National Advisory Committee on Blood and Blood Products | Comité consultatif national sur le sang et les produits sanguins

SUPPLEMENT TO THE NAC-CCNMT RECOMMENDATIONS FOR USE OF IRRADIATED BLOOD COMPONENTS IN CANADA

Transfusion-Associated GvHD and New Indications for Irradiated Blood Components

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Objective: A literature search for case reports of Transfusion-Associated Graft-vs-Host Disease (TA-GvHD) published between January 1, 2017 – January 31, 2022, was performed. A particular focus of attention was new clinical indications for irradiated blood components and new pharmaceutical agents causing TA-GvHD, along with the most recent clinical guidelines for the use irradiated blood components to prevent TA-GvHD.

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CASE REPORT OF TA-GVHD – A POTENTIAL NEW INDICATION

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 Aug;39(6):e309-e311. doi: 10.1097/MPH.0000000000000777.

Abstract:

« Hemophagocytic lymphohistiocytosis (HLH) is characterized by activation of cytotoxic T and natural killer (NK) cells, and macrophages related to a spectrum of hyperinflammatory disorders. The clinical findings mainly include high fever, cytopenia, splenomegaly, phagocytosis, and proliferation of histiocytes in lymphoreticular tissue. ***To the best of our knowledge, transfusion-associated graft versus host disease (TA-GVHD) in a 13-day old male newborn with HLH is being reported first time in the literature.***

The aim of this report was to emphasize the importance of blood products irradiation in the prevention of the development of graft versus host disease especially among high-risk subjects such as newborns with HLH. *»*

GUIDELINES WITH NEW INDICATIONS FOR IRRADIATED BLOOD COMPONENTS

Foukaneli T, Kerr P, Bolton-Maggs PHB, Cardigan R, Coles A, Gennery A, Jane D, Kumararatne D, Manson A, New HV, Torpey N; BCSH Committee. Guidelines on the use of irradiated blood components. Br J Haematol. 2020 Dec;191(5):704-724. doi: 10.1111/bjh.17015.

Justification for new recommendations identified since the last *NAC-CCNMT Recommendations for Use of Irradiated Blood Components in Canada*:

« In view of the recent case of possible TA-GvHD in an infant with congenital familial haemophagocytic lymphohistiocytosis (HLH),[34] it is reasonable to give irradiated cellular blood components for patients with suspected congenital HLH and lymphopenia, until T-cell immunodeficiency has been excluded. To date, there have been no reports of TA-GvHD occurring in patients with isolated defects of humoral immunity. »

« Cardiac surgery in neonates and infants (and older patients). There have been occasional published reports of TA-GvHD in apparently immunocompetent neonates and older patients undergoing cardio-pulmonary bypass surgery.[9,11,95] There should be a high index of suspicion concerning co-existing cardiac defects and immunodeficiency. If in doubt, blood should be irradiated until a definitive diagnosis is made. »

"Patients (adult and paediatric) undergoing peripheral blood lymphocyte collections for future CAR-T cell re-infusion should receive irradiated cellular blood components for 7 days prior to and during the harvest, to prevent the collection of viable allogeneic T lymphocytes. Irradiated blood components should continue to be used until 3 months following CAR-T cell infusion unless conditioning, disease or previous treatment determine indefinite duration, e.g. previous diagnosis of Hodgkin lymphoma or previous purine analogue treatment (1/C)."

Wiersum-Osselton JC, Slomp J, Frederik Falkenburg JH, Geltink T, van Duijnhoven HLP, Netelenbos T, Schipperus MR. 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 Dec;195(5):681-688. doi: 10.1111/bjh.17822.

New indication for irradiated blood components:

"The working group advises that irradiated components should be considered for a week prior to such harvest in view of the subsequent modification and culturing as well as difficulty distinguishing between cells of donor and autologous origin as a cause of GVHD which may arise."

Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, Tewari P, Duncan C, Traube C, McCall D, Steiner ME, Cheifetz IM, Lehmann LE, Mejia R, Slopis JM, Bajwa R, Kebriaei P, Martin PL, Moffet J, McArthur J, Petropoulos D, O'Hanlon Curry J, Featherston S, Foglesong J, Shoberu B, Gulbis A, Mireles ME, Hafemeister L, Nguyen C, Kapoor N, Rezvani K, Neelapu SS, Shpall EJ; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. *Nature Reviews Clinical Oncology*. 2019 Jan;16(1):45-63. doi: 10.1038/s41571-018-0075-2.

