppression. B-cell immunosuppression is common in B-cell chronic lymphocytic leukaemia in particular, manifested as immunoglobulin deficiency.

Although the extent of immunodeficiency may extend beyond B-cells, there is a high level of uncertainty on the TA-GVHD risk associated with mature B- or T- lymphocyte lymphoproliferative disorders. Irradiation is not recommended for TA-GVHD prevention in NHL.

Treatment of non-Hodgkin lymphoma and other mature B-and T cell lymphoproliferative disorders may include agents known to be associated with an increased risk of TA-GVHD and in these cases, recommendations pertaining to those specific therapies should be followed.

Recommendation
R27: For people with Non-Hodgkin lymphoma irradiation is not recommended, unless indicated due to specific therapies received.

5.3.8 Aplastic anaemia

Acquired aplastic anaemia due to autoimmune destruction of haematopoietic precursors results in pancytopenia and a hypocellular bone marrow. T lymphocyte immunity is generally not impaired, in fact increased T lymphocyte activity is seen in aplastic anaemia with oligoclonal expansion of CD8+/CD28- T lymphocytes responsible for haematopoietic stem cell destruction.[70] Therefore, patients with aplastic anaemia are not likely to be inherently at increased risk of TA-GVHD.

Treatment of aplastic anaemia may be with immunosuppressive therapy (IST) or haematopoietic stem cell transplant. IST includes anti-thymocyte globulin (ATG) and ciclosporin, which deplete T lymphocytes and inhibit function respectively. These drugs pose a theoretically increased risk of TA-GVHD, especially ATG. While some guidelines have suggested short term requirements for irradiation following ATG,[6,13] it is unclear for how long TA-GVHD risk may persist following ATG ,and cases of TA-GVHD following ATG for aplastic anaemia have occurred many years following treatment. Where aplastic anaemia is treated with haematopoietic stem cell transplantation, the guidelines for irradiation following this procedure should be followed. ATG has also been used in solid organ transplantation, with doses typically lower than those used for aplastic anaemia. Extensive experience has not shown an increased risk of TA-GVHD so irradiation is not recommended for solid organ transplantation with or without ATG.[32]

Recommendation
R28: For patients with aplastic anaemia, cellular components should be irradiated during and following treatment with immunosuppressive therapy including anti-thymocyte globulin or similar T lymphocyte depleting therapy (e.g., alemtuzumab) and to continue until all immunosuppression has been ceased (including ciclosporin).

5.4 Cytotoxic therapies

Some cytotoxic therapies are known to produce prolonged and profound T cell suppression following treatment of haematological malignancies and are considered risk factors for TA-GVHD. These include purine analogues (e.g. fludarabine, cladribine, clofarabine, pentostatin, bendamustine) and alemtuzumab (anti-CD52). Purine analogues have been used in conditions other than haematological malignancies, including multiple sclerosis (cladribine), and are associated with prolonged lymphopenia,[71] therefore irradiation is recommended for all patients given purine analogues.

By contrast, the doses of alemtuzumab used for T cell depletion for immune modification (including multiple sclerosis, vasculitis and solid organ transplantation) are lower than those used for haematological neoplasia and have a different depth and duration of lymphopenia and pattern of immune reconstitution.[72,73] While irradiation of transfused products is recommended after alemtuzumab therapy for aplastic anaemia and haematological neoplasia, irradiation is not required when otherwise used for immunosuppression.

Recommendation
R29: For patients treated with purine analogues, for malignant or non-malignant indications,

cellular components should be irradiated during and following treatment.

R30: For patients with haematological neoplasms treated with alemtuzumab, cellular components should be irradiated during and following treatment.

5.5 T-cell immunosuppression

Patients with severe human immunodeficiency virus infections have not shown an increased TA-GVHD risk. While severe congenital immunodeficiency is a know risk factor for TA-GVHD, more common immunodeficiency presenting in adults, is not known to be a risk factor.

