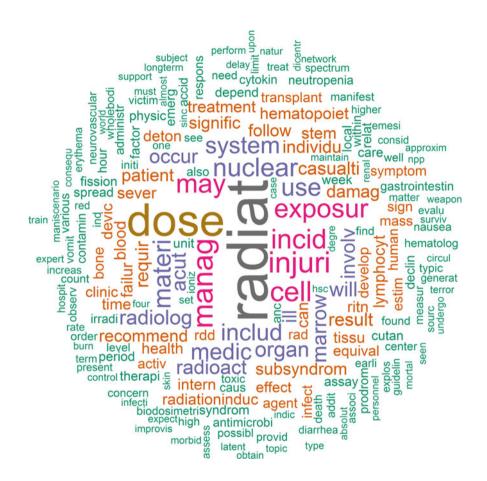# Radiological and Nuclear Terrorism: The Oncologic Emergency Response

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Introduction

A rudimentary understanding of radiation physics and the hazards associated with exposure to radiation in various scenarios is essential. Basic formal education in medical school is limited, and most physicians have never managed a casualty from a radiological incident. An introduction to the vocabulary of radiation physics, instrumentation, and illnesses is required to provide the basis for understanding radiation-induced pathophysiology and medical management.

The term "radiological event" refers to incidents or effects that involve exposure to materials that are radioactive. The term "nuclear event" refers to any radioactive material resulting from fission. Radiological materials can be relatively innocuous, or they can be extremely dangerous, depending upon their inherent physical structure, the nature of the radiation they emit, and the amount of material involved in an incident. Nuclear materials, on the other hand, present almost no significant hazard to humans in their natural form. If they undergo fission, however, newly generated radionuclides may present a significant hazard to humans and the environment from either the fission process itself or the by-products of nuclear fission. Nuclear fission is required for the detonation of improvised nuclear device (IND) and more sophisticated nuclear weapons (NW). Fission is also required to generate heat for the production of electricity in nuclear power plants (NPPs). In fission reactors, steam generated from the nuclear process is used to turn a turbine which in turn rotates a generator [1].

Measurement of radioactivity. Radioactivity (sometimes called the activity of a radiation source) is the term used for measurement of radioactive material. Radioactivity or activity is measured in curies (Ci) in the English measurement system or the becquerel (Bq) in the SI system (SI = International System of Units or Système International). A Bq is equivalent to one disintegration of an atomic nucleus per second. A Ci is equivalent to 3.7×10^{10} disintegrations per second (dps). A Bq is so small that it is much more common to see units in multiples of Bq such as megabecquerels (MBq), gigabecquerels (GBq), etc. Likewise, a curie is so large that it is much more common to see units in fractions of Ci such as millicuries (mCi), microcuries (μCi), etc.

Units of dose measurement. The unit rad is often used in the English system to describe the amount of ionizing radiation that is absorbed in a cell, tissue, organ, or the body (rad = radiation absorbed dose). It is equivalent to 100 ergs of energy deposited in 1 g of tissue. The gray (Gy) is equivalent to 1 J of energy deposited in 1 kg of tissue. One Gy is equivalent to 100 rad. The rem (rad equivalent man) is a unit of equivalent dose which is used to measure the long-term biological risk related to ionizing radiation exposure (in the USA). The sievert (Sv) is the international unit (SI) for equivalent dose. One Sv is equivalent to 100 rem. The terms Gy and Sv will be used henceforth.

Radiological and Nuclear Scenarios of Concern

Key to understanding radiological and nuclear incidents are the types of injuries and illnesses that they can cause.

The following radiation scenarios are of concern for emergency care responders:

- Radiological exposure device (RED)
- Radiological dispersal device (RDD)
- Improvised nuclear device (IND)
- Nuclear weapon detonation (NWD)
- Nuclear power plant (NPP) incident

RED. An RED is a radiation source that might be surreptitiously placed in a location that will allow unsuspecting individuals to come in contact with it or be exposed to it. The radiation-induced injuries and illnesses that result from exposure or touching the source vary depending upon the nature of the source, the radiation emitted, and the energy of the radiation emitted. It is possible for an RED to cause severe damage up to and including ARS subsyndromes as well as acute local radiation injuries (LRI) or damage to the skin and deeper tissues/organs.