« If needed, transfusions (irradiated blood products) should be ordered according to institutional guidelines for paediatric patients (without routine corticosteroid pre-medication). » (…)

« Packed red blood cells (irradiated) and/or albumin can be used to prime the collection in children weighing <30kg. »

CASE REPORTS OF TA-GVHD

M Jorge, B Sousa, A Caiado, D Espirito Santo and A Alegria. Transfusion-associated graft versus host disease: a rare transfusion complication – clinical case . The 36th International ISBT Congress, Virtual meeting, 12-16 December 2020. Vox Sang. 2020 Dec;115 Suppl 1:5-396. doi: 10.1111/vox.13031.

Case Report:

« In this case, **we describe an attenuated and non-lethal TA-GVHD in a 7-month-old boy referred to our hospital for infection and respiratory failure**. He was admitted to the Intensive Care Unit and started empirical antibiotics and high-dose of steroids. **At 2nd and 7th days, presenting with severe anaemia, he was submitted to two non- irradiated blood transfusions (same donor)**. About a week later, he developed erythematous maculopapular rash of the torso, arms and legs progressing to the palms and soles with skin exfoliation. Based on the diagnostic hypothesis of toxic epidermal necrolysis (NET), all potentially responsible drugs were discontinued.

Six weeks later, he maintained the same lesions and given the exuberance and characteristics of the rash, associated with the development of several severe viral and bacterial infections, an immune deficiency and TA-GVHD were suspected. An immunological study provided further evidence of a combined immunodeficiency and the chimerism study showed the presence of exogenous lymphocytes in circulation. Later it was confirmed that these lymphocytes belonged to the transfusion donor, allowing for the definitive diagnosis of attenuated TA-GVHD. Cyclosporine was started in combination with corticosteroid therapy leading to a slow and gradual improvement of the lesions with complete resolution of the cutaneous manifestations. After discharge, the patient was referred to the Immunodeficiency Reference Center for treatment at the Hospital.

Summary/Conclusions: It seems that the benign evolution in this case was due to the fact that the child was on high-dose corticosteroid therapy at the time of the engraftment. **The guidelines implemented in our hospital always included and complied with the transfusion of irradiated blood in all ages, in face of suspected immunodeficiency. However, in our patient, this suspicion was only raised after onset of symptoms following blood transfusion. After this event, we changed our guidelines in order to irradiate all blood components transfused to all patients up to 6 months of age. We are currently considering extending this period up to 12 months.**

Monitoring by multi-disciplinary teams is important in order to allow a swift diagnosis and provide the best treatment. The transfusion of non-irradiated blood components in the first year of life should always be considered, especially when primary immunodeficiency is suspected.

TA-GVHD may be more prevalent than reported in the literature and is possibly a misidentified cause of death. »

C Politis, J Wiersum, E Grouzi, C Richardson, G Marano, I Sandid, K Boudjedir, N Goto, J Condeco, M Asariotou and K Land. Rare transfusion reactions in the istare haemovigilance database, 2012–2016. The 36th International ISBT Congress, Virtual meeting, 12-16 December 2020. Vox Sang. 2020 Dec;115 Suppl 1:5-396. doi: 10.1111/vox.13031.

Abstract:

« Background: ISTARE, the international surveillance of transfusion-associated adverse reactions (AR) and events (AE) of the International Haemovigilance Network (IHN), collects data from member national haemovigilance systems (HVS) in order to study morbidity and mortality of AR and AE in blood transfusion, irrespective of severity or harm caused. Ultimately it aims to contribute to safety and quality of blood transfusion.

Aims: **We analyzed ISTARE data on transfusion-associated rare adverse reactions (RAR) in 2012–2016** in order to learn from the data and consider improvements in reporting and collection, with a view to harmonizing best practices for HVS.

Methods: National HVS submits to ISTARE aggregate annual data on transfusion- associated AR of definite, probable or possible imputability. Data are provided on the associated blood

components (BC), severity and imputability. Rare AR – hypotensive reactions, graft versus host disease (GvHD), post-transfusion purpura (PTP), hyperkalemia and hypokalemia - are analyzed here. Root cause analysis was based on free text comments entered into the database and additional information which was requested from the national HVS representatives.

