Update on Use of Irradiated Blood Components in Transplantation

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Overview

- Review of purpose/methodology
- Review of AABB Standards and Technical Manual
- Review of literature
- Review of local practice
- Mention of pathogen reduction

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Intended Use of Irradiation

Gamma or x-ray irradiation of cellular blood components:

- **Inactivate donor lymphocytes**
- **Prevent proliferation of the lymphocytes**
- **Avoid attack of lymphocytes on host tissues (graft versus host disease)**

Leukocyte reduction filters do not remove enough leukocytes to reliably prevent GVHD

GVHD from transfusion is 90-100% fatal because it involves the bone marrow (vs GVHD from a marrow or stem cell transplant).

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Blood Irradiators

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AABB and Indications for Irradiation

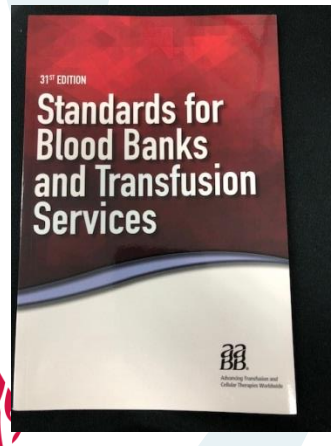
AABB Standards, 31st edition (April 2018):

5.19.3.2 At a minimum, cellular components shall be prepared by a method known to prevent transfusion-associated graft-vs-host disease when:

5.19.3.2.1 A patient is identified as being at risk for transfusion-associated graft-vs-host disease

5.19.3.2.2 The donor of the component is a blood relative of the recipient

5.19.3.2.3 The donor is selected for HLA compatibility, by typing or crossmatching



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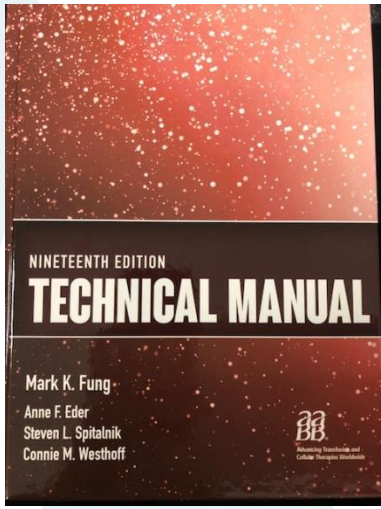
AABB and Indications for Irradiation



AABB Technical Manual, 19th Edition (2017):

Table 22-2: Well Documented Indications For Irradiated Components

- Intrauterine transfusions
- Prematurity, low birthweight, or erythroblastosis fetalis in newborns
- Congenital immunodeficiencies
- Hematologic malignancies or solid tumors (neuroblastoma, sarcoma, Hodgkin disease)
- Peripheral blood stem cell/marrow transplantation
- Components that are crossmatched or HLA matched, or from directed donations (from family members or other related donors)
- Fludarabine therapy
- Granulocyte components

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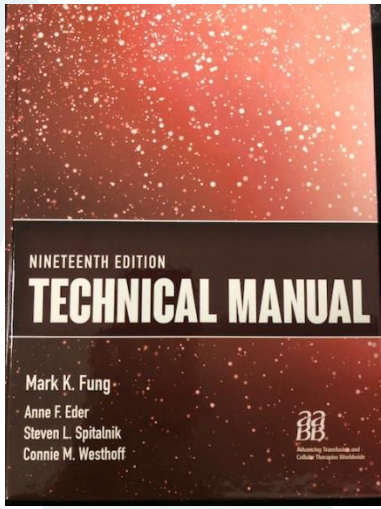
AABB and Indications for Irradiation



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Unresolved Questions for the Transplant Population

- **Is irradiated blood indicated for solid organ transplant patients?**
- **Do patients with malignancies not getting fludarabine treatment (purine analogues) or stem cell transplantation really need irradiated blood?**
- **Can we stop irradiated blood use in patients who successfully engraft after stem cell transplant (e.g. after one year following transplant)?**

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AABB Technical Manual, 19th ed.