RDD. An RDD is any device that can be used to spread radioactive material. "Dirty bombs" are a common topic of discussion in an age of increasing terrorism. Many believe that an RDD is equivalent to a dirty bomb. This is not necessarily the case because an RDD does not need to explode. An RDD is any device that can be used to spread radioactive materials. A dirty bomb or explosive RDD is any device that uses conventional explosives that when detonated will pulverize and spread particles or larger pieces of radioactive materials into the environment. Improvised explosive devices (IEDs) are detonated on a daily basis in parts of the world to cause physical harm to people or structures. The manufacture of an explosive RDD requires an IED to which is added some amount of radioactive material. An RDD could also involve the use of a device that could spread, for example, liquid radioactive materials. The consequences of an explosive RDD could involve radiation-induced injuries and illnesses, however, could also involve physical trauma and/or thermal burns.

IND and NWs. The main differences between an IND and an NW are the activity of the fissile materials used for a detonation and the sophistication required for manufacture of such a device. The NWs detonated over Japan to bring about the end of World War II in the Pacific Theater were on the order of 10–15 kilotons (KT) of TNT and involved the use of only a few pounds of U-235 or Pu-238. Weapons developed

later during the Cold War were on the order of megatons. When discussing nuclear weapons (NW), it is important to realize that they are designed and manufactured with very sophisticated nuclear, chemical, and electrical engineering skills and techniques maintained only by the international nuclear powers. In either case, the detonation of an IND or an NW could be devastating with massive infrastructure damage and mass human casualties. The fallout of radioactive material descending to the ground after being blown into the atmosphere by the detonation can result in significant human radiation exposures. The acute and subacute consequences of such detonations will involve physical trauma, thermal burns, as well as radiation-induced illnesses/injuries.

NPP incidents. NPP incidents are exceedingly rare, and when they do occur, the results can be highly variable. The Chernobyl (1986) and Fukushima (2011) incidents resulted in multiple human health effects primarily related to exposures to and contaminations with radioactive materials. At Chernobyl, there were 28 acute deaths attributed to acute radiation syndrome that were from ARS [2]. There were no reported casualties specifically related to acute radiation effects from the Fukushima incident. The Three Mile Island incident in 1976 also had no associated adverse human health effects from radiation.

The most common NPP incident relates to control of heat that is generated by a mass of fissile material undergoing fission. If there is a failure anywhere along the path of cool water provision, the reactor may overheat, may melt (thus the term meltdown), or even catch fire. This kind of incident is called a loss-of-coolant accident (LOCA). The results of environmental release of radioactive materials could be a significant source of adverse human health effects.

Radiation-Induced Injuries and Illnesses

Radiation-induced injuries and illnesses occur in a spectrum from minor to severe involving various cells, tissues, and organs. Minor injuries can merely involve exposures to the hematopoietic and cutaneous systems that require no significant medical intervention at below about 1 Gy (100 rad). Severe injuries/illnesses can result in amputations, disruption, and/or loss of vital bodily functions, up to and including death. All of these serious conditions will require timely and aggressive medical care. The systems of greatest concern are the hematopoietic, cutaneous, gastrointestinal, and the neurovascular (cerebrovascular) systems.

Radiation injuries/illnesses, unlike infectious agent exposures and chemical insults, are curious in that they usually have a prodromal period during which one may see only nonspecific symptoms and signs of injury or illness. The prodrome is often followed by a latent period during which the patient may appear relatively well, but injury to various tissues is progressing. The manifest illness phase of ARS occurs when the damage to particular cell types, tissues, and organs appear. At the end of the manifest illness phase, the cell, tissue, organ, or human either lives or dies. The prodrome begins earlier with higher doses; the latent period becomes shorter as the dose becomes higher; the manifest illness period begins earlier with higher doses. The absence of the latent period may be an ominous sign of a higher dose and ultimately significant morbidity and mortality.

Any radiation injury or illness should result in engagement of radiation health and protection experts in these matters. These personnel might include health physicists (HP), medical physicists (MP), diagnostic radiologists (including those with nuclear medicine training), radiation oncologists, hematologists, and/or medical oncologists. Key is that these personnel have experience with radiation dose extent and magnitude estimation. Early dose magnitude estimations will help guide emergency department triage and medical management before more precise dosimetric estimations are available.

