The New NAC Recommendations on Irradiation of Red Blood Cells and Platelets

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University of Toronto
Transfusion Medicine Rounds

St. Michael’s
Inspired Care. Inspiring Science.
Disclosures

- Advisory board participation
  - Alexion, Shire
- Honoraria for speaking
  - Alexion, Novartis
- Clinical trials
  - Ablynx, CSL Behring
- Research funding
  - CSL Behring, Ortho Clinical Diagnostics
Learning Objectives

- What is transfusion associated graft versus host disease (TaGVHD)?
- What can we do to prevent it?
- How does irradiation affect RBC?
- What are the new NAC recommendations on irradiation?
- How will these recommendations impact us?
Transfusion Associated Graft Versus Host Disease (TA-GVHD)

- US National Healthcare Safety Network definition
  - Fever, rash, hepatomegaly, diarrhea
  - Laboratory evidence of liver dysfunction, pancytopenia, leukocyte chimerism, findings on skin or liver biopsy
  - Between 2 days and 6 weeks after transfusion

- Very rare complication of transfusion
  - True incidence unknown (misdiagnosis, under-reporting)
  - 10-20X higher in Japan vs. North America, likely due to HLA homozygous haplotype blood components from unrelated donors

Pritchard AE and Shaz B Arch Pathol Lab Med 2016
Transfusion-associated Graft Versus Host Disease: Signs and Symptoms

Immuno-compromised States (i.e. Fetuses/newborns, Chemotherapy, Hodgkin’s and Non-Hodgkin’s Lymphoma, Leukemia, Post-transplant)

- Recipient immune system unable to clear donor T-lymphocytes
- Donor homozygous HLA type lymphocytes mount a reaction against non-matching heterozygous HLA type host

Immune response mounted by donor T-cell lymphocytes against recipient’s antigen presenting tissues

- Engraftment and proliferation of CD4+ and CD8+ T-cell lymphocytes
- Transfusion-associated graft versus host Disease (Ta-GVHD)
  - Systemic inflammation disrupts hypothalamic body-temperature regulation
  - Epidermal mononuclear cell infiltration, basal membrane degeneration, bullae formation
  - Lymphocytic infiltrates with epithelial cell apoptosis

Infiltration of systemic tissues with donor immune cells

- Donor T-cells kill bone marrow hematopoietic cells to cause aplasia
  - Pancytopenia, Hypocellular Marrow
  - Inability to mount an immune response against overwhelming infections (primarily bacterial)
  - Death (incidence of 90-100%)

Legend: Pathophysiology, Mechanism, Sign/Symptom/Lab Finding, Complications Published November 30, 2015 on www.thecalgaryguide.com
Components Associated with TA-GVHD

- Any non-frozen blood component containing viable lymphocytes can potentially cause GVHD
- Not associated in literature with GVHD
- frozen RBC, plasma, cryoprecipitate
A Systematic Review of TA-GVHD

- 348 unique cases identified in literature
- The first symptom occurred at median 11 days (IQR, 8-14 days; range, 1-198 days) from the implicated transfusion

Figure 3. Proportion of patients with reported symptoms and signs of TA-GVHD included in National Health and Safety Network case definition. Patients with TA-GVHD presented with an average of 4 of the 7 clinical findings included in the NHSN case definition.
A Systematic Review of TA-GVHD