Results: **For 2012–2016, 104 sets of annual aggregated data from 25 countries covered 106,809,459 BC issued**. All AR totalled 94,388 (incidence 88.4 per 100,000 BC issued). Fifty-three (51%) sets of annual aggregated data reported 1,586 RAR from 74,933,093 BC issued (2.1/100,000 units). These were: hypotensive 1,533 (97%), GvHD 4 (0.3%), PTP 35 (2.2%), hyperkalemia 9 (0.6%) and hypokalemia 5 (0.3%). Serious AR were 818 (52% of total; 0.1/100,000 units), including 785 hypotensive (51% of all hypotensive AR), **4 GvHD (100%)**, 22 PTP (63%), 4 hyperkalemia (45%) and 3 hypokalemia (60%). In 6 countries' reports, imputability was "definite" in 29% (37.5% in hypotensive, 33.5% in PTP and 50% in GvHD and hyperkalemia), "probable" in 19% and "possible" in 52%. Among HVS not reporting any RAR in one or more years, it is unclear whether there were no such RAR, or whether reactions are not collected in those categories. Sixteen reactions had a fatal outcome (0.012/100,000): 13 hypotensive, **2 GvHD** and 1 PTP. **One fatal TA-GvHD case was a newborn who received intrauterine transfusion with maternal blood which was neither leucodepleted nor irradiated. Chimerism studies confirmed maternal engraftment and the mother was found to be HLA homozygous. The second fatality was an adult with ALL who received 2 leucodepleted, non-irradiated RBC units. Imputability to transfusion was "probable" because of lack of biopsy**. The PTP fatality and **one GvHD were associated with multiple BC, and the other severe GvHD with RBC**. Overall, of 26 RAR analyzed, 50% were associated with RBC, 29% with plasma, 12.5% with platelets and 8.5% with multiple blood components.

Summary/Conclusions: ISTARE data on transfusion-associated hypotensive reactions, PTP, **TA-GVHD**, hypokalemia and hyperkalemia draw attention to their frequently severe or life-threatening nature. The prevailing implicated blood component is RBC followed by plasma. Hypotensive reaction is far the commonest but may not be captured by all HVS according to the relevant ISBT definition. **Regarding prevention of GvHD, ISTARE data may contribute to the discussion about the use of leucodepletion with or without combination with irradiation**. Despite the possibility of incomplete data, supranational reporting provides relevant insights into rare adverse reactions. »

Daifulah ALZahrani et al. Transfusion-Associated Graft-Versus-Host Disease Confirmed by Human Leukocyte Antigen Typing in a Patient with Severe Combined Immunodeficiency and Review of the Literature. J Clin Rev Case Rep. 2020;5(1):46-51.

Abstract:

«Background: Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, but often lethal complication of cellular blood component transfusion that produces a graft- versus-host clinical manifestation in immunodeficient patients. We report a patient who developed TA-GVHD and provide a review of the literature.

Method: We report an infant with severe combined immunodeficiency (SCID) who developed TA-GVHD. **The patient received a nonirradiated, packed erythrocyte cell suspension and platelet transfusions from unrelated donors, before the diagnosis of SCID**. The patient manifested symptoms and signs of TA-GVHD (fever, skin rash, diarrhea, icterus, eosinophilia and bone marrow failure) 3-weeks after blood product transfusions.

Result: Immunology investigation was consistent with T– B– NK+ SCID. The recto-sigmoid biopsies confirmed the gold standard features of grade-II acute GVHD. HLA typing of the patient and his parents showed that the patient has an extra-parental-allele of major histocompatibility complex (MHC) class I B*53. He received high doses of methylprednisolone, IVIG and ursodeoxycholic acid, but he had progressive hyperbilirubinemia and bone marrow failure, then he developed candidemia and pseudomonas aeruginosa sepsis and multiorgan failure then he died.

Discussion / Conclusion: SCID is one of several risks for TA-GVHD. TA-GVHD develops when transfused blood-derived immunocompetent, alloreactive T lymphocytes able to engraft in the recipient's lymphoid tissues that fail to reject them. Those lymphocytes mediate immune response causing damage and dysfunction of the skin, gastrointestinal tract, liver and bone marrow failure. Our patient showed all features of TA-GVHD that was complicated by fulminant sepsis and multiorgan failure despite aggressive management. The diagnosis of this lethal condition needs high index of suspicion and the transfusion history must be questioned in all immunodeficiency patients. The disease is fulminate and rapidly fatal in majority of patients even with aggressive treatment, while irradiation of blood products that to be given to recipients at risk is the preventive method of choice. »

Divya Doval, Sanjeev K. Sharma, Meet Kumar, Vipin Khandelwal, Anil Handoo, Tina Dadu, Dharma Choudhary. Transfusion Associated Graft Versus Host Disease: A Case Report and Review of Literature. International Journal of Clinical and Experimental Medical Sciences. 2019; 5(3):46-48. doi: 10.11648/j.ijcems.20190503.11