Early Diagnostic Evaluation of Acute Radiation Injury

The Clinical History and Laboratory Findings

Proper application of a well-structured interview technique can lead to a diagnosis of radiation injury. Clinicians should consider radiation toxicity as part of their differential diagnosis in individuals presenting with the prodromal symptoms of nausea, vomiting, and diarrhea in the setting of a radiological incident. If acute radiation injury is not considered, a prompt diagnosis will be missed. Early in the patient work-up, an initial CBC (complete blood count) with differential should be obtained and repeated every 4–6 h to monitor for a decline in the absolute lymphocyte and neutrophil counts. Blood for individual radiation dose estimates (e.g., radiation biodosimetry) should be obtained at this time.

In the delayed evaluation of patients in terrorism cases where the incident occurred 2–4 weeks previously, the treating medical team may see a patient with some or many aspects of the acute radiation syndrome with or without the cutaneous subsyndrome. Clinical signs and symptoms may include:
(1) Pancytopenia, immune dysfunction, sepsis, impaired wound healing, and GI bleeding (hematopoietic subsyndrome)
(2) Malabsorption, ileus, fluid and electrolyte imbalance, acute renal failure, and cardiovascular failure (gastrointestinal subsyndrome)
(3) Confusion, disorientation, hypotension, cerebral edema, ataxia, convulsions, and coma (neurovascular subsyndrome)

Various authors have suggested that the presence of nausea, vomiting, diarrhea, and fever may correlate with the general range of exposure dose. Zhang has noted that approximately 100 % of patients with whole-body dose greater than the LD_{50} or the dose required to cause mortality in 50 % of the population (approximately 3.5–4.0 Gy without treatment), will have early nausea and vomiting, and many will exhibit altered deep tendon reflexes [3]. In addition, Hartmann et al. have noted an increased body temperature for effective whole-body dose >2.5 Gy and acute diarrhea for dose >9 Gy [4].

Time to Emesis

Two clinical parameters are relatively quickly available for quantitative analysis of radiation injury after a severe incident: (1) the time to emesis and (2) lymphocyte depletion kinetics. In work performed at Oak Ridge Associated Universities 1964–1975, with patients undergoing long-term radiation therapy at a relatively low-dose rate ($n=502$ patients, 0.8–90 R/h), 50 percentile frequency doses were obtained as follows: $ED_{50}=1.08$ Gy for anorexia, $ED_{50}=1.58$ Gy for nausea, and $ED_{50}=2.40$ Gy for emesis. A trend is noted whereby the time to emesis decreases with increasing dose [5, 6] though there is much variability among individuals and circumstances using this as a sole biodosimeter.

Lymphocyte Depletion Kinetics

In papers by Goans et al., a simple prediction algorithm was presented to estimate effective whole-body dose within 8–12 h after moderate and high-level gamma accidents and after criticality accidents [7–9]. The algorithm is based on the observation that lymphocyte depletion follows first-order kinetics after high-level gamma accidents. Using historical data from both gamma and criticality accidents, lymphocytes are observed to follow approximately an exponential decline in time within the first 24–48 h. This algorithm has been incorporated into the Armed Forces Radiobiology Research Institute (AFRRI) Biodosimetry Assessment Tool (BAT) program [10] (Table 1).

Cytogenetic Biodosimetry

In the historical evolution of the medical management of radiation incidents, prior to 1960, determination of dose relied on the history of the event, health physics studies, time and motion simulation, and analysis of any dosimetry that might have been present. Additionally, medical management was heavily weighted toward clinical response to the evolu-

Table 1 Absolute lymphocyte count decrease and approximate estimate of absorbed dose

Absolute count 8–12 h post event	Rough estimate of absorbed dose
1700–2500/mm^3	0–4 Gy
1200–1700/mm^3	4–8 Gy
<1000/mm^3	>8 Gy
Absolute lymphocyte count 48 h postexposure	Absorbed dose estimate
1000–1500/mm^3	1–2 Gy
500–1000/mm^3	2–4 Gy
100–500/mm^3	4–8 Gy
<100/mm^3	>8 Gy

A whole-body dose of 1 Gy or less should not noticeably depress the lymphocyte count below the normal range taken as 1500–3500/mm^3 (from Goans [11])

tion of various syndrome characteristics of the ARS or of acute local cutaneous injury. Since the period 1960–1970, the dicentric chromosome assay has been extensively developed, harmonized to international standards, and is now considered worldwide to be the gold standard for biodosimetry [12].

