Chapter XXVI – Bone Marrow Transplantation – Clinical and RITN

The role of the transplant program in a nuclear accident or terrorism

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"Nuclear terrorism is still often treated as science fiction - I wish it were. But unfortunately we live in a world of excess hazardous materials and abundant technological know-how, in which some terrorists clearly state their intention to inflict catastrophic casualties." Kofi Annan, UN Secretary General, 1997 – 2006.

Introduction

The irony of this chapter should not be lost on the reader. After all, it was the nuclear detonations in Hiroshima and Nagasaki that led to the clinical observations that the bone marrow was very sensitive to the effects of radiation. Many of the victims of the nuclear detonations presented days later with pancytopenia. This bone marrow sensitivity led to the initial murine and then canine studies confirming that the bone marrow was the organ responsible for making all the blood elements and that bone marrow shielding or the transfer of bone marrow from another individual could rescue the animal from a lethal dose of radiation. Moreover, transplantation biology with the description of the major histocompatibility complex (MHC) was a direct result from these initial studies. This observation was then confirmed in humans with various maladies affecting the bone marrow or immune system who received total body irradiation followed by an autologous or allogeneic bone marrow graft. And thus the field of hematopoietic cell transplantation (HCT) was born. Our field has brought together very exciting basic science, translational medicine and clinical care to our patients leading to significantly better outcomes in many disease states. And yet, it seems we are coming around to a full circle with the increase threat of a nuclear detonation brought by a terrorist attack or a natural disaster.

Release of radioactivity, either intended or not, is an undeniable possibility and potentially catastrophic [1]. The recent tsunami and the Fukushima reactor meltdown is a stark reminder of the potential risk. If the winds were not favorable blowing radioactivity out to sea, the effects

could have been much worse [2]. Reports of nuclear proliferation in nations unfriendly to the United States and the Western World and the poisoning of a Russian dissident with Polonium-210 are further reminders of the terrorist threat [3]. In addition, more than 400 radiological accidents have occurred since 1944, resulting in over 3,000 significant exposures [4]. Approximately 10 million "sealed sources" of radioactive material (e.g. Cesium-137, Cobalt-60) are used for medical, industrial, agricultural and research purposes worldwide [5]. As of 31 December 2015, the ITDB contained a total of 2889 confirmed incidents reported by participating States. Of these 2889 confirmed incidents, 454 incidents involved *unauthorized possession and related criminal activities*, 762 incidents involved reported *theft or loss* and 1622 incidents involved *other unauthorized activities and events*1. In the remaining 71 cases, the reported information was not sufficient to determine the category of incident. (source: http://www-ns.iaea.org/downloads/security/itdb-fact-sheet.pdf)

Detonation of a nuclear device would cause unprecedented loss of life and injuries as well as economic, political, and social disruption. Many victims exposed to significant doses of radiation will develop bone marrow suppression. Thus, hematologists and oncologists, especially those with HCT experience, are uniquely suited to help evaluate and manage radiation exposure victims [6]. Depending on the scale of the event, there may be a national call for surge capacity. Hematologists, oncologists and hematopoietic cell transplantation (HCT) specialists across the country could be asked to balance the needs of their local patient populations with requests to accept patient transfers or even travel to other institutions. Therefore, we must collectively prepare for this contingency. Since a nuclear detonation would result in the most severe form of damage the rest of the chapter deals with this contingency planning, but the infrastructure suggested would be able to respond to a radiological dispersal device (e.g., a "dirty bomb") or a radiological source under a subway seat or in a park (e.g. radiological exposure device) or a nuclear power plant accident.

A public prepared to protect itself from fallout and an effective medical response could save tens of thousands of lives. Since 2001, all levels of government, academic institutions, and

professional organizations have done significant work to enhance our ability to prepare for and respond to a nuclear detonation. In the public health and medical arena, notable achievements are several different publications and websites including The Planning Guidance for Response to a Nuclear Detonation [7], the multi-paper series from the Nuclear Detonation Scarce Resources Working Group [8-23], health and medical educational material available from the Centers for Disease Control and Prevention (CDC) [24] and just-in-time material including algorithm-based management available on the Radiation Emergency Medical Management (REMM) website [25]. The Federal Emergency Management Agency (FEMA) along with interagency partners is developing improvised nuclear device (IND) National strategy and implementation plans.

