



RECOMMENDATIONS FOR USE OF IRRADIATED BLOOD COMPONENTS IN CANADA:

A NAC and CCNMT Collaborative Initiative



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BACKGROUND

Document Authorship

The National Advisory Committee on Blood and Blood Products (NAC) is an interprovincial medical and technical advisory body to the provincial and territorial health ministries and Canadian Blood Services (CBS). The NAC mandate is to:

- Provide advice on matters pertaining to blood supply, including those directly affecting the practice of transfusion medicine in hospitals;
- Share information about blood and blood product utilization and utilization management efforts, and play a supportive role in the development of guidelines and recommendations for product use;
- Identify opportunities to optimize transfusion medicine practices; and
- On a jurisdictional level, provide leadership in the identification, design and implementation of blood utilization management initiatives for the optimization of patient care.

The CBS Provincial Territorial Blood Liaison Committee (CBS PT BLC) requested that NAC develop recommendations and guidelines for the use of irradiated blood components for Canadian patients. NAC assembled an Irradiation Working Group to review current standards, published guidelines, and recent literature on the indications for irradiated components and the quality of irradiated red blood cell (RBC) components to facilitate recommendations for best practices. This group worked collaboratively with representatives of Quebec's National Advisory Committee on Transfusion Medicine (CCNMT) who joined the recommendation development process – thus forming the NAC-CCNMT Irradiation Working Group. Consultation with Canadian experts in transfusion medicine was included as a part of this recommendation development process. In addition, draft recommendations were circulated to a number of clinical stakeholder organizations for feedback prior to finalization.

This work was informed by the published guidelines on the use of irradiated blood components by the British Committee for Standards in Hematology (BCSH, 2010) and the guidelines for prevention of transfusion-associated graft-versus-host disease by the Australian and New Zealand Society of Blood Transfusion (ANZSBT, 2011). Published Transfusion Medicine practice standards including the Canadian Standards Association (CSA) Z902-15 standards (2015), Canadian Society for Transfusion Medicine (CSTM) standards (version 4, 2017), and Council of Europe (COE) standards (version 17, 2013); and recent publications on the quality of stored red cells post irradiation and practices involving irradiation of autologous blood collected by intraoperative cell salvage were consulted.

Rationale for the Use of Irradiated Blood

Irradiation of cellular blood components is a well-established intervention for the prevention of transfusion-associated graft-versus-host disease (TA-GVHD). There is a system cost of providing irradiated blood components to patients that includes higher production costs, regulatory



compliance and supply logistics. Recent publications have also emphasized the negative impact of irradiation on the RBC, and the importance of considering RBC age at the time of irradiation and the length of storage post-irradiation. The Working Group has therefore emphasized the need for conscientious management of hospital inventories to limit the provision of irradiated RBCs to those patients who have specific clinical indications to receive irradiated RBC units. Adherence to this practice would thereby minimize exposure of the general patient population to irradiated RBCs.

Data provided by CBS demonstrates some trends in irradiation practice in Canada over the past ten years. There has been a national increase in the percentage of irradiated RBCs from 4.5% (2004-2005) to 6.7% (2015-2016). There is considerable regional variation. The percentage irradiated RBC units issued by CBS ranges from 2-18%, depending on the province. The percentage of irradiated RBC units issued by Héma-Québec, in 2015-2016, was 6.0%.

TA-GVHD is a rare, usually fatal complication of transfusion resulting from the engraftment of transfused, immunocompetent donor lymphocytes and subsequent damage to recipient tissues which are perceived as foreign by the engrafted lymphocytes. Patients at most risk include those who are severely immunocompromised and those who fail to recognize the transfused donor lymphocytes as foreign if human leukocyte antigen (HLA) alleles are haploidentical.

Defining immunocompromised patient groups who should receive irradiated blood has been largely based on observational evidence, case reports, reviews and attempts to predict the degree of immunosuppression. As such, there is a lack of consistency in text books, publications and guidelines as to which patients must receive irradiated blood. Many authors address the lack of clarity by including a category of indications where there is uncertainty regarding the need for irradiated blood.

In view of growing evidence demonstrating the poor quality of post-irradiation stored RBCs, there is a need to be thoughtful about the clinical indications for irradiated blood transfusion and avoid over stocking irradiated RBC units. Without an on-site irradiator, finding a balance of stocking sufficient (but not excess) supply for patient's in-need of irradiated blood may be challenging. Concerns regarding post-irradiation component quality and storage do not apply to platelets or granulocyte concentrates due to the short shelf life of these components.