- 312 patients (89.7%) of patients died at median of 24 days (IQR, 19-32 days) after the implicated transfusion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dead (n = 312)</th>
<th>Survived (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>195 (62.5)</td>
<td>13 (44.8)</td>
<td>.098</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>59 (20, 69)</td>
<td>35 (5,50)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Condition warranting irrad., n (%)</td>
<td>102 (32.7)</td>
<td>17 (58.6)</td>
<td>.011</td>
</tr>
<tr>
<td>Time to symptom onset, days, median (IQR)</td>
<td>11 (9, 14)</td>
<td>13 (8,23)</td>
<td>.42</td>
</tr>
<tr>
<td>Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole blood, n (%)</td>
<td>89 (28.5)</td>
<td>2 (6.9)</td>
<td>.012</td>
</tr>
<tr>
<td>Leukoreduced component,* n (%)</td>
<td>16 (5.1)</td>
<td>6 (20.7)</td>
<td>.013</td>
</tr>
<tr>
<td>Component age ≤48 hours or fresh, n (%)</td>
<td>81 (26.0)</td>
<td>2 (6.9)</td>
<td>.026</td>
</tr>
<tr>
<td>Component age &gt;10 days, n (%)</td>
<td>9 (2.9)</td>
<td>1 (3.4)</td>
<td>—</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppression, n (%)</td>
<td>156 (50)</td>
<td>16 (55.2)</td>
<td>.74</td>
</tr>
<tr>
<td>Steroids, n (%)</td>
<td>142 (45.5)</td>
<td>15 (51.7)</td>
<td>.65</td>
</tr>
<tr>
<td>Cyclosporin, n (%)</td>
<td>34 (10.9)</td>
<td>3 (10.3)</td>
<td>.98</td>
</tr>
<tr>
<td>IVIg, n (%)</td>
<td>19 (6.1)</td>
<td>4 (13.8)</td>
<td>.24</td>
</tr>
<tr>
<td>ATG/ALG, n (%)</td>
<td>33 (10.6)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Bone marrow transplant, n (%)</td>
<td>5 (1.6)</td>
<td>3 (10.3)</td>
<td>.046</td>
</tr>
</tbody>
</table>
A Systematic Review of TA-GVHD

- Most implicated components were whole blood and RBC
- Criteria for component irradiation were met in 48.9% of cases
- Component storage duration was <=10 days in 94% of cases
- 23 (6.6%) were leukoreduced
- Among 84 cases with HLA data, most patients (n=60 or 71%) had no donor antigens that were foreign to the recipient at either HLA class I or II loci

![Pie chart and bar graph illustrating diagnoses in patients with TA-GVHD.](image)

Figure 2. Diagnoses in patients with TA-GVHD. Two hundred twenty-seven (65.2%) patients had no diagnosis conferring an immunocompromised state, whereas the remaining 121 (34.8%) had either a congenital or acquired immune deficiency. The stacked bar illustrates the various immune defects reported in cases of TA-GVHD. Nine patients had received purine analogs (6 fludarabine and 1 cladribine) and 2 had received anti-thymocyte globulin; all of these had alternate diagnoses (eg, lymphoma or prior stem cell transplant).
A Systematic Review of TA-GVHD

- Most important conclusions
  - The dominant mechanism of TA-GVHD in both immunocompetent and compromised hosts is exposure to **viable donor lymphocytes** not recognized as foreign by, but able to respond against, the recipient.
Prevention of TA-GVHD

- **Aim:** to prevent viable lymphocytes from engrafting/effecting cellular damage

- **Methods:**
  1. Gamma-irradiation of cellular components
  2. Pathogen inactivation
  3. Transfusion of older (>14 days) RBC
  4. Pre-storage leukoreduction
TA-GVHD and Irradiation

- Gamma irradiation dose: 25 GY from cesium 137 irradiator to the central portion of the irradiation container with at least 15 GY to all areas.
Prevention of TA-GVHD with pathogen-reduced platelets with amotosalen and ultraviolet A light

- Observational studies, animal models, in vitro studies and mechanistic studies of pathogen-reduced platelets with amotosalen (150 μm) and UVA light (UVA, 320-400 nm, 3 J/cm²) showed that inactivation of T cells are equal or even superior to γ-irradiation

- Pathogen-reduced platelets with amotosalen and UVA light can be used as a measure to prevent TA-GVHD
None of the TA-GVHD cases were associated with components older than 14 days (systematic review, n=348, Kopolovic et al, 2015).

The oldest blood transfused was 10 days for whole blood, 11 days for RBC without an additive solution, and 14 days for RBC with added mannitol, adenine and phosphate (66 definite/290 total cases of TA-GVHD referred to the Japanese Red Cross over 1992-1999, Uchida et al, 2013).

96% of 51 TA-GVHD cases received blood less than 96 hours old (the Japanese Red Cross, Jawa et al, 2015).
How Common are Requests for Irradiated RBC to the CBS?

Irradiated RBC as % of Total RBC Issued

- 2004/05: 4.0%
- 2005/06: 4.5%
- 2006/07: 5.0%
- 2007/08: 5.5%
- 2008/09: 6.0%
- 2009/10: 6.5%
- 2010/11: 7.0%
- 2011/12: 7.0%
- 2012/13: 7.0%
- 2013/14: 7.0%
- 2014/15: 7.0%
- 2015/16: 7.0%
How Common are Requests for Irradiated RBC to the CBS?