Preparedness and Planning for a Nuclear Detonation

Several types of events, either accidental or intentional, could result in radiation exposure (Table 1). Intentional events can be caused radiological exposure devices (REDs), radiological dispersion devices (RDDs), and improvised nuclear devices (INDs). An RED is a radioactive source placed surreptitiously in a public space or other location. An RDD spreads radioactive material over a wide area, either using a conventional explosive (*i.e., a* so-called "dirty bomb") or via other means (e.g., by tainting the food or air supply). Although these devices would likely produce comparatively few fatalities, large numbers of people could be exposed to small doses, engendering widespread public confusion and anxiety. Victims of events involving RDDs or REDs would most likely be treated at centers near the incident, except in specific cases that require highly specialized care for burns or marrow suppression. It is unlikely that individual hematologists in other regions of the country would be involved.

In contrast, an improvised nuclear device (IND) using fissionable material such as plutonium or uranium would have devastating consequences and require the utilization of all available resources. A nuclear detonation produces both physical damage (trauma and burns) and radiation exposure. While the blast, heat and radiation zones overlap close to the epicenter,

there can be major areas where there is physical injury without radiation exposure (upwind glass breakage injuries, thousands of vehicle accidents resulting from flash blindness while driving on congested roadways) and others where there is radiation with limited or no physical damage to the infrastructure (fallout areas). The response to a nuclear detonation is organized around 3 physical damage zones (Severe, Moderate, and Light); a Dangerous Fallout zone; and a variable fallout zone, designated (>10mR/hr), in which response activities can occur but rescue time may be limited. The Radiation TRiage, TReatment, and TRansport (**RTR) system** overlays a functional response on these response zones (Figure 1) [26].

It is estimated that approximately 40,000 hospital beds are available at any given time nationwide, a capacity far lower than the projected number of potentially salvageable casualties. Thus, medical centers around the country may be asked to accept patients from the disaster area, both victims of the event and local residents who require care for chronic or intercurrent medical conditions. These efforts would initially be coordinated as part of the National Disaster Medical System (NDMS), a federally coordinated system of public and private hospitals that augment the nations medical response. As observed in the aftermath of Hurricane Katrina, healthcare needs for displaced populations can easily overwhelm the infrastructure in regions immediately surrounding a disaster area. For patients who require intensive medical care or those with cancer, hematologic disease or other chronic diseases, this disruption can be particularly dangerous.

Responding to the consequences of a nuclear incident: concepts, information and resources

Response is based on the assumption that resource availability will vary by proximity to the incident. Moreover, response will be an iterative process that will change over time. Hospitals closest to the detonation will be quickly overwhelmed by a surge of casualties and will rapidly exhaust supplies. The plan, therefore, is to distribute patients as quickly as possible for medical assistance farther away from the affected area where it will be easier to replenish supplies and staff. Key strategies for managing medical care in scarce resource settings are summarized in Table 2.

Developing a quantitative understanding of the local capacity for non-traditional emergency response assets (private practices, skilled nursing, commercial labs, etc.) and coordinating them is crucial. Planning for proactive resource support from the surrounding region, tribal, state, and Federal entities and the use of regional staging areas in case of a catastrophic incident will greatly shorten the time to resource availability to the end users. Assembly and evacuation center planning by healthcare facilities and the community at large will greatly mitigate bottlenecks and confusion in the hours and days after an incident.

Local planning is most effective when it is integrated across the tiers of response including state and Federal systems. Effective integrated planning is facilitated through the use of planning and response tools such as the Health and Human Services (HHS) resource mapping tool, GeoHEALTH https://gis.medmap.hhs.gov/medmap/default.aspx [27]. GeoHEALTH facilitates sharing situational awareness with the local/regional responders and can show locations of healthcare facilities in relation to other overlays and demographic information. Designated local and state government partners can request access to GeoHEALTH through their HHS/ASPR Regional Emergency Coordinators.