Researchers at AFRRI and REAC/TS have established the conventional lymphocyte metaphase-spread dicentric assay and have applied it to the clinical management of several overexposure accidents. The dicentric assay is also performed at Yale University School of Medicine and other select medical institutions to determine whole-body dose in victims of radiation incidents. In addition, the premature chromosome condensation (PCC) assay has been found useful at various dose levels. Conventional metaphase-spread chromosome-aberration biodosimetry techniques are robust, but they are laborious and time-consuming. In addition, for potential high-dose irradiation above the median lethal dose, it is expected that radiation-induced cell death and delay in cell cycle progression into mitosis will interfere with dose estimation. In order to overcome this limitation, quantitative analysis of radiation-induced damage may be performed using resting peripheral lymphocytes in lieu of metaphase spreads. The use of interphase cytological assays, such as the PCC assay, can eliminate these inherent problems associated with the use of metaphase-spread cytogenetic assays.

Recently, it was suggested that the dicentric assay may be adapted for the triage of mass casualties [13–15]. Lloyd et al. described an in vivo simulation of an accident with mass casualties receiving whole- or partial-body irradiation in the 0- to 8-Gy range [13]. Faced with an urgent need for rapid results, clinical triage was accomplished by scoring as low as 20 metaphase spreads per subject, compared with the typical 500–1000 spreads scored in routine analyses for estimating dose. However, Lloyd et al. suggested increasing the analyses to 50 metaphase spreads when there is disagreement with the initial assessment or when there is evidence of significant inhomogeneous exposure [13, 16] (Table 2).

Table 2 Proposed biodosimetry technique as a function of expected dose

Dose range (Gy)	Proposed validated dosimetry method	Prodromal effects	Manifest symptoms	Survival expectancy
0.1–1	Dicentric/PCC	None to mild (1–48 h)	None to slight decrease in blood count	Almost certain
1.0–3.5	Lymphocyte depletion kinetics/dicentrics/PCC	Mild to moderate (1–48 h)	Mild to severe bone marrow damage	0–10 % death
3.5–7.5	Lymphocyte depletion kinetics/PCC	Severe (1–48 h)	Pancytopenia, mild to moderate GI damage	10–100 % death within 2–6 weeks
7.5–10.0	Lymphocyte depletion kinetics/PCC	Severe (<1–48 h)	Combined BM and GI damage	90–100 % death within 1–3 weeks
>10.0	PCC	Severe (minutes to <48 h)	GI, neurological, cardiovascular damage	100 % death (within 2–12 days)

Reprinted with permission from Prasanna et al. [16]

Table 3 Levels of hematopoietic toxicity

Symptom or sign	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes[a]	1.5×10^9 cells/L	$1–1.5 \times 10^9$ cells/L	$0.5–1 \times 10^9$ cells/L	$<0.5 \times 10^9$ cells/L
Granulocyte changes[b]	2×10^9 cells/L	$1–2 \times 10^9$ cells/L	$0.5–1 \times 10^9$ cells/L	$<0.5 \times 10^9$ cells/L
Thrombocyte changes[c]	100×10^9 cells/L	$50–100 \times 10^9$ cells/L	$20–50 \times 10^9$ cells/L	$<20 \times 10^9$ cells/L
Blood loss	Petechiae, easy bruising, normal hemoglobin level	Mild blood loss with <10 % decrease in hemoglobin level	Gross blood loss with 10–20 % decrease in hemoglobin level	Spontaneous bleeding or blood loss with >20 % decrease in hemoglobin level

See Table 3 of Dainiak et al. [28] (reprinted with permission from Dainiak et al. [28])
[a]Reference value $1.4–3.5 \times 10^9$ cells/L
[b]Reference value $4–9 \times 10^9$ cells/L
[c]Reference value $140–400 \times 10^9$ cells/L