- Considerable regional variation:
  - percentage of irradiated RBC units issued by CBS ranges from 2 to 18%, depending on the province
  - percentage of irradiated RBC units issued by Héma-Québec (2015-2016) is 6.0%
US Survey of Irradiation Practice for the Prevention of TA-GVHD

- Surveys sent from the CAP transfusion medicine resource committee along with the proficiency testing survey to 3447 laboratories
- Mean 2100 organizations responded to each question on the survey
- Marked heterogeneity observed (slightly better than in 1989)
  - Not all irradiated for widely accepted indications
  - Significant number irradiated for conditions not considered indicated
  - About 70% irradiated components by ward/unit
  - About 50-70% irradiated components by service
  - Some irradiated by patient age (0-1 years)
  - 2.6% had universal irradiation
Table 1. Respondents Indicating Irradiation Is Required by Medical Indication/Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>No./Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital immunodeficiency syndromes</td>
<td>1210/2122 (57.0)</td>
</tr>
<tr>
<td>Allogeneic/autologous hematopoietic progenitor cell transplantation</td>
<td>1340/2136 (62.7)</td>
</tr>
<tr>
<td>Transfusions from blood relatives</td>
<td>1862/2370 (78.6)</td>
</tr>
<tr>
<td>Human leukocyte antigen–matched/partially matched (platelets)</td>
<td>1552/2252 (68.9)</td>
</tr>
<tr>
<td>Granulocyte transfusions</td>
<td>995/2066 (48.2)</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>1113/2113 (52.7)</td>
</tr>
<tr>
<td>Purine analogue drugs (fludarabine, cladribine, deoxycoformycin)</td>
<td>730/2027 (36.0)</td>
</tr>
<tr>
<td>Treatment with alemtuzumab (anti-CD52) or antithymocyte globulin</td>
<td>558/1980 (28.2)</td>
</tr>
<tr>
<td>Intrauterine transfusions</td>
<td>1344/2122 (63.3)</td>
</tr>
<tr>
<td>Neonatal exchange transfusions</td>
<td>1460/2202 (66.3)</td>
</tr>
<tr>
<td>Preterm infants/low-birth-weight infants</td>
<td>1359/2200 (61.8)</td>
</tr>
<tr>
<td>Infant/child with congenital heart disease (secondary to DiGeorge)</td>
<td>783/1991 (39.3)</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>1069/2115 (50.5)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma/hematologic malignancies</td>
<td>1007/2108 (47.8)</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>765/2062 (37.1)</td>
</tr>
<tr>
<td>Solid tumors receiving intensive chemotherapy and/or radiotherapy</td>
<td>818/2076 (39.4)</td>
</tr>
<tr>
<td>Recipient and donor from a genetically homogeneous population</td>
<td>622/1986 (31.3)</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td>767/2079 (36.9)</td>
</tr>
<tr>
<td>Healthy newborns/term infants</td>
<td>951/2156 (44.1)</td>
</tr>
<tr>
<td>Human immunodeficiency virus/acquired immune deficiency syndrome</td>
<td>402/2063 (19.5)</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>357/2044 (17.5)</td>
</tr>
<tr>
<td>Donors undergoing bone marrow or peripheral stem cell collection</td>
<td>936/2100 (44.6)</td>
</tr>
</tbody>
</table>

Pritchard A and Shaz B Arch Pathol Lab Med 2016
The Danger of Selective Transfusion Protocols

- Selective transfusion protocols are prone to errors and accidents
  - rely on individual physicians, their knowledge base and clinical understanding of patient’s clinical condition
- Universal protocols are more likely to lead to homogeneous practice and compliance
  - Make it easy to do it right
- Why don’t we irradiate for all?
Cost of Irradiation

- Irradiator (plus maintenance)
- Measures to comply with the Canadian Nuclear Safety Commission regulations
- Irradiation indicator stickers
- Labour cost to perform irradiation
- Increased product cost due to reduced shelf-life
- Cost due to a delay in treatment
Effect of Irradiation on RBC

- Production of reactive oxygen species -> lipid peroxidation, alteration of intracellular purine nucleotides
- Change in membrane integrity
- Decreased cell deformability and elasticity
- Enhanced leakage of potassium ions
- Result
  - Acceleration of *in vitro* hemolysis and decrease in *in vivo* recovery
  - Adverse post-transfusion outcomes

Zimmermann et al Transfusion 2009; Zimmermann et al Vox Sanguinis 2011
Effect of Irradiation on RBC