- **"Although it is generally accepted that HSCT recipients require irradiated components during and for at least 1 year after transplantation, it is unclear whether these patients require irradiation beyond this point. Despite an absence of evidence indicating that irradiation is essential after this time has elapsed, many institutions indefinitely provide irradiated components to HSCT recipients given the potential for long-term immunosuppression."**

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2010 Literature Review and Evaluation

- **BJHaematol, Treleaven et al**
- **British Committee for Standards in Haematology blood transfusion task force**
- **Very comprehensive literature search of irradiation/TA-GVHD articles in English, 1950 - 2009**
- **Evidence-based review of each article for strength of recommendations**
- **Recommendations are grade 1 (strong/recommended) or grade 2 (suggested/weaker)**
- **Quality of evidence based as “A” (high quality), “B” (moderate) or “C” (low)**

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Recommendations

- **All recipients of allogeneic haemopoietic stem cell transplantation must receive irradiated blood components from the time of initiation of conditioning chemoradiotherapy (1B). This should be continued while the patient continues to receive GVHD prophylaxis, usually for 6 months post-transplant, or until lymphocytes are >1X10^{9}/L. If chronic GVHD is present or if continued immunosuppressive treatment is required, irradiated blood components should be given indefinitely (2C).**

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Recommendations (cont'd)

- **Allogeneic blood transfused to bone marrow and peripheral blood stem cell donors 7 d prior to or during the harvest should also be irradiated (2C).**
- **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 d before the bone marrow/stem cell harvest to prevent the collection of viable allogeneic T lymphocytes which can potentially withstand cryopreservation (2C).**

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Recommendations (cont'd)

- **All patients undergoing autologous bone marrow transplant or peripheral blood stem cell transplant should receive irradiated cellular blood components from initiation of conditioning chemo/radiotherapy until 3 months post-transplant (6 months if total body irradiation was used in conditioning) (2C).**
- **All adults and children with Hodgkin lymphoma at any stage of the disease should have irradiated red cells and platelets for life (1B).**

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Recommendations (cont'd)

- **Patients treated with purine analogue drugs (fludarabine, cladribine and deoxycoformicin) should receive irradiated blood components indefinitely (1B).**
- **It is not necessary to irradiate red cells or platelets for adults or children with acute leukaemia, except for HLA-selected platelets or donations from first- or second-degree relatives (1B).**

Note: no discussion of irradiation in organ transplant patients

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Recommendations (cont'd)

- **Irradiated blood components should be used after alemtuzumab (anti-CD52) therapy (2C).**
- **In view of the recent switch from horse anti-thymocyte globulin (ATG) to the more immunosuppressive rabbit ATG, we now recommend use of irradiated blood components for aplastic anaemia patients receiving immunosuppressive therapy with ATG (and/or alemtuzumab) (2C). We cannot make a firm recommendation as to how long irradiated components should continue to be used after ATG administration.**

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Review of Cases of TA-GVHD

Blood, 2015, Kopolovic et al.

- **348 cases from 6 databases**
- **34.8% occurred in patients that should have gotten irradiated blood but didn't**
- **5 cases did get irradiated blood – was it done correctly?**
- **The other cases were immunocompetent patients with apparently no risk factors under current guidelines**
- **89.7% of the patients died, at a median of 24 days**

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Newest Publication

Arch Pathol Lab Med May 2018 Bahar and Tormey "Prevention of Transfusion-Associated Graft-Versus-Host Disease With Blood Product Irradiation: The Past, Present, and Future."

- **Organ transplants patients do not need irradiated blood**
- **Some evidence that kidney graft recipients do better with non-irradiated blood (Opelz and Terasaki 1978)**
- **Any GVHD is from the passenger lymphocytes (Triulzi et al 2001)**

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Review of Local Practice

- **Formulated 7 question Survey Monkey**
- **Sent to 12 local health care facilities that do transplants and use irradiated blood**
- **Got 9 responses**