Acute Radiation Syndrome (ARS)

ARS (or acute radiation sickness) consists of a spectrum of diverse clinical signs and symptoms that develop after a whole-body or significant partial-body irradiation of >1 Gy delivered at a relatively high-dose rate. In 2000, an international group of subject matter experts that assembled in Ulm, Germany, categorized these findings into four organ systems (e.g., the hematopoietic, gastrointestinal, cutaneous, and neurovascular systems), each of which occurs individually or in combination [17]. ARS is best thought of as a Venn diagram with four overlapping circles, each representing a subsyndrome that corresponds to an affected organ system. Depending on radiation dose, clinical findings assigned to an organ system may occur concurrently or sequentially with those assigned to the other systems. The signs and symptoms of each of the resulting four subsyndromes of ARS are summarized in Tables 3 (hematopoietic subsyndrome) and 4 (gastrointestinal, cutaneous, and neurovascular subsyndromes). The severity of signs and symptoms for each organ system is quantified as "degrees" of toxicity (degree 1, 2, 3, or 4). The "response category" (grade 1, 2, 3 or 4) correlates with overall severity of ARS and is determined by the highest degree of toxicity within any of the organ systems.

Hematopoietic subsyndrome (HS). Radiation-induced damage is determined in part by the radio sensitivity of the affected cells with the most rapidly dividing cells (e.g., cells in the bone marrow, intestinal crypts, and testes) having the greatest sensitivity. Hematopoietic stem/progenitor cells in the bone marrow and circulation are particularly sensitive to ionizing radiation with a dose (D_0) of approximately 1 Gy at a dose rate of 0.8 Gy/min [18]. At doses of 2–3 Gy, hematopoietic stem/progenitor cells exhibit reduced capacity to divide. Morphological changes in interphase cells of the bone marrow include nuclear karyorrhexis, cytoplasmic fragments, nuclear and intercellular bridging, multinuclearity, and pseudo-Pelger-Huet anomaly [19]. Chromosomal bridges and fragments are seen in actively dividing cells of the marrow. Bone marrow hypoplasia and/or aplasia may develop at doses >5–7 Gy, resulting in severe pancytopenia weeks to months after exposure [20]. The pathophysiologic mechanisms underlying these radiation-induced effects on the bone marrow involve dose-dependent, clonal elimination of stem/progenitor cell populations and their progeny [21, 22]. Depending on dose, dose rate, and radiation quality factor, various degrees of pancytopenia develop several weeks after exposure [23, 24].

Lymphocytes are the most radiosensitive of the circulating blood cells in spite of their being terminally differentiated and largely mitotically inactive. Enhanced radiosensitivity may be explained in part by the observations that radiation alters recirculation properties and surface antigen expression of lymphocytes [25, 26]. The rate of decline in lymphocytes is exquisitely dependent on the absorbed radiation dose

Table 4 Grading system for response based on clinical signs and symptoms

Symptom	Degree			
	1	2	3	4
Gastrointestinal system				
Diarrhea				
Frequency, stools/d	2–3	4–6	7–9	10
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Persistent, large amount
Abdominal cramps or pain	Minimal	Moderate	Intense	Excruciating
Cutaneous system				
Erythema[a]	Minimal transient	Moderate (<10 % BSA)	Marked (10–40 % BSA)	Severe (>40 % BSA)
Sensation or itching	Pruritus	Slight, intermittent pain	Moderate, persistent pain	Severe, persistent pain
Swelling or edema	Present, asymptomatic	Symptomatic, tension	Secondary dysfunction	Total dysfunction
Blistering	Rare, sterile fluid	Rare, hemorrhage	Bullae, sterile fluid	Bullae, hemorrhage
Desquamation	Absent	Patchy, dry	Patchy, moist	Confluent, moist
Ulcer or necrosis	Epidermal only	Dermal	Subcutaneous	Muscle or bone involvement
Hair loss	Thinning, not striking	Patchy, visible	Complete, reversible	Complete, irreversible
Onycholysis	Absent	Partial	Partial	Complete
Neurovascular system				
Nausea	Mild	Moderate	Intense	Excruciating
Vomiting	Occasional (1 time/day)	Intermittent (2–5 times/day)	Persistent (6–10 times/day)	Refractory (>10 times/day)
Anorexia	Able to eat	Intake decreased	Intake minimal	Parenteral nutrition
Fatigue syndrome	Able to work	Impaired work ability	Needs assistance for ADLS	Cannot perform ADLS
Temperature, °C	<38	38–40	>40 for <24 h	>40 for >24 h
Headache	Minimal	Moderate	Intense	Excruciating
Hypotension	Heart rate >100 bpm, blood pressure >100/70 mm/Hg	Blood pressure <100/70 mmHg	Blood pressure <90/60 mmHg, transient	Blood pressure <80/? mmHg, persistent
Neurologic deficits[b]	Barely detectable	Easily detectable	Prominent	Life-threatening, loss of consciousness
Cognitive deficits[c]	Minor loss	Moderate loss	Major impairment	Complete impairment

