Literature Review for Blood Irradiation [1]

A significant share of blood used in transfusions is irradiated to prevent Graft-Versus-Host-Disease (GVHD). TA-GvHD is a rare but serious complication of blood transfusion caused by white blood cells called lymphocytes in the transfused blood. Even a very small number of these cells may recognize the patient receiving the blood as 'different' and cause a severe illness or even death.

GVHD is rare, but if contracted, nearly always proves fatal. To avoid failure to identify some at risk patients, some U.S. hospitals irradiate all platelets, not just those for specific patient populations. [2] Estimates of the share of the U.S. blood supply that is irradiated vary from about one-tenth to one third.[3]

Traditionally, such blood was irradiated using cesium chloride (CsCl), a powder form of the highly radioactive isotope Cesium-137 (isotopic symbol Cs-137) pressed inside a double encapsulation of metal; most irradiators currently operating in the United States still use this technology.[4]

However, in recent years, technological improvements and national, state, and local government support have led to the increasing use of X-ray blood irradiators in the United States. For example, the U.S. National Nuclear Security Administration's voluntary Cesium Irradiator Replacement Project (CIRP) program has replaced 50 CsCl blood irradiation devices as of March 2019, and has commitments for 79 additional replacements over the next several years.[5] Other countries such as Japan, France, and Norway have already undertaken or completed conversion efforts. Meanwhile a third technology—photochemical treatment—is already used in Europe and has drawn increasing interest in the United States.

Cesium-137 Advantages and Disadvantages

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[1] This paper draws heavily from Miles Pomper, Egle Murauskaite, and Tom Coppen, "Alternatives to High-Risk Radiological Sources: The Case of Cesium Chloride in Blood Irradiation," *Occasional Paper #19*, James Martin Center for Nonproliferation Studies, 2014

[2] Kopolovic, I., et al. 2015. "A systematic review of transfusion-associated graft-versus-host disease." *Blood*. 126(3):406-414.

[3] Department of Health and Human Services, the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey Report, 2015, 63; Sullivan MT, Cotten R, Read EJ, Wallace EL. Blood collection and transfusion in the United States in 2001. Transfusion 47:385–394; 2007

[4] It is estimated that about 400 cesium-137 devices were in place in April 2019. Ibid, Committee on Radiation Source Use and Replacement, National Research Council, Radiation Source Use and Replacement: Abbreviated Version (Washington, DC: National Academies Press, 2008) 86; Borchardt, R.W., "Strategy for the Security and Use of Cesium-137 Chloride Sources," Advisory Committee on the Medical Uses of Isotopes (ACMUI) CsCl Irradiator Subcommittee, November 24, 2008, Available at http://hps.org/govtrelations/documents/nrc_cscl-options_secy08-0184.pdf (accessed October 2, 2015)

[5] Communication with National Nuclear Security Administration (NNSA). In the Fiscal year 2019 National Defense Authorization Act (FY19 NDAA), Congress directed NNSA to target the elimination of all CsCl blood irradiators by 2027.

Cesium-137 provides several advantages that have encouraged its use. It requires few resources, financial or human. Traditionally, it has had low purchase and operating costs, requires little electricity and is fairly uncomplicated to use, thus not requiring specially trained personnel and typically requiring little maintenance throughout its useful life.[6]

The downsides to the use of cesium-137 include its disposal costs and requirements to prevent it from harming people accidentally or intentionally and its suitability as a source material for use in radiological dispersal devices (RDDs), such as "dirty bombs" where radioactive materials are strapped to conventional explosives. A cesium-137 RDD could cause significant adverse health effects or death to those exposed to it, could contaminate large areas denying normal operations in those areas, and cause public panic. Belligerent actors could obtain this material from operating devices in hospitals or other facilities. They could also take advantage of the fact that many countries—including the United States—lack a mechanism for disposing of disused sources - therefore these are often stored without proper security measures, or in the most extreme cases sometimes even abandoned with catastrophic economic and social consequences.