Medical Management of Acute Responses to Radiation

People exposed to high levels of radiation (usually >1-2 Gy over a short period of time may develop acute radiation syndrome (ARS). Symptoms vary according to the dose but include vomiting, diarrhea, headache, dizziness, weakness, bleeding, and redness of the skin. In a large mass casualty setting, efficient triage of irradiated casualties is essential to identify those who have received clinically significant but not invariably lethal doses of radiation estimated at 2-10 Gy of whole body exposure. These are the victims that need specialized and sometimes urgent care. In resource scarce settings, symptomatic care is given if possible and life-sustaining measures should be withheld from casualties with non-survivable trauma, thermal burns and/or radiation exposures. Extensive triage algorithms that emphasize fairness were recently

published to guide the selection of appropriate candidates for life-sustaining care in resource-limited settings in order to maximize survivability for the overall population [28].

The current management of ARS does not substantially differ from the management of pancytopenia in other settings, such as after treatment with myelosuppressive chemotherapy. Recently (2015) the FDA approved the use of Neupogen and Neulasta for the treatment of h-ARS, administering myeloid cytokines to appropriately selected victims offers two potential benefits after a mass casualty radiation incident. It can reduce morbidity and mortality resulting from neutropenia and it can lessen the need for subsequent or continued hospitalization during the post-incident period when medical resources and personnel may be extremely limited. The current challenge is that the local supply of cytokines would be quickly depleted in the absence of adequate triage to ensure that those that may not require this treatment immediately are referred for later evaluation and possibly treatment in a more resource-rich environment.

All patients with confirmed neutropenia or medical history of radiation exposure and physical injuries strongly suggestive of combined injury (radiation *plus* trauma and/or burn) are potential candidates for myeloid cytokines if they are deemed to have survivable exposure/injuries. Studies in non-human primates suggest that *initiating myeloid cytokines within 24 hours of exposure* may improve outcomes [29]. Myeloid cytokines (granulocyte-colony stimulating factor (G-CSF; Filgrastim), granulocyte monocyte-colony stimulating factor (GM-CSF; sargramostim) or pegylated G-CSF (pegfilgrastim)] can reduce the duration of neutropenia, hospital length-of-stay, and overall costs.

Myeloid cytokines should be initiated as soon as there is evidence a casualty will develop severe neutropenia (i.e., less than 500 neutrophils per mm^3). Specific indications for initiating myeloid cytokines prior to the onset of neutropenia include a projected whole body dose of 2 Gy or more based on 1) physical dose reconstruction using geographic information, 2) clinical signs, and/or 3) lymphocyte depletion kinetics. Drug should be continued until normalization of the granulocyte count. Supportive care measures are equally important. Antiemetics for vomiting,

hydration, and antibiotics to prevent bacterial infections during the neutropenic period have been shown to improve survival in animal models of ARS. These suggestions are not different from those that are in daily practice in the heme-onc or transplant wards.

The essential role of biodosimetry

Appropriate triage and care after radiation exposure depends on accurate and timely estimates of radiation dose. Dose information will be important for classifying victims into groups that: 1) will not require medical intervention, 2) could benefit from supportive care (e.g., colony stimulating factors) to facilitate autologous marrow recovery, 3) require evaluation for HSCT to treat potentially irreversible marrow damage, and 4) cannot be salvaged. A variety of information can be used to estimate an individual's radiation exposure. Unlike the homogenous dosing associated with therapeutic total body irradiation, shielding from nearby structures (e.g., buildings) during accidents or terrorist attacks will result in heterogeneous exposures. Therefore, a careful history of the victim's location and subsequent symptoms will be essential. Initial clinical assessment will include the time from event to first emesis and peripheral blood counts, with subsequent lymphocyte depletion kinetics.