New immunosuppressants are frequently being introduced into clinical practice for a variety of indications. A therapy's intensity may also vary, and this may lead to varying degrees of T-lymphocyte suppression. There is no evidence that most long-term immunosuppression regimens increased the risk of TA-GVHD. Immunosuppression following sold organ transplant, corticosteroids, m-TOR inhibitors, antimetabolites and other agents used in the longer term control of autoimmune disorders are not known to be associated with TA-GVHD and patients are not recommended for irradiated blood products in any international guidelines.[6,13,32,43] New agents should be evaluated in this context. Ascertaining CD4 counts alone is unlikely to be helpful in predicting TA-GVHD risk.

There are many new and emerging cytotoxic and immunosuppressive agents targeting T cells and it is not possible to provide evidence-based advice on all therapies within these guidelines. Individual clinical risk assessment with emerging therapies should be considered, although for most immunosuppressive agents, irradiation would not be mandated. Risk assessment may include consideration of degree of immunosuppression including the expected depth and duration of T cell lymphopenia and infection risks.

5.6 HLA-matched donors

As HLA similarity is recognized as the major cause for TA-GVHD, HLA-matched cellular products must be irradiated prior to transfusion.

Stem cells, donor T cells, CAR T cells or other cellular products required to engraft, whether allogeneic or autologous **must not** be irradiated as they will be rendered ineffective.

Recommendation
R31: Cellular components from HLA matched (HLA compatible) donors must be irradiated.

5.7 Related Donors

Related donors have a higher potential for partial HLA similarities with the recipient. Even when HLA typing is unknown, cellular products must be irradiated prior to transfusion.

Stem cells, donor T cells, CAR T cells or other cellular products required to engraft, whether allogeneic or autologous, **must not** be irradiated as they will be rendered ineffective.

Recommendation
R32: Cellular components from related donors must be irradiated.

5.8 Radiation exposure / acute radiation injury

Stem cells are susceptible to the effects of ionising radiation. Pancytopenia is a common and expected complication of radiation exposure due to its effect on bone marrow function. Lymphocytes are severely reduced,[74] potentially making the recipient at risk of TA-GVHD. Cellular blood products must be irradiated.

Recommendation
R33: Patients requiring cellular blood components due to radiation injury should receive irradiated products.

5.9 Emergency transfusion for patients at risk of TA-GVHD

The provision of irradiated blood in emergencies may be limited by stock availability and time. In patients where irradiation may otherwise be indicated, it is likely that the risks due to delays in the provision of irradiated blood will outweigh the risk of TA-GVHD. Using the oldest available red cells will also reduce the risk of TA-GVHD in recipients at risk and should be considered in critical bleeding where irradiated units are unavailable. There is no specific requirement to provide irradiated blood for critical bleeding or trauma even when large volumes are expected to be transfused.

Practice Point
PP26: In patients at risk of TA-GVHD who need emergency transfusion, the use of the shortest expiry suitable red cells is acceptable if irradiated (or equivalent) units are not available.

6. Indications removed since previous edition, not otherwise discussed.

6.1 Massive transfusion / critical bleeding

The previous edition included emergency large volume transfusion as a possible indication for irradiation. This was based on the finding of persistent B- and T- lymphoid and myeloid chimerism in the blood of trauma patients transfused with non-depleted red cells.[9] More recent data have not confirmed frequent engraftment following transfusion in trauma, despite a much larger cohort, possibly due to the effect of leukoreduction and TA-GVHD cases are not reported in this setting.[8] Furthermore, the supply of urgently needed or large numbers of red cells is difficult whether an institution relies on an on-site blood irradiator or irradiated stock from their blood service.

Recommendation
R34: Irradiation is not required for critical bleeding or trauma.