The latter concern was amply illustrated by the Goiania incident: in 1985, two persons broke into a former radiotherapy institute in Goiania, Brazil, taking a Cesium-137 teletherapy unit with them. Not realizing the hazard posed by the material contained in the unit, the thieves attempted to dismantle it in order to sell it for scrap; in the process, they accidently damaged the cesium-137 container, which led to the eventual unwitting dispersal of the radioactive material inside it. The health effects of the incident were severe. Four people died of radiation sickness. In total, 249 persons were contaminated, internally or externally, of which twenty needed to be hospitalized. Overall, 112,000 persons had to be monitored for possible adverse health effects amounting to 10% of the total population. Those highly exposed corresponding to 250 individuals, required long-term monitoring. In terms of clean-up costs, decontamination alone cost tens of millions of U.S. dollars; the effort took three years. [7]

A purposeful dispersion of cesium -137in densely populated areas or key economic or industrial zones could have even greater consequences, making an attack with a Cesium-137-based RDD a legitimate national and international security threat. This threat is exacerbated by several other characteristics of CsCl. The fact that it is supplied in the form of a salt, or a talc-like powder, makes it easy to handle and disperse, therefore enlarging the potential area that would be affected by an RDD. Cesium-137 is, moreover, easily soluble in water, which creates further opportunities for the belligerents to spread the material; it also means that upon entering the human body, CsCl will disperse quickly throughout the whole body. When dispersed, CsCl easily binds itself to surfaces and migrates into concrete, further complicating the task of decontaminating an

[6] U.S. National Academy of Sciences, Committee on Radiation Source Use and Replacement, —Radiation Source Use and Replacement, ‖ 2008, p.35.
[7] IAEA, —The Radiological Accident in Goiania‖, STI/PUB/815, Vienna, 1988, http://www-pub.iaea.org/mtcd/publications/pdf/pub815_web.pdf

environment affected by a cesium-137 l-based RDD.[8] Indeed, Norway's decision to phase out cesium-137 blood irradiators in favor of x-rays—a job that was completed in 2015—was influenced by two key factors: a government study on the potential economic impact of a radiological dirty bomb detonation and the contents of a manifesto written by the perpetrator of two terrorist attacks that killed 77 people on the same day in 2011.[9] As well, disposal requirements are a key concern of users who have cited as their second most important reason (after security requirements) for wishing to convert from Cesium-137 to x-ray technology.[10]

Cost comparisons between the technologies are complicated. The Nuclear Threat Initiative (NTI) has investigated the operating, training, and regulatory and termination costs of switching from using cesium-137 radioactive source irradiators to X-ray irradiators. [11] In general, cesium-137 because of its potential to cause mass harm is more tightly regulated and has extensive security requirements. All of these add up to substantial starting and recurring annual costs. However, the NTI report stresses that there are also liability and termination costs. While the security and regulatory requirements are calculated by the user into the costs, the latter liability and termination costs are not. The NTI report warns that should an incident happen where there is loss of control of the source the facility may be held liable for billions of dollars. In addition, the lifetime costs of end of life disposition of the sources is not reflected in the costs of purchasing the cesium-137 sources. The NTI report includes a useful worksheet for facilities to be able to assess whether switching to X-ray irradiators is cost effective for their specific context.

Alternative Technologies X-rays and Photochemical Treatment

X-rays technology, based on a non-isotopic source, comes in two forms designed to ensure a uniform radiation dose: either a machine where a drawer holding blood bags is irradiated between two X-ray tubes, or a design where the blood bags are placed on a carousel which moves in a full circle to ensure equal exposure from a single x-ray tube. The latter design is particularly useful because it makes use of the vast majority of X-rays that normally would be absorbed in the x-ray tube itself.[12] The unique design of the rotator typically allows users to increase their throughput and treat more blood products in less time (e.g. some models allow simultaneous irradiation of 6 blood products (i.e. whole blood, platelets, and loaded Syringes) in 5 minutes during a single cycle). Other models have self-contained cooling systems and wheels for easy transportation, making the irradiator more ergonomic and easier to use and maintain and a new

[8] U.S. National Academy of Sciences, Committee on Radiation Source Use and Replacement, —Radiation Source Use and Replacement, ‖ 2008, p.28

[9] Nuclear Threat Initiative, *Preventing a Dirty Bomb: Effective Alternative Technologies for Radiological Security*

[10] American Association of Physicists in Medicine (AAPM), "2013-10-17 AAPM Irradiator Survey—Final," presentation to the Nuclear Alternate Technology Working Group, April 7, 2015; While the survey had a limited sample size, it illustrates the main concerns and considerations for alternative technologies

[11] Ioanna Iliopulos, *Major Lifecycle Cost Considerations for Cesium-137 Irradiators and X-ray Irradiators*, Nuclear Threat Initiative, Nov 2018.
https://www.nti.org/media/documents/Major_Lifecycle_Cost_Considerations_II_Nov2018.pdf