Approaches that use only clinical and routine laboratory findings to stratify victims into risk groups are valuable for a small-sized accident, but their utility during large events is not clear [30-32]. Biodosimetry, the use of biologic markers to assess dose, can enhance the predictive value of clinical findings after radiological or nuclear events. The "gold standard" for biodosimetry is the quantification of dicentric chromosomes using metaphase cytogenetics in peripheral blood lymphocytes. Unfortunately, dicentric quantification requires multiple days to perform and is currently available only in select centers. Plans have been formulated to develop major radiation laboratory networks to perform dicentric quantification on a mass scale [33]. Newer methods for biologic dosimetry, including rapid genomic analysis of PBLs, serum proteomics and measurements of DNA damage, are also under development [34-43]. Treating hematologists will need to calculate radiation doses using the information they have available. Online algorithms for estimating dose based on clinical and biological data are available from the

Radiation Emergency Medical Management (REMM) website at http://www.remm.nlm.gov/ars_wbd.htm or from the Armed Forces Radiobiologic Research Institute at http://www.afrri.usuhs.mil/www/outreach/biodostools.htm#software.

Radiation Injury Treatment Network (RITN)

Beginning in 2001, the National Marrow Donor Program (NMDP) established a working group to address the issue of a nuclear disaster. In 2006, the American Society for Blood and Marrow Transplantation (ASBMT) formally joined this effort and established the Radiation Injury Treatment Network (RITN), a voluntary consortium of 77 (and growing) HCT centers, donor centers and umbilical cord blood banks (Figure 2), made possible through partnerships with the Office of Naval Research and the Center for International Blood and Marrow Transplant Research. The goals of RITN (www.ritn.net) are:

1) to develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure,
2) to educate health care professionals about pertinent aspects of radiation exposure management,
3) to coordinate situation response after a radiation event,
4) to provide comprehensive evaluation and treatment for victims at participating HCT centers, and
5) to collect data on the outcomes of treatment.

The European Group for Blood and Marrow Transplantation (EBMT) is establishing a similar network to offer training courses and improve cooperation between institutions [29].

The number of patients who will require care after a large-scale event, such as an improvised nuclear device, exceeds the capacity of RITN centers by many orders of magnitude. For example, if a device similar to the bomb detonated over Hiroshima struck a metropolitan area, the number of casualties would depend on many factors, such as the size of the device, the time of day, type of buildings, weather conditions, and the precise location of the detonation.

Models suggest that as many as 175,000 victims would require intensive medical care and nearly 30,000 would need intensive management for myelosuppression [44]. Such an event would clearly overwhelm any health system. The care of such victims would require altered standards of care, including the use of alternative treatment sites such as armories, auditoriums or gymnasiums. Thus the logistical complexity for planning is clearly daunting, some would say too daunting. However, despite the obstacles, experience from radiation accidents indicates that many victims can be salvaged with appropriate care. The LD_{50} (lethal dose to 50% of persons exposed) for total body irradiation in humans is approximately 3.5-4 Gy without supportive care, but the use of antibiotics and transfusions may increase the LD_{50} to 4.5-7 Gy and survival at doses greater than 10 Gy may be possible with HCT [45]. If a significant fraction of victims with acute injuries could be saved with supportive care alone, appropriate planning and response after a large-scale event could save thousands of people. Thus, a large-scale event will offer extraordinary opportunities for qualified practitioners at large and small centers throughout the United States and potentially internationally to support such an effort. Who would be more qualified than hematologists and oncologists, especially HCT physicians, if properly trained?

Resources for assisting hematologists with clinical management

Acute radiation syndrome (ARS) can affect virtually any organ but primarily manifests as injury to the hematologic, dermatologic, gastrointestinal and central nervous systems. The severity of ARS increases proportionally with the radiation dose from mild (<1-2 Gy) to invariably lethal (>10-20 Gy). The clinical course of ARS generally includes a prodromal phase, followed by a period of apparent clinical remission, manifest illness and ultimately recovery or death. Importantly, the latency between exposure and severe manifestations of ARS affords the time to transport victims to RITN sites.