In addition to irradiation as a TA-GVHD mitigation strategy, recent observational evidence suggests that the pre-storage leukoreduction and length of time since donation may modify recipient TA-GVHD risk. To date, both pre-storage leukoreduction and increased RBC storage time have not been shown to have an equivalent efficacy for eliminating TA-GVHD risk, however.

In a recent systematic review of 348 reported TA-GVHD cases, the authors reported that greater than 94% of cases of TA-GVHD occur when the blood is less than 10 days old, with none of the TA-GVHD cases associated with components older than 14 days from collection (Kopolovic *et al*, 2015). A review of 290 cases referred to the Japanese Red Cross (JRC) from 1992-1999 identified 66



cases of definite TA-GVHD by microsatellite DNA analysis. The oldest blood transfused in this series was 10 days for whole blood, 11 days for RBCs without an additive solution, and 14 days for RBCs with added mannitol, adenine and phosphate (Uchida *et al*, 2013). In another report from the JRC, 96% of 51 cases received blood less than 96 hours old (Jawa *et al*, 2015). Thus, transfusion of blood stored for more than 14 days represents a potential risk mitigation strategy for patients in whom there is uncertainty regarding the degree of immune compromise.

The potential risk mitigation afforded by leukoreduction is supported by data from the Serious Hazards of Transfusion (SHOT) surveillance system in the United Kingdom. A total of 14 cases of TA-GVHD have been reported to SHOT since 1996, which include only 3 cases since the introduction of universal leukoreduction in 1999. Two of these patients were confirmed to have received leukoreduced components. The first case involved a patient with multiple myeloma, reported in 1999. The second case occurred in 2001, and involved a 14-year-old patient with relapsed acute lymphoblastic leukemia. Donors from potentially implicated units were not recalled for HLA typing. The most recent case, reported in 2012, followed an emergency intrauterine transfusion of non-irradiated, non-leukoreduced maternal red cells. The mother was subsequently found have a homozygous HLA haplotype (Bolton-Maggs, 2012). There have been no further TA-GVHD cases reported to SHOT since 2012 (Bolton-Maggs, 2016).

Further observational evidence of the risk reduction associated with leukoreduction can be found in the aforementioned systematic review of 348 TA-GVHD cases. Of these, only 23 were in patients who had received leukocyte reduced components, 2 of which were pre-storage, 10 bedside and 11 unspecified (Kopolovic *et al*, 2015). Together with SHOT surveillance, these findings suggest that leukoreduction reduces, but does not eliminate, the risk of TA-GVHD.

It should be noted that following the 2001 terrorist attacks in New York, a decision was made in the UK to increase blood stocks. As a result, the mean age of blood issued to hospitals after 2002 went from 8 days to 12-14 days and may have also contributed to reducing TA-GVHD risk (Williamson *et al*, 2007).

Document Scope and Guide

Upon review of the best-available information, the NAC-CCNMT Irradiation Working Group has compiled this recommendations document to help Canadian clinicians determine which patients should receive irradiated components, and define the age of RBCs at the time of irradiation and the length of storage post-irradiation.

Special annotations following each recommendation have been included to inform the reader of the recommendation reference:

- An asterisk (*), to indicate a verbatim statement from the referenced guideline.
 - A level of evidence description for the recommendation may be included from the original guideline document, if available.
- Recommendation statements without a reference are considered best practice statements by NAC and the Working Group, based upon published guidelines or literature.



Recommendations pertaining to the RBC age and the length of storage post-irradiation are consistent with the COE standards (17th edition) and the newest version of the CSTM standards (version 4, 2017), but are more restrictive than current AABB (29th ed, 2014) and CSA standards (CSA Z902-15, 2015).

In defining patients who should receive irradiated cellular components, the Working Group supports the majority of published BCSH 2010 and ANZSBT 2011 guidelines. A cautious approach for small volume (top-up) transfusions in very low birth weight neonates is maintained, given that there is variation in expert opinion in the published literature. Recommendations for neonatal transfusion include consideration of the 2016 Canadian neonatal transfusion practice survey results (see *Supplement*). Unless otherwise specified, recommendations made within this document may be assumed to apply to both adult and pediatric populations.