[12] http://radsourcetechnologies.blogspot.com/2010/08/revolutionary-x-ray-tube-design.html

generation of flat panel x-ray devices is under development.[13] In general, electronic systems power the X-ray tubes and operate timers to control interlocks and exposure. X-ray devices typically weigh about 2000 pounds, significantly less than the 3000-4000-pound cesium-137 irradiators. The X-ray units require far less security and shielding, eliminate liability, and do not require expensive disposal at the end of the machine's life-cycle.[14]

Photochemical treatment is an alternative to irradiating blood components (platelets and plasma) to prevent GVHD. In 2014, the FDA approved two separate ultraviolet (UV) systems to treat plasma and platelets, respectively, to reduce the risk of pathogens that could cause transfusion-transmitted infections, but not specifically GVHD. The European Union had already approved their use for irradiating these components.[15] Both systems introduce the molecule amotosalen into the blood bag which when exposed to UV light prevents the RNA and DNA in pathogens and white blood cells from replicating. The result is pathogen inactivation, meaning that harmful bacterial and other viral infections are eliminated from the blood components (e.g. hepatitis B and C, HIV, West Nile virus and bacteria, as well as emerging pathogens such as Chikungunya, malaria and dengue).

Another UV system uses a combination of riboflavin (vitamin B2), a non-toxic, naturally occurring compound, and a specific spectrum of ultraviolet light to inactivate viruses, bacteria, parasites and white blood cells that may be present in collected blood products through the formation of reactive oxygen species. The FDA has not approved either the amotosalen- or the riboflavin-based systems to treat red blood cells or whole blood limiting their ability to fully replace cesium-137 devices.

Alternative Technologies vs CsCl:

As the Federal government's Radiation Source Protection and Security Task Force noted, efforts to replace "radioactive sources with effective alternatives have become increasingly successful for blood irradiation, in large part due to technological advances that have improved the reliability and cost of non-isotopic blood irradiation devices," particularly X-rays.[16] Previously a major perceived drawback of x-ray devices in comparison with cesium-137 blood irradiators, was their greater maintenance requirements, costs, and potential downtime over their lifetime.[17]

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[14] https://www.nti.org/analysis/articles/alternative-and-emerging-technology/

[15] U.S. Food and Drug Administration, "FDA approves pathogen reduction system to treat platelets," December 19, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427500.htm

[16] U.S Radiation Source Protection and Security Task Force, The 2018 Radiation Source Protection and Security Report, p. 19 https://www.nrc.gov/docs/ML1827/ML18276A155.pdf, p. 22

[17] Bakken, Erik, Katie Cary, Allison Derrick, Ellen Hildebrand, Kyle Schroeckenthaler, and Malika Taalbi, "Cost-Benefit Analysis of Switching from Cesium-Chloride to X-ray Blood Irradiators," (University of Wisconsin-Madison, 2013).

However, both U.S. public health agencies and private studies have concluded that several X-ray irradiators meet the same medical requirements for TA-GVHD as gamma irradiators by delivering ionizing radiation of 25 gray or greater to the midpoint of the target product. [18] The FDA has found x-ray devices from two manufacturers to be "substantially equivalent" to gamma source irradiators in preventing TA-GvHD.[19] The FDA can grant equivalence to premarket medical devices that meet several conditions, including a demonstration that a device with different technological characteristics does not "raise new questions of safety and effectiveness" and is "at least as safe and effective as the legally [U.S.] marketed device."[20]

The FDA conclusions are backed up by several private studies that did not find any clinically important differences between the two technologies.[21] In addition, Japan with a homogenous population deemed to be at a higher risk of GVHD is one of the most prominent advocates for the use of X-ray based irradiators, with no reported GVHD cases since 2000, when the technology was introduced.[22]

The UV systems are not yet FDA approved specifically for GvHD prevention, but separate FDA approval is not required for this application: rather, it is left to the discretion of medical practitioners. Already, some U.S. blood banks have begun using the technology after American Association of Blood Bank standards recognized amotosalen-UVA systems as equally effective as irradiation for GvHD prevention.[23] Some studies, in fact, have indicated that the amotosalen-UVA systems may be more effective in GVHD prevention than gamma irradiation.[24]

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[18] Regan, Donna and Miriam A. Markowitz. American Association of Blood Banks. "Changes to the 30th edition of *Standards for Blood Banks and Transfusion Services*." Association Bulletin #16-05 to AABB Members. March 17, 2016.