See Table 3 of Dainiak et al. [43] (reprinted with permission from Dainiak et al. [43])
BSA body surface area, *ADLS* activities of daily living
[a]The extent of involvement is decisive and should be documented for all skin changes
[b]Reflex status (including corneal reflexes), papilledema, seizures, ataxia, and other motor signs or sensory signs
[c]Impaired memory, reasoning, or judgment

(see above discussion of the decline in absolute lymphocyte count (ALC) as an individual radiobiodosimeter).

Other hematological findings include a decline in the absolute neutrophil count (ANC) and the platelet count. The ANC may briefly increase within hours after exposure, a phenomenon first described by Fliedner as an "abortive rise" [17]. The abortive rise is believed to be due to migration of preformed myeloid elements across the marrow-blood barrier into the circulation, although demargination cannot be excluded as a mechanism for this transient effect. Thereafter, the ANC declines over several days to weeks, depending on radiation dose. The abortive rise is typically seen with HS-1 and HS-2 and appears to indicate reversible marrow damage from a survivable exposure. The absence of an abortive rise in ANC is observed in HS-3 and HS-4 and is felt to auger irreversible bone marrow damage. Neutropenia and thrombocytopenia reach a nadir at 1–2 weeks after exposure to >3–4 Gy. Anemia follows due to impaired erythropoiesis and hemorrhage from the gastrointestinal tract and other organs as a consequence of thrombocytopenia.

The most significant consequences of lymphopenia and neutropenia are disruption of immune defenses and predisposition to life-threatening infections. ANCs of <500–1000 cells/mm³ (HS-3 and HS-4) are associated with bacterial, viral, and fungal infections, similar to what occurs in the setting of neutropenia and lymphopenia from any other cause. Management of febrile neutropenia and attendant infections should follow guidelines recommended by the Infectious Diseases Society of America (IDSA), using broad-spectrum prophylactic and therapeutic antimicrobial agents [27]. Prophylaxis may include amoxicillin plus clavulanate or a fluoroquinolone with streptococcal coverage, an antiviral agent (such as acyclovir or valacyclovir) for patients who are positive for herpes simplex virus (HSV) or cytomegalovirus

(CMV), and an antifungal agent (such as fluconazole or posaconazole for mucosal and invasive infections with drug-sensitive *Candida* species). Whenever possible, prophylactic antimicrobial agents should be administered before the onset of critical leukoneutropenia (HS-4). Additional antimicrobials should be added to broaden coverage as clinically indicated based on clinical course, culture and sensitivity results, and laboratory findings.

Management of the HS includes administration of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) when the dose is expected to be >2 Gy and/or when it is anticipated that the ANC will decline to <500 cells/mm^3 for 7 days or longer [28]. A strong recommendation for cytokine therapy was made by a panel of subject matter experts that was convened at the World Health Organization in 2009 to evaluate the quality of published evidence and develop recommendations for treatment of ARS in a hypothetical scenario involving hospitalization of 100–200 victims [28]. The Food and Drug Administration (FDA) has approved these myeloid colony-stimulating factors for use in a radiological incident. Cytokine therapy should be initiated with 24 h of exposure and should continue until the ANC reaches and maintains a level of >1000 cells/mm^3 in the absence of active infection. For individuals with active infection, cytokines should be continued together with antimicrobial agents, according to guidelines of the IDSA [27].