GENERAL RECOMMENDATIONS

The NAC-CCNMT Working Group supports the following general recommendations pertaining to the type of blood component that requires irradiation, information sharing and communications of a patient's requirement for irradiated blood components. In addition, the Working Group recommends voluntary alignment with the COE standards (17th edition) for the age of the units and post-irradiation storage conditions.

1. Blood components that should be irradiated

- A. Recommendation: For at-risk patients, all red cell, platelet and granulocyte concentrates should be irradiated, except cryopreserved red cells after deglycerolization. It is not necessary to irradiate fresh frozen plasma, cryoprecipitate or fractionated plasma products.
(BCSH 2010, Grade 1 recommendation; level B evidence)*
- B. Recommendation: All transfusions from first- or second-degree relatives must be irradiated, even if the patient is immunocompetent.
- C. Recommendation: All HLA-selected platelets must be irradiated, even if the patient is immunocompetent.
- D. Recommendation: All granulocyte components must be irradiated before issue.

2. Age of cellular blood components and post-irradiation storage timelines

Recent evidence has shown that the age of RBCs at the time of irradiation is important and that prolonged storage of pre-irradiated units is associated with high potassium levels, in vitro



hemolysis, and decreased post-transfusion recovery (Serrano *et al*, 2014). This has implications for patient safety as well as hospital inventory management practices.

The current North American standards (AABB, 29th ed, 2014 and CSA Z902-15, 2015) specify that RBCs shall have a maximum expiration time of 28 days after irradiation or shall retain the original outdate, whichever is shorter, and do not limit the age of RBC at the time of irradiation. The NAC-CCNMT Working Group is recommending voluntary alignment with the COE Standards (17th edition) to reduce the age of units selected for irradiation and timeline of post-irradiation storage. This more restrictive timeline is endorsed in the newest version of the CSTM Standards (version 4, 2017).

- A. Recommendation: Red cell components may be irradiated up to 28 days after collection. Irradiated cells must be transfused as soon as possible, but no later than 14 days after irradiation, and in any case, no later than 28 days after collection. (Council of Europe Standards, 17th edition, 2013)*

- B. Recommendation: Platelets can be irradiated at any stage during storage and can thereafter be stored up to their normal shelf life after collection. (BCSH 2010, Grade 1 recommendation; level A evidence)*

3. Patient awareness

- A. Recommendation: Patients at risk of TA-GVHD should be made aware of their need for irradiated blood components. It is the responsibility of the most responsible health care practitioner to inform patients at risk of TA-GVHD of their need for irradiated blood components.

4. Communication

- A. Recommendation: To ensure consistency of patient care across jurisdictions, particularly between hospital facilities that participate in the shared care of patients, a communications process between clinicians and the transfusion medicine laboratory facilitating sharing details of special transfusion requirements should be implemented and maintained as a best practice policy. In an ideal setting, an electronic automatic notification identifying pharmaceutical history or indication for irradiated blood to the transfusion medicine laboratory would be in place.



INVENTORY MANAGEMENT RECOMMENDATIONS

As stated, prolonged storage of pre-irradiated units is associated with high potassium levels, in vitro hemolysis and decreased post-transfusion recovery (Serrano *et al*, 2014). Maintaining large inventories of irradiated red cells results in potentially harmful transfusion of irradiated red cells to patients who do not require irradiated cellular blood components.

Proactive inventory management must take into consideration the perceived risk of TA-GVHD in the local patient population, the risks of transfusing irradiated red cells to patients who do not require irradiated cellular components and the logistics of providing irradiated components for elective transfusions. Irradiation of RBCs should therefore occur as near-to as possible to the time of transfusion.

5. Irradiated blood component availability

- A. Recommendation: For elective transfusions reliance on a regional hub site for on-demand irradiation or limited pre-irradiated stock is recommended.
- B. Recommendation: Overstocking of pre-irradiated units for emergency transfusion is not recommended. If storage of pre-irradiated inventory is absolutely necessary, then red cells that have been irradiated within 14 days of collection should be obtained, if possible.