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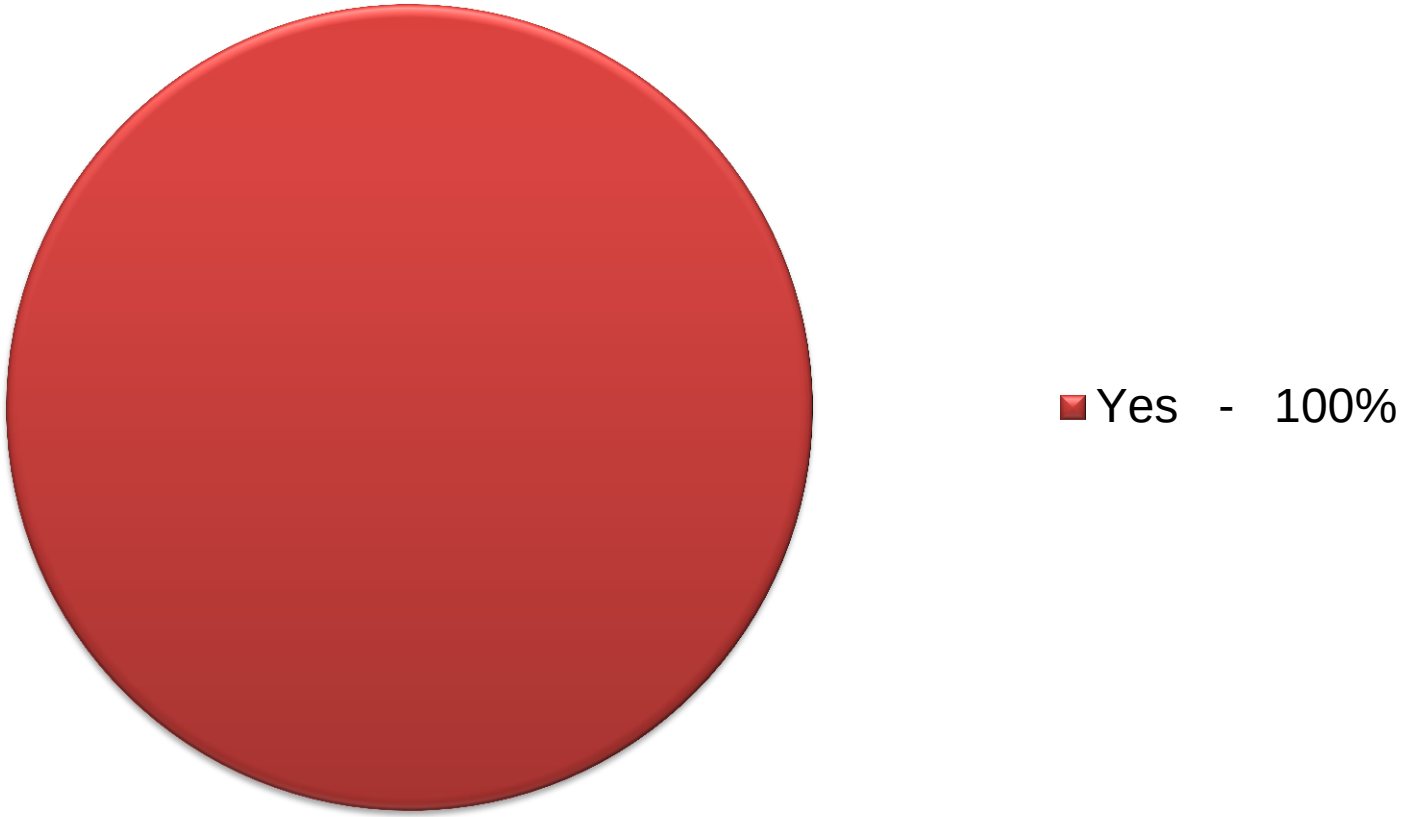
As a transfusion service, do you flag the records of patients who get orders for irradiated blood?