Acknowledgements

ANZSBT CPIC would like to thank all members who have contributed to the development of these guidelines by providing input and feedback. For contributions to development of paediatric and neonatal sections, we would particularly like to thank Drs Ben Saxon, Michael Stark, Bronwyn Williams and Gemma Creighton.

7. References

1. 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.
2. 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(2):385-392.
3. Fiebig E, Hirschkorn DF, Maino VC, Grass JA, Lin L, Busch MP. Assessment of donor T-cell function in cellular blood components by the CD69 induction assay: effects of storage, gamma radiation, and photochemical treatment. *Transfusion*. 2000;40(7):761-770.
4. Mykhailova O, Turner TR, Olafson C, et al. Hypothermic storage of leukoreduced red blood cells for greater than 21 days is a safe alternative to irradiation. *Transfusion*. 2021;61(4):1247-1257.
5. Kopolovic I, Ostro J, Tsubota H, et al. A systematic review of transfusion-associated graft-versus-host disease. *Blood*. 2015;126(3):406-414.
6. Foukaneli T, Kerr P, Bolton-Maggs PHB, et al. Guidelines on the use of irradiated blood components. *Br J Haematol*. 2020;191(5):704-724.
7. Schroeder ML. Transfusion-associated graft-versus-host disease. *British Journal of Haematology*. 2002;117(2):275-287.
8. Jackman RP, Utter GH, Lee TH, et al. Lack of persistent microchimerism in contemporary transfused trauma patients. *Transfusion*. 2019;59(11):3329-3336.
9. Lee TH, Paglieroni T, Ohto H, Holland PV, Busch MP. Survival of donor leukocyte subpopulations in immunocompetent transfusion recipients: frequent long-term microchimerism in severe trauma patients. *Blood*. 1999;93(9):3127-3139.
10. Dwyre DM, Holland PV. Transfusion-associated graft-versus-host disease. *Vox Sang*. 2008;95(2):85-93.
11. Jawa RS, Young DH, Stothert JC, Kulaylat MN, Landmark JD. Transfusion-associated graft versus host disease in the immunocompetent patient: an ongoing problem. *J Intensive Care Med*. 2015;30(3):123-130.
12. Uchida S, Tadokoro K, Takahashi M, Yahagi H, Satake M, Juji T. Analysis of 66 patients definitive with transfusion-associated graft-versus-host disease and the effect of universal irradiation of blood. *Transfus Med*. 2013;23(6):416-422.
13. Wiersum-Osselton JC, Slomp J, Frederik Falkenburg JH, et al. Guideline development for prevention of transfusion-associated graft-versus-host disease: reduction of indications for irradiated blood components after prestorage leukodepletion of blood components. *Br J Haematol*. 2021.
14. Trentino KM, Farmer SL, Sanfilippo FM, et al. Systematic reviews and meta-analyses comparing mortality in restrictive and liberal haemoglobin thresholds for red cell transfusion: protocol for an overview of systematic reviews. *BMJ Open*. 2019;9(8):e029828.
15. Estcourt LJ, Desborough M, Hopewell S, Doree C, Stanworth SJ. Comparison of different platelet transfusion thresholds prior to insertion of central lines in patients with thrombocytopenia. *Cochrane Database Syst Rev*. 2015(12):CD011771.
16. Moroff G, Leitman SF, Luban NL. Principles of blood irradiation, dose validation, and quality control. *Transfusion*. 1997;37(10):1084-1092.
17. Pelszynski MM, Moroff G, Luban NL, Taylor BJ, Quinones RR. Effect of gamma irradiation of red blood cell units on T-cell inactivation as assessed by limiting dilution analysis: implications for preventing transfusion-associated graft-versus-host disease. *Blood*. 1994;83(6):1683-1689.
18. Luban NLC, Drothler D, Moroff G, Quinones R. Irradiation of platelet components: inhibition of lymphocyte proliferation assessed by limiting-dilution analysis. *Transfusion*. 2000;40(3):348-352.
19. Eshghifar N, Maghsudlu M, Amini Kafi-Abad S. The Effect of Pre-Storage Irradiation Blood on Quality of Red Blood Cells. *Int J Hematol Oncol Stem Cell Res*. 2021;15(1):1-6.