As described above, observational evidence from UK SHOT data (Williamson *et al*, 2007), a recent systematic review of 348 cases of TA-GVHD (Kopolovic *et al*, 2015) and three reviews of Japanese Red Cross data has provided some evidence for the risk mitigating effect of universal pre-storage leukoreduction and the transfusion of older RBCs with reduced lymphocyte viability (>14 days post donation) (Uchida *et al*, 2013; Jawa *et al*, 2015).

- C. Recommendation: In the event of emergency transfusion in the absence of on-site irradiation or pre-storage irradiated inventory, pre-storage leukoreduced red cells that have been stored for more than 14 days should be provided to patients with an indication for irradiated blood transfusion.
- D. Recommendation: Where there is concern about the immunosuppressive potency of new drugs and uncertainty about the risk of TA-GVHD, in the absence of on-site irradiation or pre-storage irradiated inventory, pre-storage leukoreduced red cells that have been stored for more than 14 days should be provided.



- E. Recommendation: Pathogen inactivation or reduction technologies cannot yet be considered an alternative or equivalent to irradiation as TA-GVHD mitigation strategies, though data in this area continues to evolve.

CLINICAL RECOMMENDATIONS

To arrive at the following clinical recommendations NAC-CCNMT Working Group has drawn primarily upon the BCSH 2010 and ANZSBT 2011 guidelines. In addition, the 2016 survey of current practices at Canadian hospitals with Level 3 neonatal intensive care units informed neonatal transfusion recommendations (see *Supplement*).

For clinical conditions listed, the patient medication history must be taken into consideration by the most responsible healthcare practitioner requesting blood transfusion, as a treatment received may necessitate irradiated cellular component use. Local practices may be dictated by the ability of hospital transfusion medicine services to obtain the patient's medication history.

Appendix A provides a quick-reference of the clinical indications for transfusion of irradiated blood components, Appendix B lists immunosuppressive medications, and the *Supplement* summarizes results of the 2016 Canadian National Survey of Irradiation Practices in Neonatal Transfusion.

6. Acute leukemia

There is no definitive evidence to support the need for irradiated blood transfusion to patients with a diagnosis of acute leukemia (any type) in adult and pediatric patients, in the absence of identified TA-GVHD risk factors. Chemotherapy regimens for acute leukemia typically do not include pharmacotherapeutic agents known to be risk factors for TA-GVHD development. However, individual treatment protocols should be reviewed to ensure that there is no indication for irradiated blood transfusion (see Section 15 or Appendix B below).

- A. Recommendation: It is not necessary to irradiate red cells or platelets for adults or children with acute leukemia, except for HLA-selected platelets or donations from first- or second-degree relatives.
(BCSH 2010, Grade 1 recommendation; level B evidence)*

7. Allogeneic bone marrow or peripheral blood stem cell transplantation

Published clinical practice guidelines are in agreement with the provision of irradiated blood components to allogeneic bone marrow transplant recipients from the time conditioning chemotherapy is initiated. However, there is less certainty as to the definition of when transfusion of irradiated blood components can stop post-transplant. Some experts have suggested that if



transplant recipients have completed GVHD prophylaxis immunosuppression and a threshold lymphocyte count of at least $1 \times 10^9/L$ has been achieved (approximately 6-12 months post-transplant), then the indication for irradiated blood component transfusion may be removed.

Due to the paucity of evidence, the decision to discontinue transfusion of irradiated blood components should remain at the discretion of the transplant physician team.

- A. Recommendation: All recipients of allogeneic hematopoietic stem cell transplantation (HSCT) must receive irradiated blood components from the time of initiation of conditioning chemoradiotherapy. (BCSH 2010, Grade 1 recommendation; level B evidence)*
- B. Recommendation: Irradiated blood components should be continued while the patient continues to receive graft-versus-host disease (GVHD) prophylaxis. The indication for ongoing transfusion of irradiated blood components should be reviewed at least yearly. If chronic GVHD is present or if continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely.
- C. Recommendation: Allogeneic blood transfused to bone marrow and peripheral blood stem cell donors 7 days prior to or during the harvest should also be irradiated. (BCSH, Grade 2 recommendation; level C evidence)*

8. Aplastic anemia

- A. Recommendation: We recommend use of irradiated blood components for severe aplastic anemia patients receiving immunosuppressive therapy with ATG and/or alemtuzumab.
- B. Recommendation: We cannot make a firm recommendation as to how long irradiated blood components should continue to be used after ATG administration. (BCSH 2010)*
- C. Recommendation: In the absence of indications necessitating irradiated component transfusion, patients with aplastic anemia do not otherwise require transfusion of irradiated red cells and platelets.