Abstract:

« Transfusion associated graft versus host disease (TA-GvHD) is a rare but usually fatal complication of transfusion of cellular blood products. It is seen usually in immunosuppressed individuals due to engraftment of viable T lymphocytes but it may also occur in immunocompetent individuals. Patients present with fever, skin rash, diarrhoea, hepatic dysfunction and bone marrow aplasia which manifests as pancytopenia. The diagnosis of TA-GvHD is often delayed because of lack of awareness due to the non-specific manifestations and often these symptoms are attributed to the underlying illness. **We present here a case report of fatal TA-GvHD in an immunocompetent patient, post coronary artery bypass grafting surgery after transfusion of blood products**. The patient died 27 days after a blood transfusion. **An increased risk of TA-GvHD following bypass grafting and other surgical procedures where cardiopulmonary bypass is required has been perceived**. TA-GvHD is under reported and the incidence is felt to be too low to warrant routine irradiation of cellular products. Physicians,

surgeons and transfusion centers should be aware of this rare but devastating complication of blood transfusion so as to either diagnose it early or rather prevent it. »

Politis C, Nomikou E, Giannouli S, Panagos I, Cheropoulou A, GrouzieE, et al. Rare adverse reaction in the transfusion recipient in Greece. A case report of TA-GvHD. Blood Transfus. 2018;16(Suppl. 3): S402–3

International Haemovigilance Seminar

2013 Case report. 55 year old with acute lymphoblastic leukemia who received a Fludarabine-based chemotherapy regime, and was transfused with 2 units of non-irradiated leukoreduced blood components.

Thirunda Suttipong, Jettawan SIriaksorn, Piti Techavichit, Phandee Watanaboonyongcharoen. Transfusion-associated graft-versus-host disease: a case report; J Hematol Transfus Med. 2019;29:237-40.

Abstract:

« Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of blood transfusion resulting from donor's T-lymphocyte engrafts, proliferates and attacks to recipient's cells. Clinical manifestations include fever, rash, hepatomegaly, liver dysfunction and pancytopenia occurring up to 6 weeks after transfusion. **We present here a case of TA-GVHD in an infant with severe combined immunodeficiency (SCID).**

A 3-month-old male infant at a province hospital presented fever, anemia and tachypnea and subsequently received a diagnosis of severe pneumonia. Non- irradiated leukocyte poor red cells (LPRC) was given for anemia correction. He was transferred to the King Chulalongkorn Memorial Hospital 2 days after the transfusion and symptoms deteriorated. Given the history of his two older brothers, who died of pneumonia at the age of 3 months, peripheral blood flow cytometry was performed showing the absence of B/T lymphocytes and NK cells. He was diagnosed with SCID at the age of 4 months. At six weeks after hospital admission, he developed hepatomegaly with elevated liver enzymes and pancytopenia. HLA typing from the patients' peripheral blood was made and the results showed a total mismatch with his parents. In addition, HLA typing from his buccal epithelial cells was matched with his parents. Subsequently, he was diagnosed with TA-GVHD and died of severe pneumonia and respiratory failure at age 6 months.

Clinical manifestations of the patient that occurred within 6 weeks after blood transfusion met the diagnostic criteria of TA-GVHD. The HLA typing result from his peripheral blood might have resulted from active T-lymphocytes in transfused nonirradiated LPRC. Transfusion with irradiated blood products can prevent the risk of TA-GVHD because radiation is used to deactivate T-lymphocytes in blood products. »

PHARMACEUTICAL AGENTS

A literature search was performed focussing on new pharmacotherapeutic agents and fludarabine analogues. The results were compared with the agents known to cause TA-GvHD listed in the last NAC-CCNMT recommendations.

3 agents were identified:

1. Nelarabine
2. Tioguanine
3. Mercaptopurine

Nelarabine is not a new drug but it is listed as a therapy that requires subsequent transfusion with irradiated blood components in documents from 2019 and 2016:

- Quick Reference Guide - MRSA Topical Eradication (swagcanceralliance.nhs.uk)
- redcellstxpocketguideweb2016.pdf (hematology.org)
- Wessex Paediatric Oncology Supportive Care Guidelines: Transfusion & Coagulation. (piernetwork.org)

However, I was unable to identify any articles or case reports that linked cases of TA-GvHD to the use of this medication.

No recent relevant articles or studies were identified to the other 2 drugs.