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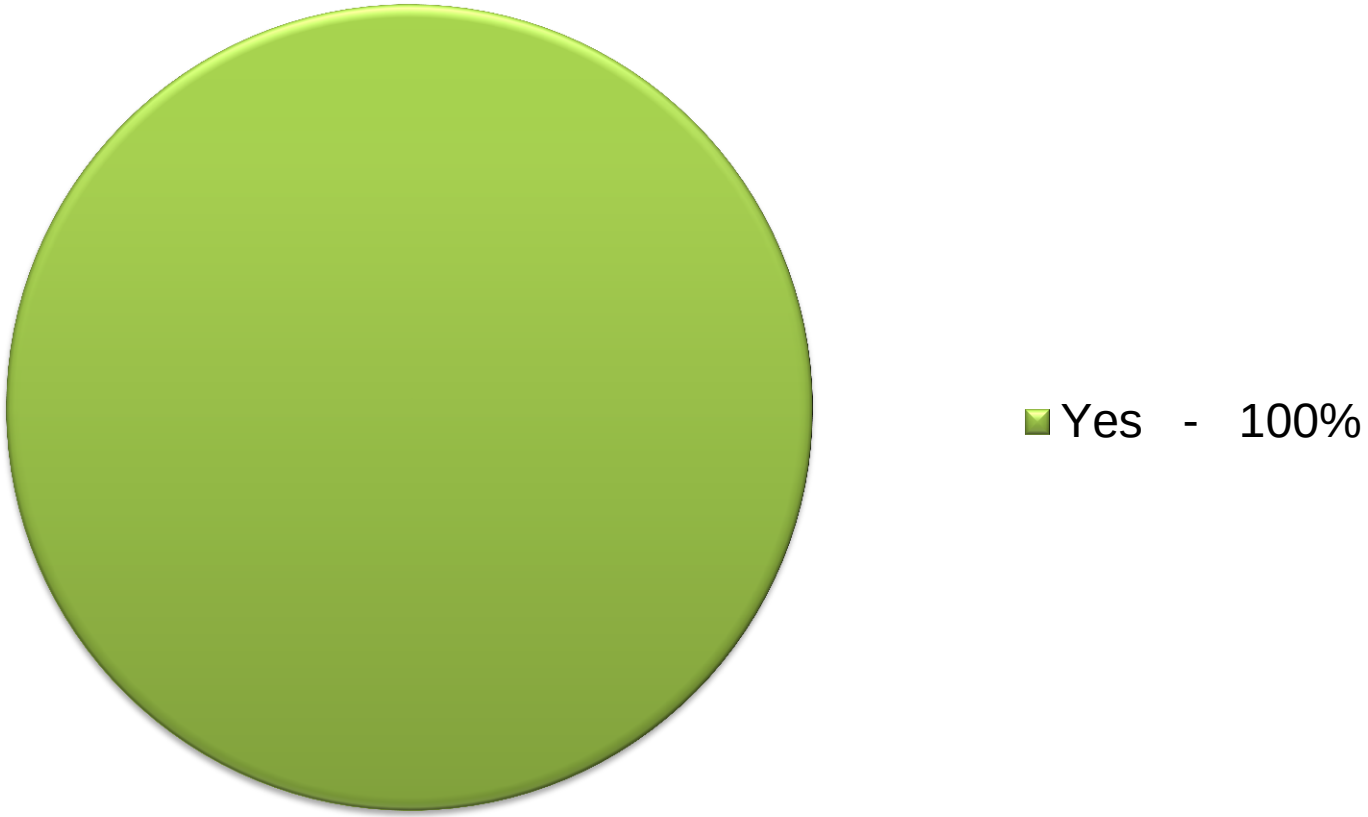
Once a patient gets an order for irradiated blood, does the transfusion service continue to provide irradiated blood until the doctor specifically orders otherwise, despite whether the current order indicates “irradiated”?