9. Autologous bone marrow or peripheral blood hematopoietic stem cell transplantation

- A. Recommendation: Patients undergoing bone marrow or peripheral blood stem cell 'harvesting' for future autologous re-infusion should receive irradiated cellular blood components during and for 7 days before the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially withstand cryopreservation.



(BCSH 2010, Grade 2 recommendation; level C evidence)*

- B. Recommendation: All patients undergoing autologous bone marrow transplant or peripheral blood stem cell transplant should receive irradiated cellular components from initiation of conditioning chemo/radiotherapy until 3 months post-transplant (6 months if total body irradiation was used in conditioning).
(BCSH 2010, Grade 2 recommendation; level C evidence)*

10. Immunodeficiency states, acquired

- A. Recommendation: There is no indication for irradiation of cellular blood components for infants or children who are suffering from a common viral infection, who are HIV antibody positive or who have AIDS. There is also no indication for routine irradiation of cellular blood components for adults who are HIV antibody positive or who have AIDS. (BCSH, Grade 2 recommendation; level B evidence)*

11. Immunodeficiency states, congenital

- A. Recommendation: All severe T lymphocyte immunodeficiency syndromes should be considered as indications for irradiation of cellular blood components. Once a diagnosis of immunodeficiency has been suspected, irradiated components should be given while further diagnostic tests are being undertaken. A clinical immunologist should be consulted for advice in cases where there is uncertainty.
(BCSH 2010, Grade 1 recommendation; level A evidence)*

12. Lymphoma

There is overarching consensus in published guidelines based on the literature that the risk of TA-GVHD in Hodgkin lymphoma is greater than in those with non-Hodgkin lymphoma, and appears to be unrelated to disease stage or treatment modality. Although a diagnosis of non-Hodgkin lymphoma is not in itself an absolute indication for transfusion of irradiated blood components, pharmacotherapeutics used in treatment protocols may necessitate transfusion of irradiated components to mitigate TA-GVHD risk (see Section 15 or Appendix B below). However, there is a lack of evidence and therefore controversy surrounding the time-span following which irradiated blood component transfusion is required after patients complete their treatment course with an at-risk medication.

- A. Recommendation: All adults and children with Hodgkin lymphoma at any stage of the disease should have irradiated red cells and platelets for life.
(BCSH 2010, Grade 1 recommendation; level B evidence)*



- B. Recommendation: All patients with non-Hodgkin lymphoma receiving purine analogues and related drugs should receive irradiated cellular blood components from the time of therapy initiation. Due to the paucity of evidence, we cannot make a firm recommendation regarding the time at which irradiated component provision may be discontinued.

13. Neonatal Transfusions

A survey was completed to better understand current practices in Canada regarding the use of irradiated blood components specifically for neonatal populations to inform these recommendations. The survey focused on three clinical scenarios: intrauterine transfusions, neonatal top-up (small volume) transfusions, and neonatal exchange. The survey was sent to the medical directors of transfusion medicine in Level 3 neonatal intensive care nurseries (defined according to the Neonatal Classification Tool developed in British Columbia). The *Supplement* to this recommendations document contains a copy of the survey distributed and collated results.

The NAC-CCNMT Working Group recommendations for neonatal transfusions are as follows:

Intra-Uterine Transfusions (IUT) and Neonatal Exchange Transfusion:

- A. Recommendation: All components for IUT must be irradiated. To minimize the effect of potassium load, red cells for IUT must be as fresh as possible, and must be transfused within 24 hours of irradiation.
- B. Recommendation: Irradiated cellular components are recommended for neonates who have received an IUT, in which case irradiated components should be administered until 6 months after the expected delivery date (40 weeks gestation).
- C. Recommendation: It is essential to irradiate blood for neonatal exchange transfusion if there has been a previous IUT or if the donation comes from a first- or second-degree relative.
(BCSH 2010, Grade 1 recommendation; level B evidence)*
- D. Recommendation: For other neonatal exchange transfusion cases, irradiation is recommended provided this does not unduly delay transfusion.
(BCSH 2010, Grade 1 recommendation; level C evidence)*
- E. Recommendation: Red cells for neonatal exchange transfusion should be as fresh as possible, and must be transfused within 24 hours of irradiation.