OTHER NOTABLE PUBLICATIONS

Elliot J, Narayan S, Poles D, Tuckley V, Bolton-Maggs PHB. Missed irradiation of cellular blood components for vulnerable patients: Insights from 10 years of SHOT data. Transfusion. 2021;61:385–392. Doi:10.1111/trf.1618

Abstract:

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

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

There were 956 incidents of failure to receive irradiated components all due to errors. One hundred and seventy two incidents were excluded from analysis, 125 of 172 (72.7%) because of missing essential information. No cases of TA-GvHD were reported in this cohort. The 784 patients received 2809 components (number unknown for 67 incidents). Most failures occurred in patients treated with purine analogues (365) or alemtuzumab (69), or with a history of

Hodgkin lymphoma (HL) (192). Together these make up 626 of 784 (79.9%). Poor communication is an important cause of errors.

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

Commentary on Norwegian guidelines: Irradiation to prevent a fatal transfusion complication | Tidsskrift for Den norske legeforening (tidsskriftet.no)

Bhatti S et al. Bestråling for å hindre en fatal transfusjonskomplikasjon. Tidsskrift for den Norske Laegeforening. 2021; 141(9):1-7. doi:10.4045/tidsskr.20.0977

Abstract:

« The right blood component for the right patient, based on a correct and well-founded indication, is fundamental to sound transfusion practice (1). Severely immunocompromised patients should be given irradiated blood components to prevent transfusion-associated graft-versus-host disease. It is the responsibility of the doctor ordering the blood to provide the necessary information to the blood bank and to order irradiated blood components.

Transfusion-associated graft-versus-host disease was first described in 1965, and is a rare and usually fatal (> 90 %) complication of transfusion (2, 3).

A review of 348 published cases showed that half the patients who developed the condition had obvious risk, but that they had not received irradiated blood (3). Several countries have guidelines for which patient groups should receive irradiated blood components, but these vary from country to country. In this article we compare the Norwegian guidelines with those of the UK, Canada and Australia/New Zealand. We see that several patient groups are not mentioned in the Norwegian guidelines, and therefore propose harmonisation with the more detailed international guidelines. The new chemotherapies and immunotherapies that lead to severe immunosuppression should be evaluated together with clinicians with respect to the risk of transfusion- associated graft-versus-host disease. The Norwegian guidelines must be updated continuously in accordance with the evaluations. »

South Australia :2019- Irradiated Blood Components for Clinical Use Clinical Guidance:

- SA Health Fact Sheet Template - Green on White - Helix Position A
- Clinical Guidance Summary Irradiated Blood Products_FINAL 2Sep2019 (sahealth.sa.gov.au)

Zantek ND, Parker RI, van de Watering LM, Josephson CD, Bateman ST, Valentine SL, Delaney M; Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI); Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Recommendations on Selection and Processing of RBC Components for Pediatric Patients From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med. 2018 Sep;19(9S Suppl 1):S163-S169. doi: 10.1097/PCC.0000000000001625.

Abstract:

« Objectives: To present the recommendations and supporting literature for selection and processing of RBC products in critically ill children developed by the Pediatric Critical Care Transfusion and Anemia Expertise Initiative.

Design: Consensus conference series of international, multidisciplinary experts in RBC transfusion management of critically ill children

Methods: The panel of 38 experts developed evidence-based, and when evidence was lacking, expert-based clinical recommendations as well as research priorities for RBC transfusions in critically ill children. The RBC processing subgroup included five experts. Electronic searches were conducted using PubMed, EMBASE, and Cochrane Library databases from 1980 to May 2017. Agreement was obtained using the Research and Development/UCLA Appropriateness Method. Results were summarized using the Grading of Recommendations Assessment, Development, and Evaluation method.

Results: Five recommendations reached agreement (> 80%). Irradiated cellular products are recommended for children at risk of transfusion-associated graft versus host disease due to severe congenital or acquired causes of immune deficiency or when the blood donor is a blood relative. Washed cellular blood components and avoidance of other plasma-containing products are recommended for critically ill children with history of severe allergic reactions or anaphylaxis to blood transfusions, although patient factors appear to be important in the pathogenesis of reactions. For children with history of severe allergic transfusion reactions, evaluation for allergic stigmata prior to transfusion is recommended. In children with severe immunoglobulin A deficiency with evidence of antiimmunoglobulin A antibodies and/ or a history of a severe transfusion reaction, immunoglobulin A–deficient blood components obtained either from an immunoglobulin A–deficient donor and/or washed cellular components is recommended.

Conclusions: The Transfusion and Anemia Expertise Initiative consensus conference developed recommendations for selection and processing of RBC units for critically ill children. Recommendations in this area are largely based on pediatric and adult case report data. »