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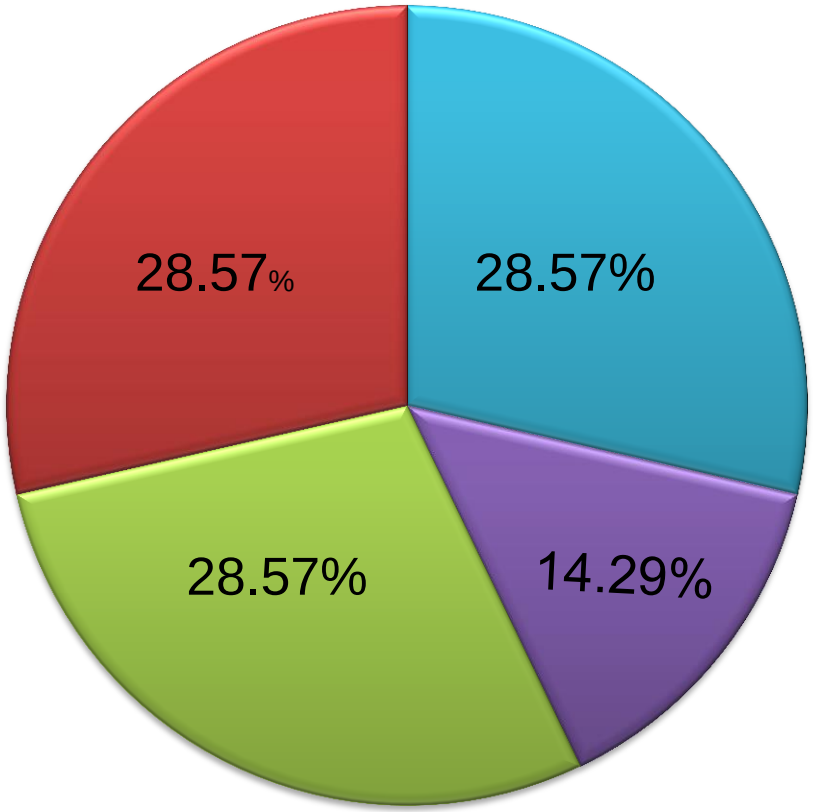
Do solid organ transplant patients at your institution get irradiated blood?



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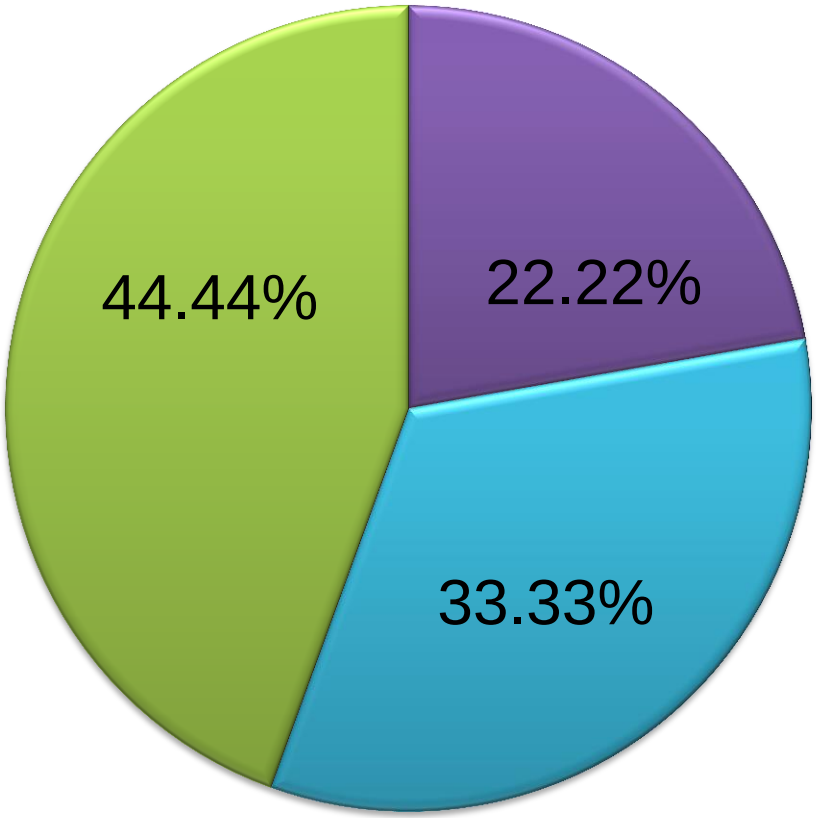
Do patients with solid malignancies at your institution get irradiated blood?