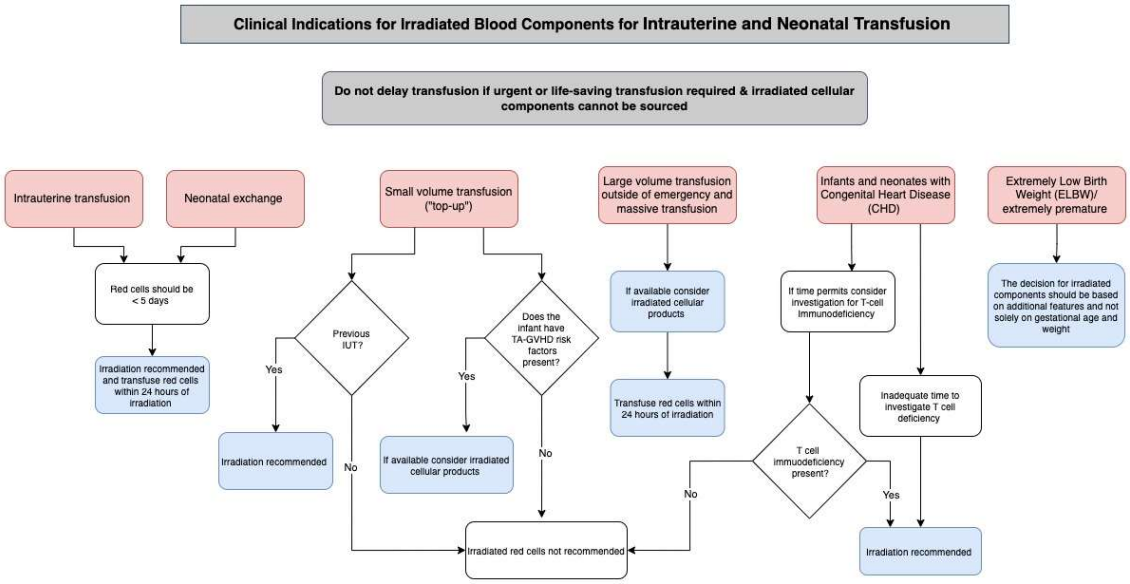
20. Winter KM, Johnson L, Kwok M, et al. Understanding the effects of gamma-irradiation on potassium levels in red cell concentrates stored in SAG-M for neonatal red cell transfusion. *Vox Sang*. 2015;108(2):141-150.
21. Marks DC, Webb RG, Linnane C, Aung HH, Dennington PM, Tan JCG. X- and gamma-irradiation have similar effects on the in vitro quality of stored red cell components. *Transfusion*. 2021.
22. Lu X, Zhu X, Chen D, et al. Metabolic profile of irradiated whole blood by chemical isotope-labeling liquid chromatography-mass spectrometry. *J Pharm Biomed Anal*. 2021;204:114247.
23. Espersen GT, Ernst E, Christiansen OB, Jersild C, Grunnet N. Irradiated blood platelet concentrates stored for five days--evaluation by in vitro tests. *Vox Sang*. 1988;55(4):218-221.
24. Read EJ, Kodis C, Carter CS, Leitman SF. Viability of platelets following storage in the irradiated state. A pair-controlled study. *Transfusion*. 1988;28(5):446-450.
25. Van Der Meer PF, Pietersz RNI. Gamma irradiation does not affect 7-day storage of platelet concentrates. *Vox Sanguinis*. 2005;89(2):97-99.
26. Davis AM, Aung HH, Costa MJ, Dennington PM, van der Wal DE, Marks DC. X-irradiation and gamma-irradiation inactivate lymphocytes in blood components. *Transfusion*;n/a(n/a).
27. Janatpour K, Denning L, Nelson K, Betlach B, Mackenzie M, Holland P. Comparison of X-ray vs. gamma irradiation of CPDA-1 red cells. *Vox Sang*. 2005;89(4):215-219.
28. Bashir S, Naik F, Cardigan R, Thomas S. Effect of X-irradiation on the quality of red cell concentrates. *Vox Sanguinis*. 2011;101(3):200-207.
29. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. X-ray irradiation of blood components. London: JPAC; 2020.
30. Meli A, Balanant MA, New HV, et al. A comparison of the effect of X and gamma irradiation on red cell storage quality. *Vox Sang*. 2021.
31. Johnson L, Vekariya S, Wood B, et al. The in vitro quality of X-irradiated platelet components in PAS-E is equivalent to gamma-irradiated components. *Transfusion*. 2021.