Neonatal Small-volume (Top-up) Transfusions:

For small volume transfusions in neonates, the NAC-CCNMT Working Group recognizes that there is insufficient data to firmly guide transfusion practice. The BCSH 2010 guidelines do not recommend transfusion of irradiated RBC for small-volume transfusion, while the ANZSBT 2011 guidelines recommend transfusion of irradiated RBC in very low birth weight infants of less than 1300 grams. Many neonatal studies have defined very low birth weight as 1200 to 1300 grams to assess outcomes and interventions, though the World Health Organization defines very low birthweight as less than 1500g. The NAC-CCNMT Working Group leaves the decision of a very low birthweight cut-off to the discretion of local neonatology experts at hospital-based services.

- F. Recommendation: Irradiated cellular components are recommended for small-volume transfusions given to neonates born with a very low birthweight, up to 4 months of age.

- G. Recommendation: Where the patient is at particular risk of hyperkalemia, it is recommended that red cells be transfused within 24 hours of irradiation. Red cells stored for greater than 24 hours from irradiation must at least undergo centrifugation and supernatant plasma removal prior to transfusion.

The practice of sterile docking and splitting an adult RBC unit for sequential neonatal transfusion evolved during an era of greater risk for transfusion transmitted infection. Limiting donor exposure in neonates continues to be a priority. However, the enhanced safety of the blood system through improved donor screening, nucleic acid testing, and access to public health surveillance allows for greater emphasis to now be placed on blood component quality. This represents a shift in the risk paradigm from donor exposure towards component quality and supports the practice of sharing split portions of a single donor adult RBC unit amongst several neonates. Not only does this facilitate preservation of limited group O RBC inventory, (which is likely to be further stressed by shorter outdating with the COE standards), but it also provides an option for facilities without irradiators, as described below.

Ideally, facilities with Level 3 neonatal intensive care units should have an on-site irradiator to facilitate irradiation of RBC aliquots at the time of issue.

For hospitals without an on-site irradiator, it may be necessary to maintain a small stock of RBC units irradiated by the supplier or a regional hub hospital. In this setting, the practice of sharing a unit amongst more than one neonate should be considered as a mechanism of optimally utilizing a freshly irradiated RBC unit and minimizing the length of storage post irradiation. For a neonate requiring repeat RBC transfusion, this practice may increase donor exposure, but should facilitate a regular inventory rotation (e.g. weekly) of a shared pre-storage irradiated RBC unit, and thereby mitigate the risks associated with component quality. It remains the prerogative of the



transfusion medicine medical director or attending physician to request a single donor unit for neonates who are likely to require multiple transfusions.

In all cases of neonatal small volume transfusion, aliquots must be less than 14 days post-irradiation and no more than 28 days since donation. (Council of Europe Standards, 17th edition, 2013). Aliquots more than 24 hours from irradiation must have at least undergone centrifugation and supernatant plasma removal. A recent study has demonstrated that supernatant reduction by centrifugation is preferable to gravity settling. (Serrano *et al*, 2017). The final hematocrit should not exceed 0.80 L/L (CSA Z902-15 Standards, 2015). All manipulation should be performed as near-to as possible to the time of RBC release for transfusion.

Emergency Transfusions:

- H. Recommendation: For emergency transfusions of unmatched group O, D-negative red cells for neonatal resuscitation due to obstetrical complications and/or accidents, irradiated cellular components are NOT required.

Congenital Cardiac Abnormalities:

The presence of a congenital cardiac abnormality identified in a neonate or infant may raise the suspicion of chromosome 22q11 deletion syndrome, commonly associated with a congenital T cell immunodeficiency. Cardiac abnormalities most frequently associated with chromosome 22q11 deletions include: Tetralogy of Fallot, ventricular septal defect, interrupted aortic arch, combined pulmonary atresia and ventricular septal defect, and truncus arteriosus. (Ryan *et al*, 1997)

- I. Recommendation: There is no need to irradiate red cells or platelets for infants undergoing cardiac surgery unless clinical or laboratory features suggest a coexisting T lymphocyte immunodeficiency syndrome. (BCSH 2010, Grade 2 recommendation; level B evidence)*
- J. Recommendation: All neonates with complex cardiac abnormalities should receive irradiated cellular components until a congenital immune deficiency disorder is excluded by diagnostic testing for 22q11.2 deletion associated with immunodeficiency states, which include DiGeorge Syndrome. If a congenital immune deficiency disorder is confirmed, irradiated cellular components should be provided for life.