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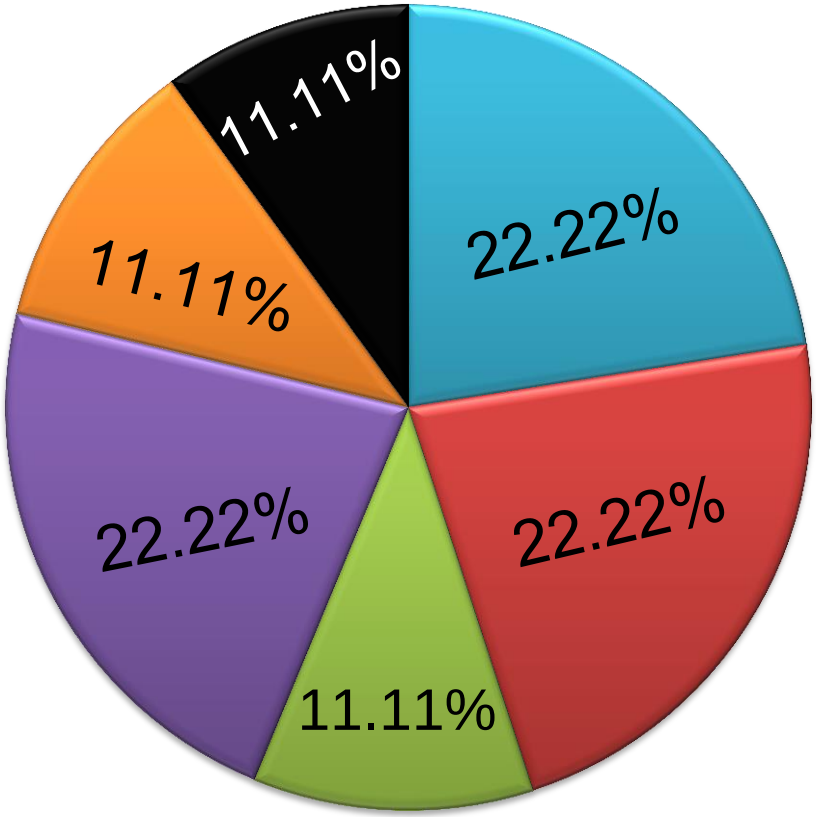
Do patients with leukemias or lymphomas get irradiated blood products at your institution?



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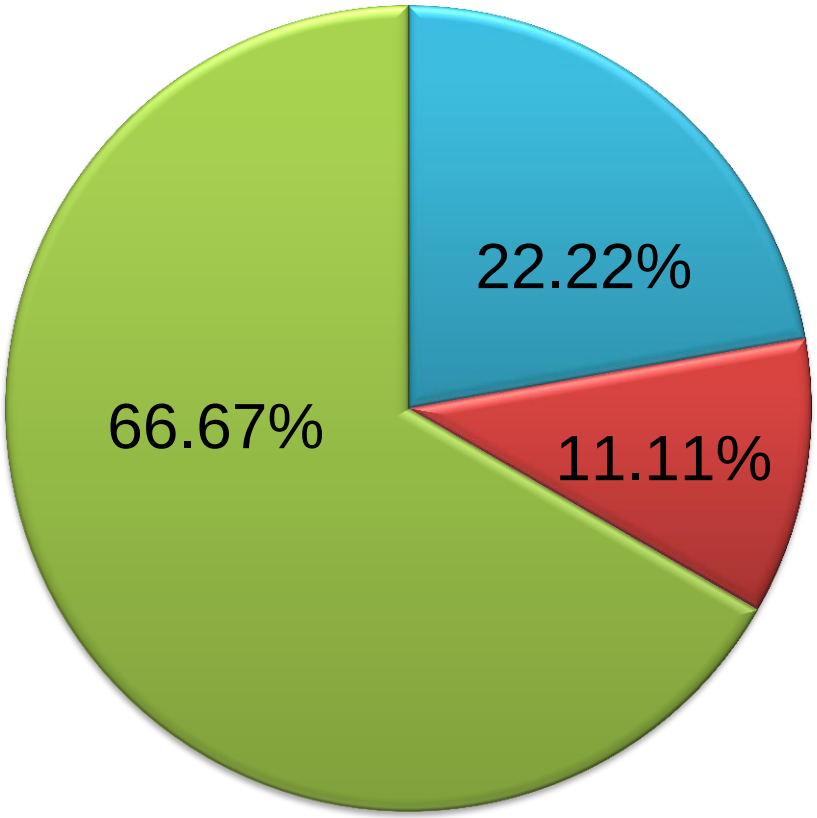
If your facility does hematopoietic progenitor cell transplants, when do you start giving irradiated blood to the patient?