32. Morrison D, Prokopchuk-Gauk O, Devine D, et al. Recommendations for Use of Irradiated Blood Components in Canada: A NAC and CCNMT Collaborative Initiative. Quebec: National Advisory Committee on Blood and Blood Products; 2018.
33. Castro G, Merkel PA, Giclas HE, et al. Amotosalen/UVA treatment inactivates T cells more effectively than the recommended gamma dose for prevention of transfusion-associated graft-versus-host disease. *Transfusion*. 2018;58(6):1506-1515.
34. Fast LD, Nevola M, Tavares J, Reddy HL, Goodrich RP, Marschner S. Treatment of whole blood with riboflavin plus ultraviolet light, an alternative to gamma irradiation in the prevention of transfusion-associated graft-versus-host disease? *Transfusion*. 2013;53(2):373-381.
35. Lachert E, Woźniak J, Antoniewicz-Papis J, et al. Study of CD69 antigen expression and integrity of leukocyte cellular membrane in stored platelet concentrates following irradiation and treatment with Mirasol® PRT System. *Adv Clin Exp Med*. 2017;26(1):7-13.
36. Marschner S, Fast LD, Baldwin WM, 3rd, Slichter SJ, Goodrich RP. White blood cell inactivation after treatment with riboflavin and ultraviolet light. *Transfusion*. 2010;50(11):2489-2498.
37. Mintz PD, Wehrli G. Irradiation eradication and pathogen reduction. Ceasing cesium irradiation of blood products. *Bone Marrow Transplant*. 2009;44(4):205-211.
38. Pohler P, Müller M, Winkler C, et al. Pathogen reduction by ultraviolet C light effectively inactivates human white blood cells in platelet products. *Transfusion*. 2015;55(2):337-347.
39. Sim J, Tsoi WC, Lee CK, et al. Transfusion of pathogen-reduced platelet components without leukoreduction. *Transfusion*. 2019;59(6):1953-1961.
40. Kleinman S, Stassinopoulos A. Transfusion-associated graft-versus-host disease reexamined: potential for improved prevention using a universally applied intervention. *Transfusion*. 2018;58(11):2545-2563.