Erythroid-stimulating agents (ESAs) should be administered to individuals with prolonged anemia and/or a significant decline in hemoglobin level [28]. The rationale for ESA therapy is to avoid the need for red blood cell infusion. The lowest dosage that induces a hemoglobin level of >9–10 g/dL should be used. Oral iron supplementation should be considered in conjunction with ESA therapy.

Although other growth factors (including stem cell factor, interleukin-3, and the pegylated form of erythropoietin and G-CSF) have been administered sequentially or concomitantly with G-CSF and/or GM-CSF to victims of a radiological incident [28], their limited use and lack of documentation of response to the specific growth factor preclude recommendation of their use in a radiological incident at this time.

Because radiation injury to the bone marrow is typically heterogeneous, leaving areas of unirradiated or minimally irradiated/damaged marrow that are capable of reconstituting lymphohematopoiesis over time, a watch-and-wait approach is recommended after initiating myeloid growth factor therapy. Administration of hematopoietic stem cells (HSCs) should be considered only after failure of a 2–3-week trial of cytokine treatment has been demonstrated [28]. A review of 31 patients undergoing HSC transplantation for accidental radiation injury found that 27 patients died, and the remaining four patients survived with a rejected allograft [29]. Causes of death after therapeutic HSC transplantation

include burns (55 %), hemorrhage (41 %), infection (15 %), and acute respiratory distress syndrome (ARDS) (15 %) [30]. Since survival outcomes are poor among HSC transplant recipients with radiation burns, GS, renal failure, and/or adult ARDS, HSC transplantation should not be performed in individuals with nonhematopoietic organ failure and/or active infection [28, 31–33]. In the case of a large radiological incident, the Radiation Injury Treatment Network (RITN), a voluntary consortium consisting of >70 transplant centers, donor centers, and umbilical cord blood banks, will be activated [34, 35].

When transfusion is indicated for severe cytopenia, blood products should be irradiated (25 Gy) to prevent transfusion-associated graft-versus-host disease (TA-GVHD). Since TA-GVHD is almost universally fatal in this population, its prevention by prior irradiation of blood products is mandatory. Leukoreduction may lessen febrile reactions and the immunosuppressive effects of blood transfusion, limit platelet alloimmunization, and reduce CMV infection [36, 37]. Leukoreduction is recommended whenever feasible.

National Network for Management of Mass Radiation Casualties

In the USA, a network has been developed of transplant centers, hospitals, blood donation centers, and stem cell banks to provide resource-intense medical management of mass casualties from a radiological event. The Radiation Injury Treatment Network (RITN) provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries (like those caused by mustard agent). Many of the casualties with radiation injury will be salvageable but require specialized outpatient and/or inpatient care. Recognizing this need, the US National Marrow Donor Program/Be The Match Marrow Registry, the US Navy, and the American Society for Blood and Marrow Transplantation collaboratively organized RITN, which provides expertise in the management of bone marrow failure, blood component therapy, stem cell collection, and umbilical cord blood banking across the USA.

The RITN is preparing for the resulting medical surge of radiation only casualties from the detonation of an improvised nuclear device.

The goals of RITN are:
- To develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure
- To educate health-care professionals about pertinent aspects of radiation exposure management through training and exercises
- To help coordinate the medical response to radiation events
- To provide comprehensive evaluation and treatment for victims at participating centers

The RITN collaborates with the Department of Health and Human Services and the Assistant Secretary for Preparedness and Response to ensure coordination following a mass casualty marrow toxic incident that would require their involvement in a national response. The RITN has developed ARS Treatment Guidelines and Referral Guidelines for local hospitals that receive individuals who show early signs of ARS [38]. In addition, the RITN has, in collaboration with staff managing the Radiation Emergency Medical Management (REMM) website, developed treatment orders for adults and children [33].