14. Pharmacotherapeutics: Purine analogue drugs and other potent immunosuppressive drugs

It is difficult to provide a clear recommendation for or against the use of irradiated blood in the context of all available immunosuppressive and biologic therapies in the absence of published evidence for specific agents in specific clinical contexts. This is particularly the case for new pharmacotherapeutic agents, such as tumor necrosis alpha (TNF- α) inhibitors and interleukin



inhibitors. The decision to provide irradiated blood for patients on specific immunosuppressive agents should be made in consultation with the patient's most responsible physician, with consideration given to the perceived benefits and risks of irradiated blood transfusion and availability of irradiated blood. Where there is uncertainty or concern regarding the immunosuppressive potency of a particular agent, discussion with a Transfusion Medicine expert is encouraged.

Appendix B includes a comprehensive list of potent immunosuppressive medications cited to increase TA-GVHD risk, and for which irradiated component transfusion should be considered.

- A. Recommendation: Patients treated with purine analogue drugs (fludarabine, cladribine and deoxycoformicin) should receive irradiated blood components indefinitely. (BCSH 2010, Grade 1 recommendation; level B evidence)*

Irradiated blood transfusion is not required for patients treated with the purine analogues 6-mercaptopurine (6-MP) and azathioprine. These medications are not considered to have the same immunosuppressive potency as the above-listed chemotherapeutic agents, and based on available literature, have not been identified to be associated with an increased TA-GVHD risk.

- B. Recommendation: The situation with other purine antagonists and new or related agents, such as bendamustine and clofarabine, is unclear, but use of irradiated blood components is recommended as these agents have a similar mode of action. Irradiated blood components should be used after alemtuzumab (anti-CD52) therapy. Their use after rituximab (anti-CD20) is not recommended at this time. As new potent immunosuppressive drugs and biological agents are introduced into practice there is a need for regular review of these recommendations. (BCSH 2010, Grade 2 recommendation; level C evidence)*

- C. Recommendation: Due to the lack of high-quality data to firmly define a period of time following which irradiated blood components must be used in patients following treatment with purine analogues and new or related agents, consideration may be given to discontinuation of their use after at least 1 year.

Anti-thymocyte globulin (ATG) is a potent immunosuppressive agent which is available as a derivative of both horse and rabbit sources, and used in a number of clinical contexts. There is expert consensus that irradiated blood components should be provided to patients with severe aplastic anemia who receive ATG (see Section 8 above). There is no evidence of increased TA-GVHD risk in solid organ transplant recipients conditioned with ATG, and as a result, current guidelines for solid organ transplantation do not cite a specific requirement for transfusion of irradiated blood in this population (KDGIO Transplant Work Group, 2009). The risk of TA-GVHD in patients undergoing reduced-intensity conditioning with ATG alone for allogeneic bone marrow transplantation is unknown.



15. Routine surgery, solid tumors, solid organ transplantation, autoimmune disorders, acquired immunodeficiency

- A. Recommendation: It is not necessary to irradiate blood components for patients undergoing routine surgery, those with solid tumours, HIV infection, autoimmune diseases or after solid organ transplantation (unless alemtuzumab (anti-CD52) has been used in the conditioning regimen). The effects of new regimens of chemo- and immunotherapy entering clinical practice must continue to be monitored. (BCSH 2010, Grade 2 recommendation; level C evidence)*

Intraoperative autologous red blood cell salvage techniques are important to reduce the rate of and associated risks of allogeneic blood transfusion during major surgery. In patients with cancer, the use of intraoperative cell salvage (ICS) has been controversial due to the theoretical risk of metastasis propagation from reinfusion of autologous blood contaminated with metastatic cells. However, a recent meta-analysis of 10 studies showed no significant difference in cancer recurrence rates between patients who received ICS compared to those who did not during their surgeries (Waters *et al*, 2012). A systematic review evaluating the use of ICS in metastatic spine tumor surgery (Kumar *et al*, 2014) also did not identify a greater risk of tumor dissemination or metastasis in patients who received reinfusion of autologous ICS blood, though a caution was noted in situations of tumor rupture.