41. Bello-López JM, Hernández-Rodríguez F, Rojo-Medina J. Bactericidal effect of γ-radiation with (137)Cesium in platelet concentrates. *Transfus Apher Sci*. 2016;55(3):347-352.
42. Chun S, Phan MT, Hong S, et al. Double-filtered leukoreduction as a method for risk reduction of transfusion-associated graft-versus-host disease. *PLoS One*. 2020;15(3):e0229724.
43. Asai T, Inaba S, Ohto H, et al. Guidelines for irradiation of blood and blood components to prevent post-transfusion graft-vs.-host disease in Japan. *Transfusion Medicine*. 2000;10(4):315-320.
44. Chang H, Voralia M, Bali M, Sher GD, Branch DR. Irreversible loss of donor blood leucocyte activation may explain a paucity of transfusion-associated graft-versus-host disease from stored blood. *Br J Haematol*. 2000;111(1):146-156.
45. Klein HG. Transfusion-associated graft-versus-host disease: less fresh blood and more gray (Gy) for an aging population. *Transfusion*. 2006;46(6):878-880.
46. Satake M, Suto Y. Universal or selective irradiation: a comparison of approaches. *Transfus Apher Sci*. 2022;61(2):103403.
47. McCarty JR, Raimer SS, Jarratt M. Toxic epidermal necrolysis from graft-vs-host disease. Occurrence in a patient with thymic hypoplasia. *Am J Dis Child*. 1978;132(3):282-284.
48. Farrugia A, Shea N, Knowles S, et al. Cryopreservation of red blood cells: effect of freezing on red cell quality and residual lymphocyte immunogenicity. *J Clin Pathol*. 1993;46(8):742-745.
49. Kurtz SR, Van Deinse WH, Valeri CR. The immunocompetence of residual lymphocytes at various stages of red cell cryopreservation with 40% w/v glycerol in an ionic medium at -80 C. *Transfusion*. 1978;18(4):441-447.
50. Valeri CR, Pivacek LE, Cassidy GP, Ragno G. In vitro and in vivo measurements of gamma-radiated, frozen, glycerolized RBCs. *Transfusion*. 2001;41(4):545-549.
51. Winter KM, Johnson L, Webb RG, Marks DC. Gamma-irradiation of deglycerolized red cells does not significantly affect in vitro quality. *Vox Sang*. 2015;109(3):231-238.
52. European Committee on Blood Transfusion 20th Edition. Guide to the preparation, use and quality assurance of blood components (ed 20th). Strasbourg: European Directorate for the Quality of Medicines & HealhtCare of the Council of Europe; 2020.
53. Ohto H, Anderson KC. Posttransfusion graft-versus-host disease in Japanese newborns. *Transfusion*. 1996;36(2):117-123.
54. 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. *New England Journal of Medicine*. 1974;290(7):359-363.
55. Sanders MR, Graeber JE. Posttransfusion graft-versus-host disease in infancy. *The Journal of Pediatrics*. 1990;117(1, Part 1):159-163.
56. Burke M, Sinha P, Luban NLC, Posnack NG. Transfusion-Associated Hyperkalemic Cardiac Arrest in Neonatal, Infant, and Pediatric Patients. *Front Pediatr*. 2021;9:765306.
57. Williamson LM, Stainsby D, Jones H, et al. The impact of universal leukodepletion of the blood supply on hemovigilance reports of posttransfusion purpura and transfusion-associated graft-versus-host disease. *Transfusion*. 2007;47(8):1455-1467.
58. Morsheimer M, Brown Whitehorn TF, Heimall J, Sullivan KE. The immune deficiency of chromosome 22q11.2 deletion syndrome. *Am J Med Genet A*. 2017;173(9):2366-2372.
59. Mustillo PJ, Sullivan KE, Chinn IK, et al. Clinical Practice Guidelines for the Immunological Management of Chromosome 22q11.2 Deletion Syndrome and Other Defects in Thymic Development. *J Clin Immunol*. 2023;43(2):247-270.
60. Adams SP, Kricke S, Ralph E, Gilmour N, Gilmour KC. A comparison of TRECs and flow cytometry for naive T cell quantification. *Clin Exp Immunol*. 2018;191(2):198-202.
61. Franz AR, Engel C, Bassler D, et al. Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants: The ETTNO Randomized Clinical Trial. *Jama*. 2020;324(6):560-570.
62. Villeneuve A, Arsenault V, Lacroix J, Tucci M. Neonatal red blood cell transfusion. *Vox Sang*. 2021;116(4):366-378.