A large fraction of patients with radiation exposure significant enough to induce cytopenias will have multi-organ system damage. Persons exposed to radioactive material may present unique and exceedingly complex management challenges. Few physicians are familiar with the basic manifestations of acute radiation injury or have training in the prospective management of

patients with significant radiation exposure. In addition, esoteric aspects of care such as decorporation therapy for internal radiation contamination are extremely important but very few healthcare practitioners have experience in this realm. A number of resources are available to assist with the evaluation and care of radiation exposure victims. Among these, the Radiation Emergency Medical Management website (www.remm.nlm.gov) was developed in a collaboration among the National Library of Medicine, Office of the Assistant Secretary for Preparedness and Response and medical experts from around the world. With assistance from RITN members, REMM includes admission and treatment order templates directed toward victims of radiological or nuclear events.

To ensure optimal care and enhance preparedness for subsequent events, it is essential that, to whatever extent possible, data on exposure and clinical complications be collected prospectively from victims and compiled centrally. The NMDP has developed a data collection protocol (http://www.nmdp.org/RITN/GUIDELINES/DOCS/data_collection_prot.pdf) for use at RITN centers across the United States. After a large-scale event, centers that accept patients with radiation injury may be asked to contribute patient data to central repositories, either through RITN or governmental agencies.

A role for stem cell transplantation?

Some victims of a large-scale event may receive doses of radiation to cause irreversible myeloablation. As discussed above, these patients will commonly have multi-organ damage. What remains unclear is whether allogeneic HCT can be a life-sustaining measure in this setting. To date, 31 patients have undergone allogeneic HCT after accidental radiation exposure. Median survival after transplant for these patients is ~1 month [4]. All 4 patients who survived >1 year reconstituted autologous hematopoiesis, raising the question whether the HCT provided any benefit. Particularly troubling was the contribution of GVHD to mortality in >20% of patients. More recently previously unavailable data on the use of stem cell administration to aid recovery of victims of the Chernobyl disaster became available [46]. There were nine patients heretofore unreported in the scientific literature who underwent intraosseous injections of

allogeneic bone marrow cells in Kyiv. Transplantation was associated with significantly shortened time to recovery of granulocyte and platelet counts in these patients. While current guidelines would certainly include the use of cytokines, these data provide an indication of the effectiveness of stem cell transplant to treat victims of radiation exposure.

In many regards, patients with myeloablation from radiation exposure are similar to those with aplastic anemia. A reduced intensity conditioning regimen for severe aplastic anemia (where immunosuppression but not myeloablation is required) is being tested in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN Protocol 0301) [47]. Of note, NMDP has plans in place to conduct large numbers of urgent searches for victims following an event, recognizing that only a few searches would likely lead to transplants.

Current efforts to develop medical radiation countermeasures

Several promising medical countermeasures are under development. However, the complex nature of radiation injury is such that no single drug is likely to provide benefit in all circumstances and against all aspects of radiation injury. Antioxidants and radioprotectants are presumably most effective if present at the time of irradiation, while therapeutics such as a growth factor may target one or more but not all affected organ systems. For this reason, many experts believe that combination therapy will be required to produce substantial improvements in outcomes.

The US government, particularly the Department of Defense, has a long-standing interest in the development of medical countermeasures against radiation. Beginning in 2005, the Radiation Countermeasures Program at the US National Institute of Allergy and Infectious Diseases (NIAID) has supported the development of medical countermeasures for civilian populations exposed to radiological or nuclear hazards as a result of accidents or terrorist attacks [48].

Conclusion

Whether a radiological or nuclear incident occurs domestically or abroad, work continues to ensure that the US is prepared to assist in planning and response. Many governmental and non-governmental agencies are involved in the planning. Although the logistical difficulties inherent to any large-scale event are enormous, the potential for life-saving measures is equally large. Future efforts will focus on streamlining these processes, providing training to medical practitioners around the country, and validating medical countermeasures to reduce the morbidity and mortality of radiation exposure. Practitioners and institutions across the country are encouraged to become involved and participate in the planning. The widespread availability of radioactive material has made future exposure events, accidental or intentional, nearly inevitable. Hematologists, oncologists and HSCT physicians are uniquely suited to care for victims of radiation exposure, creating a collective responsibility to prepare for a variety of contingencies.