- Increase in mean number of microparticles (Cho et al Ann Lab Med 2016)
  - Specifically, CD41 +ve MP increased -> potentially increased thrombotic risk
- Accentuation of metabolic alterations of cold storage (Patel et al Transfusion 2015)
  - Metabolites involved in cellular membrane are the most prominently affected
## Irradiation Guidelines and Standards

<table>
<thead>
<tr>
<th>Age of unit at irradiation</th>
<th>AABB CSA</th>
<th>COE</th>
<th>BCSH</th>
<th>NAC CSTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age after collection</td>
<td>Up to 28 days after collection</td>
<td>Up to 14 days after collection</td>
<td>Up to 28 days after collection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expiration of irradiated unit</th>
<th>AABB CSA</th>
<th>COE</th>
<th>BCSH</th>
<th>NAC CSTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days after irradiation or original expiry if sooner</td>
<td>14 days after irradiation and within 28 days after collection</td>
<td>14 days after irradiation</td>
<td>14 days after irradiation and within 28 days after collection</td>
<td></td>
</tr>
</tbody>
</table>
Influence of late irradiation on the in vitro RBC storage variables of leucoreduced RBCs in SAGM

- 160 SAGM, pre-storage leukoreduced RBC:
  - 40 irradiated on day +14, 40 on day +28, 40 on day +35, and 40 as non-irradiated controls
  - Irradiation induced leakage of potassium ions and lactate dehydrogenase, enhanced in vitro haemolysis rate

Conclusion

- The current limitation of the age of RBCs on the day of irradiation be replaced by staged limitations depending on the time of irradiation
- COE shortened the allowable post-irradiation storage time from 28 days to 14 days
The effect of timing of gamma-irradiation on hemolysis & potassium release in leukoreduced RCC stored in SAGM

- 896 SAGM, pre-storage leukoreduced RBC were irradiated (25Gy) 8-40 days post-collection and stored for 1-28 days
- Another 84 RBC were irradiated at 7, 10, 14, 21, 35 and 40 days
- Starting at 2 days post irradiation, testing at regular time intervals (Hct, Hgb, K)

Serrano et al Vox Sanguinis 2014
The effect of timing of gamma-irradiation on hemolysis & potassium release in leukoreduced RCC stored in SAGM

- Length of storage before or after irradiation predicted hemolysis
- 40 RBC (4.5%) exceeded hemolysis levels of 0.8% allowable by standards
- RBC irradiated in the 4th week and stored for 15-21 days had the highest hemolysis
The effect of timing of gamma-irradiation on hemolysis & potassium release in leukoreduced RCC stored in SAGM

- Extracellular K levels increased rapidly post irradiation
- Within 3 days of irradiation, K levels were comparable to those of non-irradiated 42 day old RBC!
- Beware of post-transfusion hyperkalemia: neonates, renal insufficiency, massive transfusion
NAC/CCNMT Irradiation Working Group

- Formed in late 2015
- Composition
  - Doug Morrison (Chair) and Oksana Prokopchuk-Gauk (Co-chair)
  - adult and pediatric TM experts
- Draft recommendations released Sept 26, 2016 and distributed for stakeholder consultation
- Revisions to the existing draft April to mid-September 2017
- Final document to be posted in October 2017
Age of RBC at Irradiation

- For at-risk patients, all red blood cell, platelet and granulocyte concentrates should be irradiated.

- Red blood cells 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.

- Supported by the COE and CSTM standards; likely be reflected in the next edition of the CSA standards.

- CBS will voluntarily adopt this recommendation until CSA standards change.
Communication

- 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.

- 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.

- Notes: What about communication between pharmacy and TM, patient and TM? How to design/implement a robust process for communication between “clinicians” and TM?
Communication

PATIENT CARD RECIPIENT LETTER

Date: ____________________

Dear First Name LAST NAME:

We would like to inform you that, if you require a blood transfusion, you may need irradiated blood. This determination was based on your past medical history. Please make your doctor(s) aware as well as your next of kin.

On the reverse side of this letter you will find a fact sheet that provides additional information on irradiated blood and its indications.

Also enclosed is a wallet card. Please carry this card with you and present to your doctor(s) and healthcare team if blood transfusion or surgery is planned. It is possible that policies on irradiated blood may differ between hospitals however, this information will provide your treating physician with necessary background and contact information to make the best decision on your blood transfusion.