63. Australian and New Zealand Society of Blood Transfusion. Guidelines for Transfusion and Immunohaematology Laboratory Practice (ed 1st (Revised)). Sydney: Australian and New Zealand Society of Blood Transfusion; 2020.
64. Saito-Benz M, Bennington K, Gray CL, et al. Effects of Freshly Irradiated vs Irradiated and Stored Red Blood Cell Transfusion on Cerebral Oxygenation in Preterm Infants: A Randomized Clinical Trial. *JAMA Pediatr*. 2022;176(5):e220152.
65. Ozdemir A, Gunes T, Chiang SCC, Unal E. A Newborn With Familial Hemophagocytic Lymphohistiocytosis Complicated With Transfusion Associated Graft Versus Host Disease. *J Pediatr Hematol Oncol*. 2017;39(6):e309-e311.
66. Bode SF, Ammann S, Al-Herz W, et al. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. *Haematologica*. 2015;100(7):978-988.
67. Held JL, Druker BJ, Kohn SR, Byrnes W, Margolis RJ. Atypical, nonfatal, transfusion-associated, acute graft-versus-host disease in a patient with Hodgkin's disease. *J Am Acad Dermatol*. 1992;26(2 Pt 1):261-262.
68. Miller DG, Lizardo JG, Snyderman RK. Homologous and heterologous skin transplantation in patients with lymphomatous disease. *J Natl Cancer Inst*. 1961;26:569-583.
69. Twomey JJ, Laughter AH, Farrow S, Douglass CC. Hodgkin's disease. An immunodepleting and immunosuppressive disorder. *J Clin Invest*. 1975;56(2):467-475.
70. Young NS, Scheinberg P, Calado RT. Aplastic anemia. *Curr Opin Hematol*. 2008;15(3):162-168.
71. Nabizadeh F, Mohamadi M, Rahmani S, et al. Safety and efficacy of cladribine in multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci*. 2023;44(9):3045-3057.
72. Shim YE, Ko Y, Lee JP, et al. Evaluating anti-thymocyte globulin induction doses for better allograft and patient survival in Asian kidney transplant recipients. *Sci Rep*. 2023;13(1):12560.
73. Rolla S, Maglione A, De Mercanti SF, Clerico M. The Meaning of Immune Reconstitution after Alemtuzumab Therapy in Multiple Sclerosis. *Cells*. 2020;9(6).
74. Gale RP, Armitage JO. Use of molecularly-cloned haematopoietic growth factors in persons exposed to acute high-dose, high-dose rate whole-body ionizing radiations. *Blood Rev*. 2021;45:100690.