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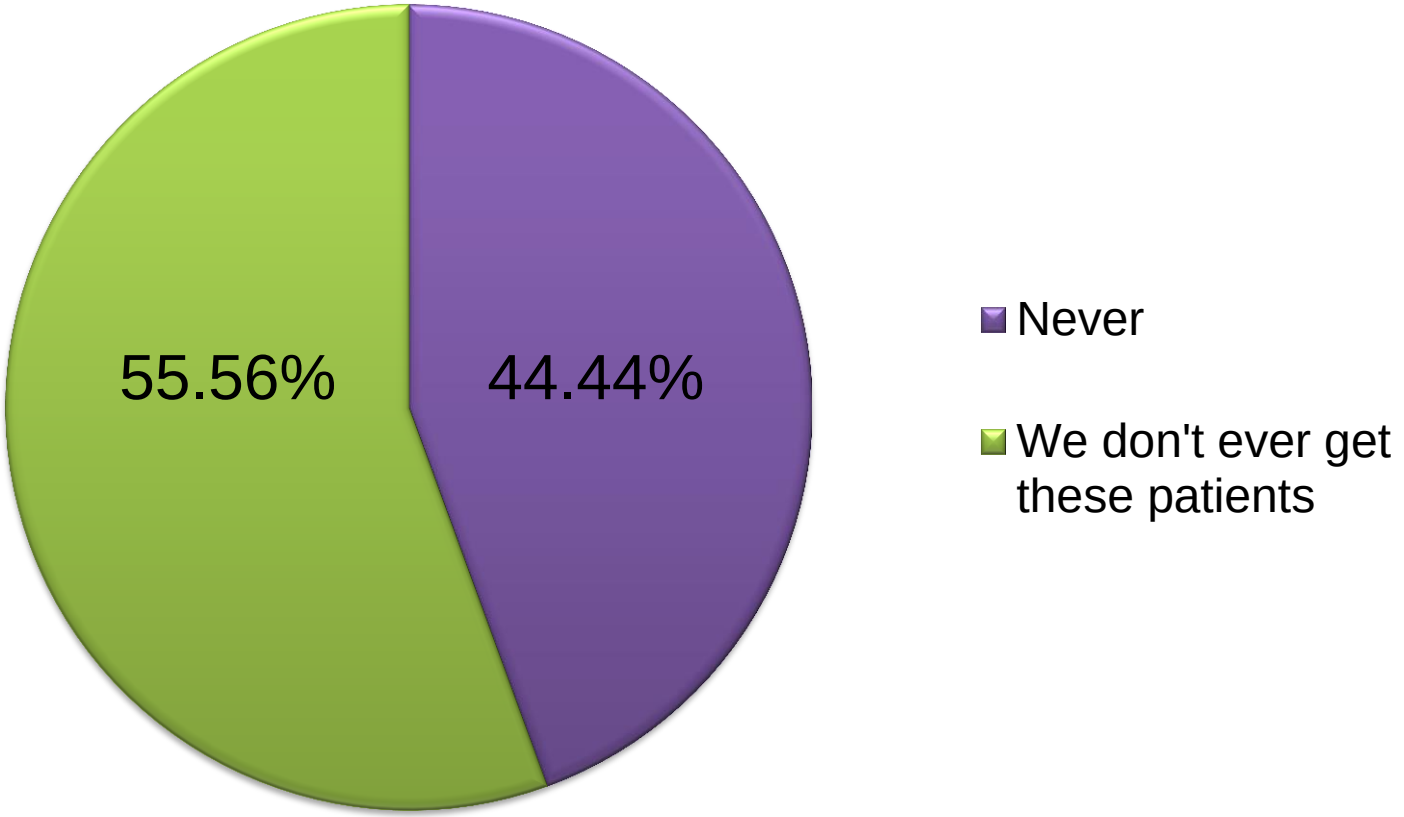
If your facility has hematopoietic progenitor cell transplant patients at any point, when do you stop giving irradiated blood?