You may consider registering with Medic Alert® Canada. Medic Alert® Canada is a universally recognized organization that provides first responders and emergency medical personnel with important medical information on your behalf. Please visit www.medicalert.ca to register.

Further patient information is available at www.transfusionontario.ca. If you have any questions or concerns, please do not hesitate to contact us.

Yours sincerely,

St. Michael's
Inspired Care. Inspiring Science.

Name: RUBBLE, Barney
DOB: Nov. 4, 1956
ABO/Rh: B Positive

THIS PATIENT REQUIRES:
- [X] Irradiated Cellular Blood Components
- [ ] Antigen Negative RBC
- [ ] Other:

Known Antibodies:

Date of Transplant: March 23, 2016

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WHY IS IRRADIATED BLOOD NEEDED?

Irradiated blood is given to prevent a rare but serious transfusion reaction called transfusion-associated graft-versus-host disease (TA-GvHD).

WHAT IS TA-GvHD?

TA-GvHD is caused by the donor white blood cells in the transfused blood and can lead to severe illness.

WHICH PATIENTS ARE AT INCREASED RISK OF TA-GvHD?

Some patients are at particular risk of TA-GvHD:
- Patients with certain immune system disorders
- Patients who have been treated with certain chemotherapeutic or immunosuppressive medications (for example, fludarabine or thymoglobulin)
- Bone marrow/stem cell transplant recipients

HOW DOES IRRADIATION WORK?

Irradiation of blood changes the white blood cells in the transfused blood, so that they cannot cause TA-GvHD. Irradiation does not damage the blood. The blood does not become 'radioactive' and will not harm you or anyone around you.

IS ALL BLOOD ROUTINELY IRRADIATED?

No. Red cell and platelet transfusions are not routinely irradiated and need to be irradiated ‘on demand’. It is important that you tell your medical team of your need for irradiated blood.

WHAT IF BLOOD IS NEEDED IN AN EMERGENCY?

Although irradiated blood is recommended for you, if you receive non-irradiated blood the risk of TA-GvHD is still very small. In emergencies, there may not be enough time to arrange for irradiated blood to be provided as it may be more important to provide blood quickly. The medical team treating you will judge the balance of these risks.

Please carry the attached card with you and show it to your physician or nurse if a blood transfusion is being considered.
Inventory Management

- For **elective transfusions** reliance on a **regional hub** site for on-demand irradiation or **limited pre-irradiated stock** is recommended.

- **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.

- 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.

- 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.
## Clinical Recommendations

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>All recipients</td>
<td>• Directed donation (blood from first- and second-degree relatives)</td>
</tr>
<tr>
<td></td>
<td>• HLA-selected/matched platelets</td>
</tr>
<tr>
<td></td>
<td>• Granulocyte transfusion</td>
</tr>
<tr>
<td>Hematology</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td></td>
<td>• HLA-selected/matched platelets</td>
</tr>
<tr>
<td></td>
<td>• directed donations</td>
</tr>
<tr>
<td></td>
<td>• current or previous treatment with at risk medications</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>• Current or previous treatment with ATG and/or alemtuzumab</td>
</tr>
<tr>
<td>Hodgkin Lymphoma (any stage, indefinitely)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>• Current or previous treatment with at risk medications</td>
</tr>
</tbody>
</table>
### Clinical Recommendations: Fetuses and Neonates

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Condition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>Intrauterine, fetal transfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Irradiate the <strong>freshest</strong> possible unit and transfuse within 24 hrs</td>
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</tr>
<tr>
<td>Neonates</td>
<td>Neonatal exchange transfusion:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Previous IUT, until 6 months after the expected delivery date (40 wks gestation)</td>
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<tr>
<td></td>
<td>• All neonatal exchange transfusions (provided no undue delay in transfusion)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Irradiate the <strong>freshest</strong> possible unit and transfuse within 24 hrs</td>
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<td></td>
<td>Neonatal small volume (top-up) transfusions</td>
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<tr>
<td></td>
<td>• Previous IUT, until 6 months after the expected delivery date (40 wks gestation)</td>
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<tr>
<td></td>
<td>• Very low birth weight infants, until 4 months of age</td>
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<tr>
<td></td>
<td>• Consult local policies in uncertain situations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital severe T cell immune deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Suspected or confirmed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex congenital cardiac abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Suspected or confirmed 22q11.2 deletion</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Recommendations: Fetuses and Neonates