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Table 1. The spectrum of potential events involving radioactive material. Numbers of deaths are rough estimates.

Categories	Description	Number of deaths
Radioactive source accident	Loss or theft of a radiological source (*e.g.* Goiana, Thailand, Mexico)	0-10s
Nuclear reactor accident	Release of radioactive gas or material (*e.g.* Chernobyl, Mayak)	0-100s
Radiological dispersal device	Device or scheme for dispersing radioactive isotope (*e.g.,* dirty bomb[1] or radioactive material in the food supply)	0-1,000s
Radiological exposure device	Radioactive material intended to expose people in the vicinity (e.g. Cesium source placed on a train, China)	0-100s
Improvised nuclear device	Incorporates radioactive material intended to produce a nuclear explosion	1,000s to >1,000,000

[1]Only a small fraction of deaths would be expected to result directly from radiation exposure

Table 2: Strategies for Scarce Resource Situations

- **Prepare** – stock disaster supplies and increase par levels on commonly needed items such as tetanus vaccines, laceration trays, narcotic analgesics, dressing, etc.
- **Substitute** – use a clinically equivalent item or staff person; ENREF 12
- **Adapt** – use items or technologies to provide sufficient care (use transport ventilators or anesthesia machines instead of full-featured ventilators), use staff with similar or congruent skill-sets (specialty surgeons assisting with trauma surgeries), or adapt locations of care (performing surgical procedures outside of the OR environment);
- **Conserve** – use less of a resource by lowering dosage or changing utilization practices
- **Re-use** – after appropriate disinfection/sterilization, re-use supplies;

Re-allocate – prioritize a therapy in scarce supply so that it is only given to those with a higher chance of benefit or greater need

Table 3. Websites containing additional information on approaches to medical triage, assessment and management after radiation exposure.

Source	Website
American Academy of Pediatrics	www.aap.org/policy/radiation.htm
American Medical Association Center for Public Health Preparedness and Disaster Response	www.ama-assn.org/ama/pub/category/6206.html
Armed Forces Radiobiology Research Institute	www.afrri.usuhs.mil
Centers for Disease Control and Prevention	www.bt.cdc.gov/radiation/
Federal Emergency Management Agency	www.fema.gov/hazard/index.shtm
Health Physics Society	www.hps.org
National Institute of Allergy and Infectious Diseases Radiation Countermeasures Program	http://www3.niaid.nih.gov/research/topics/radnuc/
Radiation Emergency Assistance Center/Training Site	www.orau.gov/reacts
Radiation Emergency Medical Management	www.remm.nlm.gov
Radiation Injury Treatment Network	www.ritn.net
Uniformed Services University of the Health Sciences Center for Disaster and Humanitarian Assistance Medicine	www.usuhs.mil/mem/cdham.html
U.S. Department of Veteran Affairs Emergency Management Strategic Healthcare Group	www1.va.gov/emshg
U.S. Food and Drug Administration Office of Crisis Management	www.fda.gov/oc/ocm
U.S. Nuclear Regulatory Commission	www.nrc.gov

Figure legends

Figure 1. Schematic for triage and response to a large-scale radiation event developed by the Office of the Assistant Secretary for Preparedness and Response. Triage centers are located in concentric rings around the affected area, providing initial stabilization and decontamination (RTR1-3), more extensive medical care (MC), and rapid screening of unexposed or minimally exposed individuals at Assembly Centers (AC). Patients who require further care are evacuated to referral centers in unaffected regions.

Damage Zones:

- Severe Damage (SD) zone: extensive infrastructure damage and few survivors
- Moderate Damage (MD) zone: probably not readily passable due to physical damage but can be cleared, with variable to no levels of radiation, which, if present, decrease fairly rapidly over time the first hours to day
- Light Damage (LD) zone: passable, most damage is glass breakage, with little or no radiation other than where fallout areas overlap the LD zone

Functional Response System: the RTR system helps organize the response[6, 7] (Figure 1). This system includes several types of sites:

A) *Spontaneously forming* RTR sites (casualty collection points):

1) RTR1: at or near major physical damage with significant radiation present early on radiation present;
2) RTR2: limited physical damage and varying radiation present that declines over the first few hours to day, likely near the DF zone; and
3) RTR3: minimal damage and no radiation.