The use of either gamma irradiation or a small-pore microfiber leukocyte reduction filter have been identified to be effective strategies to reduce the risk of metastatic cell transmission from ICS blood in patients with malignancy undergoing surgery (Trudeau *et al*, 2012). Leukoreduction filters are more accessible than on-site hospital irradiators and do not impose damage to the RBC membrane, making their use a much more common in practice. The risks and benefits of intraoperative cell salvage in the setting of surgery in patients with suspected or known malignancy must be weighed by the perioperative team, and discussed together with the patient prior to use.

- B. Recommendation: In patients with malignancy undergoing surgery, it is not necessary to irradiate autologous blood collected by intraoperative cell salvage if a small-pore microfiber leukocyte reduction filter is used prior to blood reinfusion.



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APPENDIX A: Quick reference of clinical indications for irradiated blood component transfusion

Patient Category	Condition
General Transfusion Practice	Directed donation (blood from first- and second- degree relatives)
	HLA-selected/matched platelets
	Granulocyte transfusion
Pregnancy	Intrauterine, fetal transfusion
Neonates	Neonatal exchange transfusion: <ul style="list-style-type: none"> • Previous IUT, until 6 months after the expected delivery date (40 weeks gestation) • All neonatal exchange transfusions provided it does not unduly delay transfusion
	Neonatal small volume (top-up) transfusions <ul style="list-style-type: none"> • Previous IUT, until 6 months after the expected delivery date (40 weeks gestation) • Very low birth weight infants, until 4 months of age • Consult local policies in uncertain situations
	Congenital severe T cell immune deficiency <ul style="list-style-type: none"> • Until has been proven, and when confirmed present
	Complex congenital cardiac abnormalities: <ul style="list-style-type: none"> • Until 22q11.2 deletion has been excluded • Confirmed 22q11.2 deletion
Hematology	Acute leukemia, only in the following situations: <ul style="list-style-type: none"> • HLA-selected/matched platelets • Donations from first- or second- degree relatives • Current or previous immunosuppressive pharmacotherapy (see Appendix B)
	Aplastic Anemia <ul style="list-style-type: none"> • Patients receiving immunosuppressive therapy with ATG (and/or alemtuzumab)
	Hodgkin's Lymphoma, at any stage
	Non-Hodgkin's Lymphoma treated with purine analogues and related drugs (see Appendix B)



Allogeneic Bone Marrow Transplant	Allogeneic haematopoietic stem cell or bone marrow transplant recipients, <ul style="list-style-type: none"> • from the time of initiation of conditioning chemotherapy • while the patient continues to receive GVHD prophylaxis • indefinitely if chronic GVHD is present or if continued immunosuppressive therapy is required
	Allogeneic blood transfused to stem cell or bone marrow transplant donors for 7 days prior to and during the stem cell harvest
Autologous Bone Marrow Transplant	Autologous stem cell or bone marrow transplant recipients from the initiation of conditioning chemo/radiation therapy to 3 months post-transplant (6 months if total body irradiation was used in conditioning)
	Patients undergoing harvesting for future autologous reinfusion, during and for 7 days before the bone marrow/stem cell harvest
Solid Organ Transplant	Recipients of alemtuzemab conditioning therapy only

APPENDIX B: Quick reference of potent immunosuppressive medications cited to increase TA-GVHD risk, and for which irradiated component transfusion should be considered

GENERIC Name	TRADE Name*
Fludarabine	Fludara
Cladribine or 2-CDA	Leustatin
Deoxycoformicin	Pentostatin or Nipent
Alemtuzumab (anti-CD52)	Campath, Lemtrada
Bendamustine	Treakisym, Ribomustin, Levact and Treanda
Clofarabine	Clolar
Anti-thymocyte globulin (ATG), rabbit or horse - When used in the setting of severe aplastic anemia only	Rabbit: Thymoglobulin Horse: Atgam

* *Note:* This list of pharmaceutical trade names may not be exhaustive, due to the nature of branding changes.



REVISION HISTORY

Date	Summary of Revisions
2018-02-13	Addition of Lemtrada as a TRADE name of alemtuzumab to APPENDIX B Addition of *Note to APPENDIX B
2018-05-14	Correction of systematic review total number of TA-GVHD cases to 348 in Background.