- Where the patient is at particular risk from hyperkalemia (e.g. intrauterine or neonatal exchange transfusion), it is recommended that red cells be transfused within 24 hours of irradiation or that cells have at least undergone centrifugation and supernatant plasma removal.
Supernatant reduction of stored gamma-irradiated RBC minimizes potentially harmful substances present in transfusion aliquots for neonates

Supernatant reduction by centrifugation effectively reduces K⁺, mannitol and RMV in RBC aliquots stored up to 21 days

Serrano et al. Transfusion 2017
Clinical Recommendations: Fetuses and Neonates

- 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, ANZSBT 2011)
Clinical Recommendations: Fetuses and Neonates

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.

Notes: What are the clinical and laboratory features? Dysmorphic features, craniofacial abnormalities, hypocalcaemia and lymphopenia are suggestive of an immunodeficiency syndrome.
Clinical Recommendations: Fetuses and Neonates

- 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.

- Notes: Although 22q11.2 deletion syndrome (encompasses DiGeorge Syndrome) is most commonly associated with conotruncal lesions, the variety of heart defects described in patients with this syndrome is extensive. In order to avoid missing a neonate or young infant with immunodeficiency, it is recommended that neonates and young infants with congenital heart defects receive irradiated cellular components up to 6 months of age, at which time those suspected of having 22q11.2 deletion syndrome should have been tested for this disorder.
Complex cardiac abnormalities of del 22q11

<table>
<thead>
<tr>
<th>Condition</th>
<th>No</th>
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</tr>
</thead>
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<td>Other clinically non-significant</td>
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<tr>
<td>Ventricular septal defect</td>
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</tr>
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<td>Interrupted aortic arch</td>
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<td>Pulmonary atresia/ventricular septal defect</td>
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<tr>
<td>Truncus arteriosus</td>
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<td>Pulmonary valve stenosis</td>
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<tr>
<td>Atrial septal defect</td>
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<tr>
<td>Atrioventricular septal defect</td>
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<tr>
<td>Transposition of great arteries</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Complex heart disease</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Other significant abnormalities</td>
<td>26</td>
<td>5</td>
</tr>
</tbody>
</table>
## Clinical Recommendations

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Condition</th>
</tr>
</thead>
</table>
| **Allogeneic Hematopoietic Stem Cell or Bone Marrow Transplant** | **Recipients:**  
  • From the time of initiation of conditioning  
  • While the patient continues to receive GVHD prophylaxis  
  • Indefinitely if chronic GVHD is present or if continued immunosuppressive therapy is required  

**Donors:**  
• Allogeneic blood transfused to stem cell or bone marrow transplant donors for 7 days prior to and during the harvest |

| **Autologous Hematopoietic Stem Cell or Bone Marrow Transplant** | **Recipients:**  
  • From the initiation of conditioning until 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 |
Clinical Recommendations: Allogeneic Bone Marrow or Hematopoietic Stem Cell Transplantation

- Irradiated blood components should be continued while the patient continues to receive GVHD prophylaxis. If chronic GVHD is present or if continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely.

- Notes: Timing is controversial - For 6 months post-transplant or until the lymphocyte count is greater than $1 \times 10^9/L$ vs. 12 months vs. indefinitely vs. discretion of BMT physician with suggested discontinuation criteria.
Clinical Recommendations: Non-Hodgkin Lymphoma

• All patients with non-Hodgkin lymphoma on purine analogues and related drugs should receive irradiated cellular blood components indefinitely

• Notes: Controversy: indefinite vs. 12 months vs. at discretion of treating physician with required re-assessment after 12 months

• NZ guidelines: All patients treated with nucleoside analogues must receive irradiated cellular blood components; there are however, currently no data to support a stated period of time to use irradiated red cells and platelets for patients following treatment with nucleoside analogues; however, continued use for at least 1 year is recommended, and indefinite use could be considered.
Clinical Recommendations: At Risk Medications

- Fludarabine (Fludara)
- Cladribine or 2-CDA (Leustatin)
- Deoxycoformicin (Pentostatin, Nipent)
- Alemtuzumab (anti-CD52) (Campath)
- Bendamustine (Treakisym, Ribomustin, Levact and Treanda)
- Clofarabine (Clolar)
- Anti-thymocyte globulin (ATG), (rabbit: thymoglobulin, horse: Atgam)
  - When used in the setting of severe aplastic anemia only
Use of Non-irradiated Blood Components in Campath Treated Renal Transplant Patients