[19] U.S. Food and Drug Administration, *Radiological Devices Advisory Panel, Blood Irradiators—Unclassified: Executive Summary*, April 12, 2012, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/UCM299255.pdf (accessed Sept. 23, 2015).

[20] "Premarket Notification 510(k)," U.S. Food and Drug Administration, last updated September, 16, 2015, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/.

[21] Advisory Committee on the Medical Uses of Isotopes, Report on 137CsCl Irradiators,‖ October 13, 2008 (based on Brian Dodd and Richard J.Vetter, Replacement of 137Cs Irradiators with X-Ray Irradiators,‖ Health Physics, June 17, 2008) ; Jenny Trelevean et al., Guidelines on the Use of Irradiated Blood Components prepared by the British Committee for Standards in Haematology Blood Transfusion Task Force, British Journal of Haematology, 2011, Vol. 152 No. 1, pp. 35-51; K. Janatpour et al., "Comparison of X-ray vs. gamma irradiation of CPDA-1 red cells", Vox Sanguinis, Vol. 89, 2005, pp. 215-219

[22] Franz F. Wagner and Willy A. Flegel, —Transfusion-Associated Graft-Versus-Host Disease: Risk Due to Homozygous HLA Haplotypes, Transfusion, 1995, Vol. 35 No. 4, pp. 284-291

[23] Regan, Donna and Miriam A. Markowitz. American Association of Blood Banks. "Changes to the 30th edition of *Standards for Blood Banks and Transfusion Services*." Association Bulletin #16-05 to AABB Members. March 17, 2016.

[24] Jean-Pierre Cazenave, —Towards Universal Pathogen Inactivation in Blood Cells, in Transfusion Medicine: Looking to the Future, edited by Patrick Herve, Jean-Yves Muller, Pierre Tiberghien (Paris: John Libbey and Company, 2006), p. 38; Van Rhenen et. al, —Transfusion of pooled buffy coat platelet components prepared with

The UV systems have been used by blood centers in European countries including Belgium, France, Norway, Slovenia, Spain, Sweden, and Switzerland, as well as the Middle East and Russia since 2002. Whole blood, plasma, and platelet UV treatment using the Riboflavin-based technology have received the CE Marking—the legal requirement to place a medical device on the market in the European Community; the amotosalen technology has received the CE marking for plasma and platelets only. However, some EU countries (France, Germany, Switzerland, and Austria) required additional regulation before they would approve the UV systems for prevention of GVHD. The UV-amotosalen technology has received specific regulatory authority to be used to prevent GvHD in these countries. It also now in routine use in Sweden.[25]

There is a dearth of cost comparisons related to UV systems. However, one potential advantage of such machines is they could be used to prevent a host of pathogens beyond GVHD. In contrast, platelet components treated by gamma or x-ray irradiation for TA-GvHD risk must first go through an additional process to identify pathogen and bacterial contamination, which adds additional time and cost. A recent study used data from several large hospitals and blood centers to assess potential cost savings related to the use of certain UV systems for pathogen inactivation, primarily resulting from the elimination of the additional testing sometimes necessary for blood products irradiated using gamma sources. The assessment also identified the potential for additional savings should the FDA approve seven day platelet storage, which may be enabled by pathogen inactivation systems.[26] While the study concluded that the per-unit savings from system implementation could be significant, the authors noted that the amount of savings, if any, would vary depending upon the operational specifics at these facilities. [27] The systems also have a far smaller footprint than the gamma or x-ray systems—they are the size of a desktop scanner and thus highly portable. However, they may require other reorganization of storage and processing areas.

photochemical pathogen inactivation treatment: the euroSPRITE trial, Blood, Vol. 101 No. 6, March 15, 2003, pp. 2426-2433.J

[25] Sandgren, P. and B. Diedrich, "Pathogen inactivation of double-dose buffy-coat platelet concentrates photochemically treated with amotosalen and UVA light: preservation of in vitro function," 2015, Vox Sang 108(4): 340-349

[26] U.S. Department of Health and Human Services (HHS), "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion: Draft Guidance for Industry," March 2016, http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf

[27] McCullough, J., Goldfinger, D., Gorlin, J., Riley, W. J., Sandhu, H., Stowell, C., Ward, D., Clay, M., Pulkrabek, S., Chrebtow, V. and Stassinopoulos, A., "Cost implications of implementation of pathogen-inactivated platelets," Transfusion, 2015, 55: 2312–2320. doi:10.1111/trf.13149.