8. Appendices

8.1 Appendix 1: Flow chart for clinical indications for irradiation in intrauterine, neonatal and paediatric transfusions

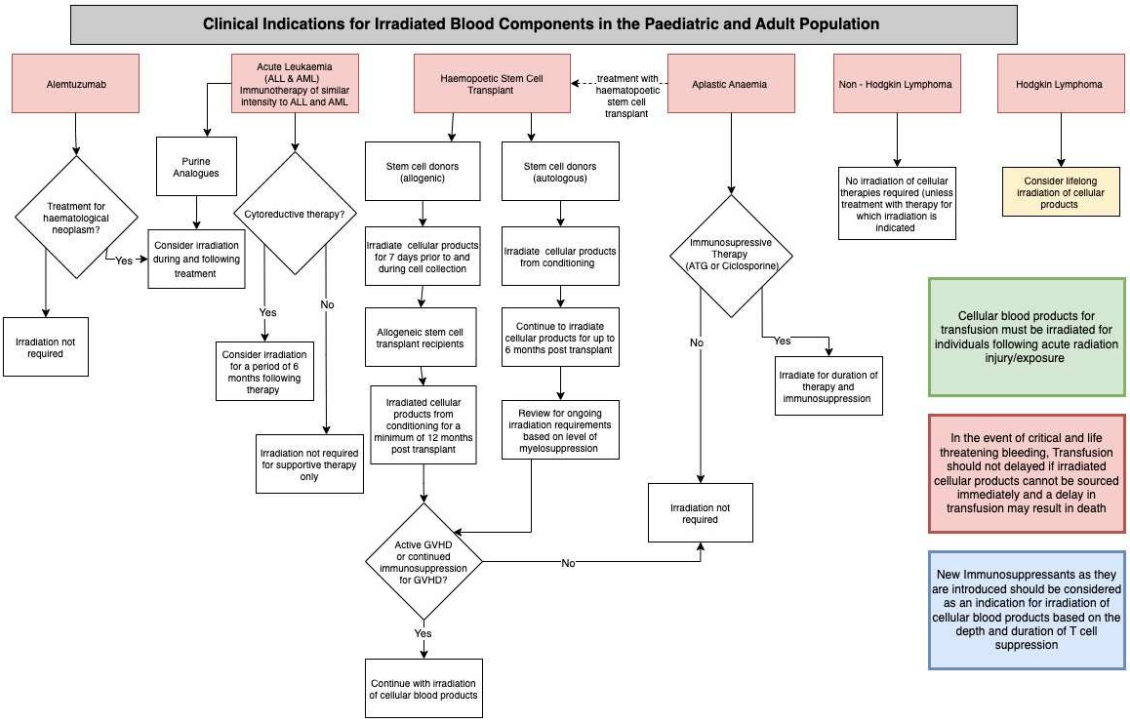


Neonatal Small volume transfusion:
10-20ml/kg, given over 4 hours

Neonatal Large volume transfusion:
At least equivalent to a single circulating blood volume (approximately 80 ml/kg for neonates) over 24 hours or 50% of the circulating volume (approximately 40ml/kg for neonates) within 3 hours

Includes CPB or ECLS with large volume transfusion

8.2 Appendix 2: Flow chart for clinical indications for irradiation in adult and paediatric transfusions



8.3 Appendix 3: Risk Assessment

All transfusions are at risk of TA-GVHD. For most, the risk is small, related to the chance of having a HLA partially matched random donor.

Risk is increased by:

HLA matching / related donors

T cell immunodeficiency in the host

Risk is reduced by:

Leucodepletion by modern pre-storage filtration

Older blood

Risk is eliminated by:

Irradiation

Pathogen reduction technologies

Blood age >21 days

Risk assessment by clinical indications

Patient Group	Risk increased by				Mitigating factors	Overall
	Actual or higher probability of HLA match	Usually receive fresher blood	T cell Immunodeficiency	Increased component T-cell exposure		
HLA-matched products	+++	++	Unk	+		Very high
IUT	-	+++	++	+++		Very high
Top up prior IUT	_	++	++	++		High
Exchange	-	+++	+	+++		High
Neonates and infants with cardiac abnormalities	-	+++	+/-	+++	Large volume reflects priming in some cases ? impact on lymphocyte dose. Identification of severe immunodeficiency in neonatal cardiac centres.	Moderate
Small volume neonatal transfusions	`	++	-	+		Low
Acute myeloid leukaemia	-	-	-	++		Low

Acute lymphoblastic leukaemia	-	-	-	++		Low
High intensity chemotherapy (equivalent to AML or ALL induction / consolidation)	-	-	++	++		Moderate
Hodgkin lymphoma	-	-	++ - +++	-		Moderate
Non-Hodgkin lymphoma	-	-	-	-		Low
Purine analogues	-	-	++ - +++	-		Moderate
Aplastic anaemia	-	-	-	+		Low
Immune suppressive therapy for aplastic anaemia	-	-	+++	+		High
Anti-T cell antibodies (other than for aplastic anaemia)	-	-	+ - ++	-		Low to moderate
Allogeneic stem cell transplant	-	-	+++	++		High
Autologous stem cell transplant	-	-	+++	+		High
Emergency transfusion / critical bleeding	-	-	-	++		Low
Radiation accidents	-	-	+++	++		High