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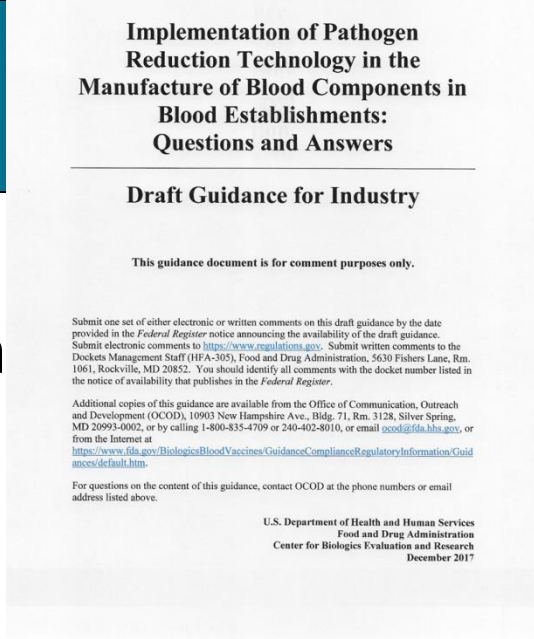
Pathogen Reduction



Implementation of Pathogen Reduction Technology in the Manufacture of Blood Components in Blood Establishments: Questions and Answers

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2017

FDA has indicated in a draft guidance document (December 2017) that pathogen reduced components could be an acceptable substitute for irradiated components:

"Can pathogen reduction using the INTERCEPT® Blood System substitute for irradiation of platelets to prevent the risk of transfusion-associated graft versus host disease (TA-GVHD)?

The manufacturer's instructions (operator's manual and processing sets package inserts) indicate that treatment of platelets with the INTERCEPT® Blood System potentially lowers the risk of TA-GVHD. The transfusion medicine physician and/or treating physician should determine whether to replace irradiation with pathogen reduction to prevent TA-GVHD."

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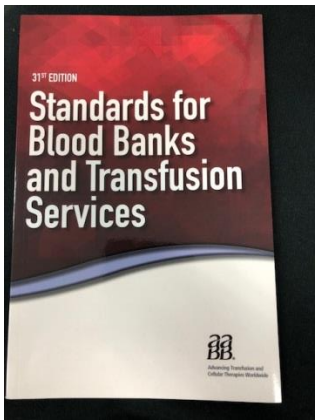
Pathogen Reduction

AABB Standard 5.19.3.1 (new in the 31st edition) addresses the use of pathogen reduction to prevent graft versus host disease:

"Methods known to prevent transfusion-associated graft-vs-host disease shall be used, and include either irradiation or the use of a pathogen reduction technology that is known to inactivate residual leukocytes and is cleared or approved by the FDA or Competent Authority."



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References

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- **Survey of irradiation practice for the prevention of transfusion-associated graft-versus-host disease. AE Pritchard and BH Shaz. *Arch Pathol Lab Med* 2016 140(10):1092-7.**
- **A systematic review of transfusion-associated graft-versus-host disease. I Kopolovic, J Ostro, H Tsubota, Y Lin, CM Cserti-Gazdewich et al. *Blood* 2015 126(3):406-14.**
- **Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force. J Treleaven, A Gennery, J Marsh, D Norfolk et al. *Brit J Haematol* 2010 152:35-51.**
- **Microchimerism, GVHD, and tolerance in solid organ transplantation. DJ Triulzi and MA Nalesnik. *Transfusion* 2001 41(3):419-26.**
- **Improvement of kidney graft survival with increased numbers of blood transfusions. G Opelz and PI Terasaki. *N Engl J Med* 1978 299(15):799-803.**

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