• Retrospective study of 647 Campath-treated renal transplant patients transfused with non-irradiated components

• None developed TA-GVHD

• Conclusion
  • Irradiation is “an unnecessary requirement” with “clinical delay and cost implications”
Methods

Retrospective review at an academic hospital (onsite irradiator) of all irradiated RBC units: January 1, 2016 to December 31, 2016

Timing of irradiation

- Age at irradiation*
- Date of transfusion*

Irradiation indications

- Local Policy
- Compliance with NAC†

- Age < 6 months old
- Listed for, undergoing & following HSCT
- Lymphoproliferative disorder
- Congenital immunodeficiency
- Purine analogues, anti-CD52 & rabbit ATG (all uses, including SOT)

Compliance with NAC†

*Local policy recommends BCSH guidelines (14 days)
†Draft NAC recommendations (Sep 26, 2016)
Results

791 RBC units irradiated for 204 patients

Number of Units

Age of RBCs at Irradiation

Median age: 20 days (IQR 14-27)
636 (80%) were irradiated at ≤ 28 days

- 36 of 636 units (5.6%) had D- requirement
- 22 of 636 units (3.4%) had D- requirement
- 22 of 155 units (14%) had D- requirement

D Positive:
- 20 days (14-26)

D Negative:
- 29 days (18-34)
Results

725 units (92%) were transfused the same day

- 66 units (8%) transfused between 1-7 days after irradiation
- 26 units (39%) redirected to non-indicated patients
  (Overall 55 units redirected to non-indicated patients)
- 43 units (65%) transfused within 28 days of collection
- 23 units (35%) transfused after 28 days of collection
  14 units (61%) were irradiated after 28 days of collection
Results

627 units (79%) meet NAC recommendations
## Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Indicated</td>
<td>680</td>
<td>86%</td>
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<tr>
<td>Redirected</td>
<td>55</td>
<td>7%</td>
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<tr>
<td>Lymphoproliferative (HL/meds)</td>
<td>93</td>
<td>12%</td>
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<tr>
<td>Lymphoproliferative (other)</td>
<td>122</td>
<td>15%</td>
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<tr>
<td>Autotransplant (&gt; 3 months)</td>
<td>34</td>
<td>4%</td>
</tr>
<tr>
<td>Solid-organ Transplant (ATG)</td>
<td>352</td>
<td>45%</td>
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<tr>
<td>Congenital Immunodeficiency</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>Myeloid: MDS, AML, MF</td>
<td>89</td>
<td>11%</td>
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<tr>
<td>HIV</td>
<td>20</td>
<td>3%</td>
</tr>
<tr>
<td>Other: solid cancer, aHUS</td>
<td>7</td>
<td>1%</td>
</tr>
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</table>

As per NAC policy: 111 units (14%) irradiated appropriately
Conclusions

Feasibility?

Timing

- Visual cues based on RBC unit collection date
- Two expiry conditions:
  - 14 days post-irradiation or 28 days post-collection
  - Issues with LIS

Indications

- % appropriateness depends on hospital population
- Compliance with NAC reduces unnecessary exposure
  - Requires agreement among clinical groups on indication
  - Requires better medication history infrastructure
  - Reduces issuing delays & lab time
Implementing NAC Guidelines
## Implementing NAC Guidelines

**RBC IRRADIATION CHART**

**CONFIRM RBC UNIT TO BE IRRADIATED IS ≤ 28 DAYS OLD**

**ONCE IRRADIATED, IT EXPIRES 14 DAYS LATER**

**OR WHEN IT IS 28 DAYS OLD, WHICHEVER COMES FIRST**

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<tr>
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<th>APRIL</th>
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Summary

- TA-GVHD is very rare but severe complication of transfusion
- TA-GVHD is prevented by irradiating cellular components
- Irradiation is not benign to red blood cells
- The new NAC recommendations advocate changes to the timing and indications of irradiation to make practice safer
Thank You

- Materials related to the NAC recommendations
  - Oksana Prokopchuk-Gauk
  - Doug Morrison
  - The NAC-CCNMT Irradiation Working Group
- Materials related to SMH irradiation audit
  - Matt Yan and Elizabeth Krok
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June 2 – June 6, 2018 / Du 2 juin au 6 juin, 2018
Toronto, Canada