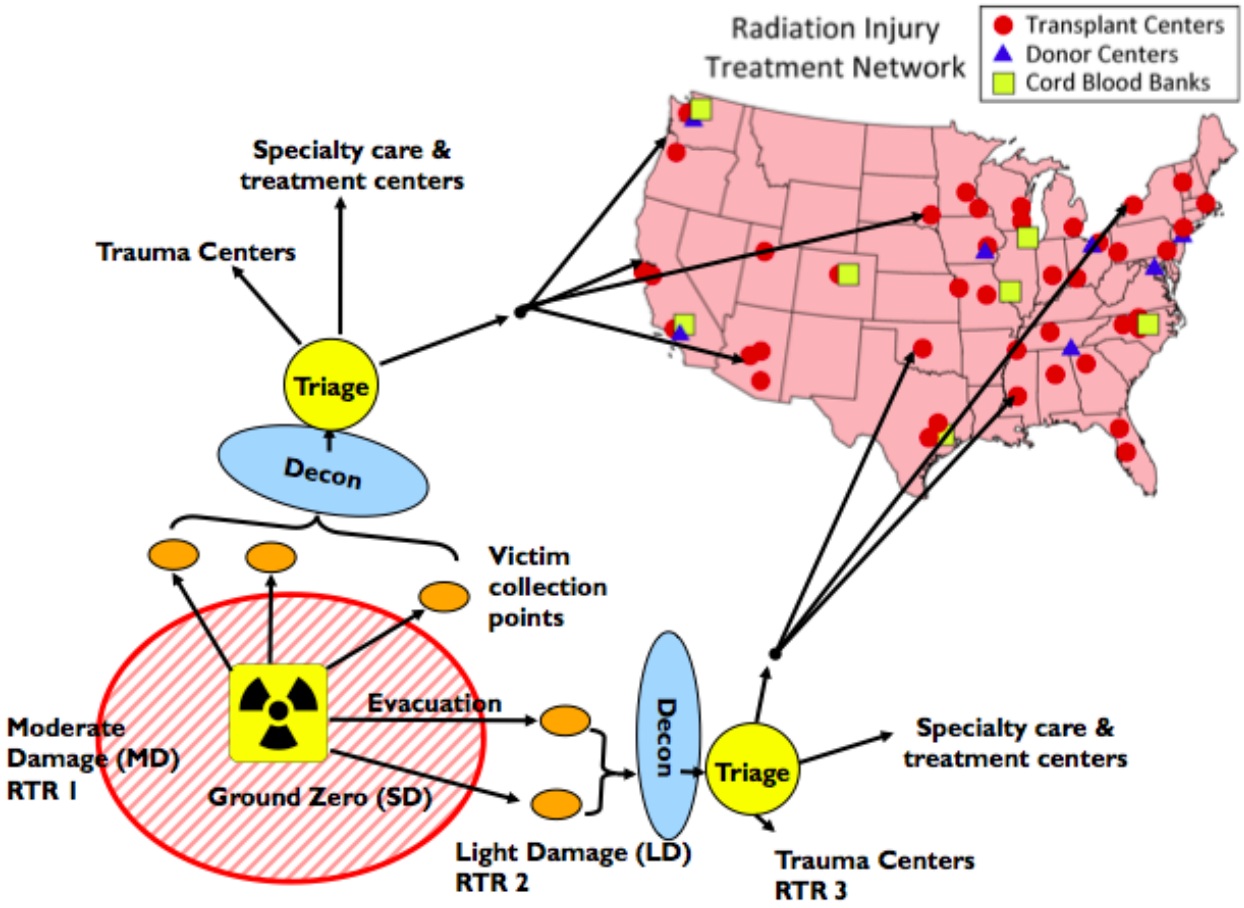

Figure 1: Physical Damage, Radiation, and RTR Zones

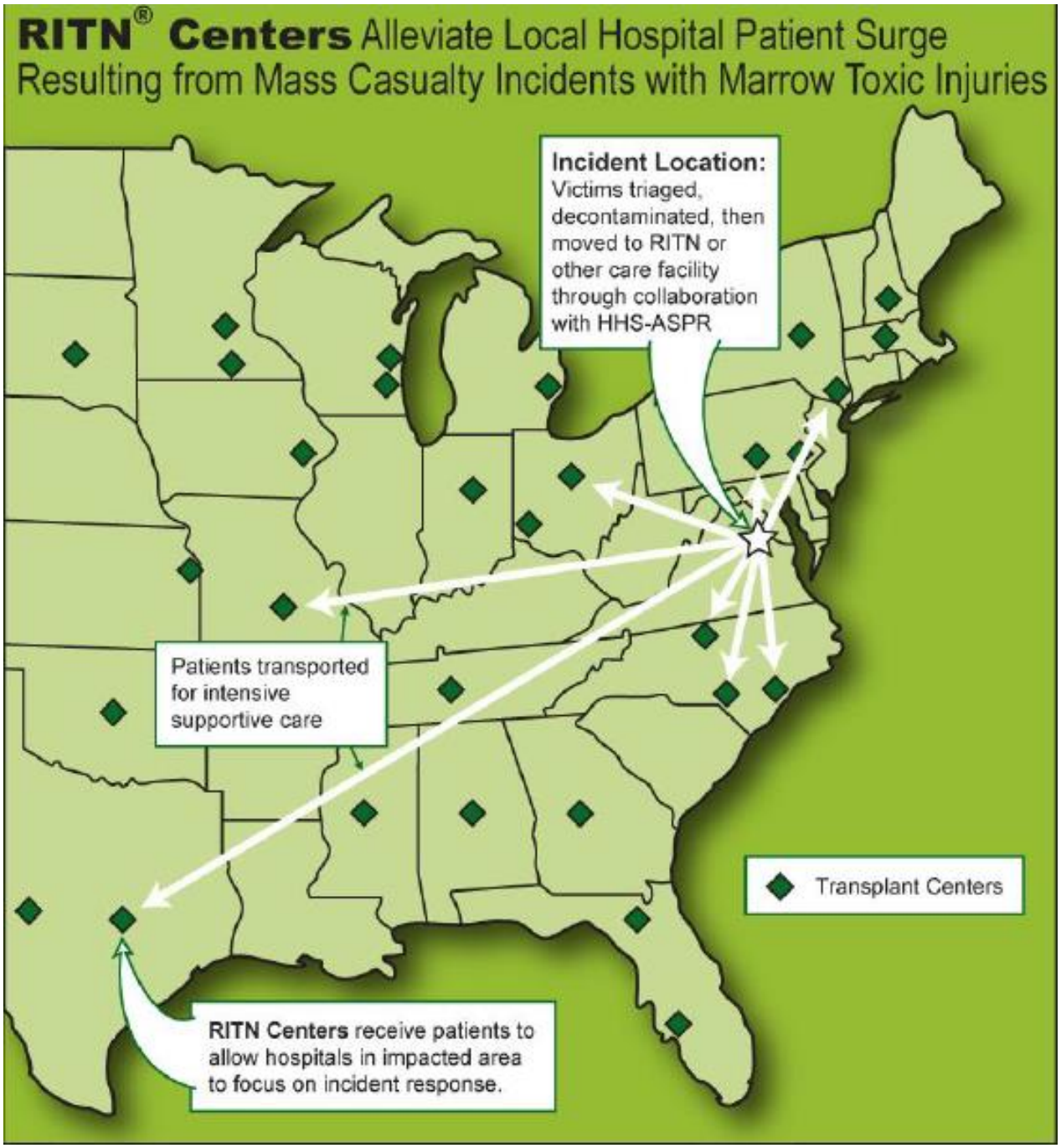

Figure 2. The Radiation Injury Treatment Network (RITN). Transplant centers, donor centers and umbilical cord blood banks are divided into ten regions designated by the US Federal Emergency Management Agency (FEMA). Primary transplant centers act as the lead institutions within their region during event response.