The RITN estimates that of survivors from an IND detonation, only 1 % of radiation only casualties will be candidates for hematopoietic stem cell transplantation. Approximately 30 % of casualties are expected to require specialized supportive care in an inpatient setting that involves isolation to protect individuals with febrile neutropenia. Finally, nearly 70 % of casualties are expected to require ambulatory care for treatments such as administration of cytokines and antimicrobials, serial assessment of the CBC, and calculation of the absolute lymphocyte count [39].

RITN medical staff are specialists in hematology and oncology who have daily experience in treating patients with hematologic signs and symptoms that characterize HS. Hospitals that participate in RITN have established standard operating procedures (SOPs) for managing mass casualties. They coordinate locally with emergency management personnel and public health officials and conduct annual training and exercises to constantly improve their level of preparedness.

Cutaneous subsyndrome (CS). Injury to the skin and subcutaneous tissues is highly dependent on localized radiation dose [40–42]. At 3–4 Gy, transient epilation occurs (CS-1). At 6–10 Gy, persistent erythema (CS-2) may occur. The degree of erythema may wax and wane and must be distinguished from an early or prodromal erythema that disappears during the latent period. This prodromal erythema should not be confused with the persistent erythema found in the manifest illness phase of the CS at doses of 10–15 Gy. At higher doses, moist desquamation and ulceration (localized dose of 20–25 Gy) and blisters and bullae (CS-3, localized dose of >30 Gy) are observed. Damage to subcutaneous tissues (CS-4) is highly dependent upon the type and energy of the radiation as well as the duration of irradiation.

Management of CS includes topical steroids, topical antihistamines, and topical antibiotics [43]. Systemic steroids are not recommended, unless there is another indication for their use. Ulcers, necrosis, and intractable pain require surgical excision, skin grafts, and skin flaps [44]. Intractable pain from compression of cutaneous nerve bundles has been successfully treated by local infusion of mesenchymal stem cells [45]. Adipose-derived and bone marrow-derived stem cells are showing promise as treatment for radiation-induced tissue injuries but still lack long-term follow-up for possibilities of genomic instability and malignant transformation [45–47].

Gastrointestinal subsyndrome (GS). The GS may be seen at doses as low as 1 Gy (100 rad). Only the prodromal phase of mild anorexia, nausea, vomiting, and diarrhea is seen at doses of <1.5 Gy (100–150 rad, GS-1 and GS-2) [48]. At doses of >5 Gy (500 rad), damage occurs to stem cells of the small intestine that are found in crypts at the base of microvilli. The GS is manifest by severe nausea and vomiting within 30–60 min of exposure at these doses (GS-3 and GS-4) [23, 24]. These findings may be accompanied over time by hematemesis, hematochezia, fluid and electrolyte shifts, hypovolemia with eventual renal failure, and cardiovascular collapse.

Sloughing of the lining of the GI tract removes the barrier to bacterial translocation from the intestinal lumen to the bloodstream. Bacterial translocation occurs at a time of immunocompromise from neutropenia and lymphopenia, predisposing to sepsis [49]. If the HS is not appropriately treated, death will almost certainly ensue from the GS.

Management of the GS includes antimicrobial prophylaxis and therapy to achieve therapeutic drug levels (rather than bowel decontamination), replacement of fluids and electrolytes, bowel decontamination (with concomitant systemic antibiotics), loperamide to control diarrhea, and a serotonin receptor antagonist to control emesis [43].

Neurovascular subsyndrome (NS). Also known as the cerebrovascular syndrome, the NS typically occurs at radiation doses that are not compatible with life. Acute, irreversible neurotoxicity occurs at whole-body doses of >10 Gy (1000 rad) (NS-2, NS-3, and NS-4). Signs and symptoms include disorientation, fever, ataxia, headache, neurologic deficits, seizures, and coma. At lower doses (3–4 Gy), a milder form of NS consisting of mild headache, limited vomiting (once daily) and tachycardia without fever, hypotension, or neurological deficits (NS-1) may occur as well. Management of typical NS includes symptom control and supportive care for the patient and family. Administration of a serotonin receptor antagonist, mannitol, furosemide, antiseizure medications, and analgesics is recommended, as needed on an individual basis [43].

Other considerations. Involvement of the tracheobronchial tree and lungs is observed at 1–6 months following exposure to a high radiation dose [50]. Edema and leukocyte infiltration of the lung parenchyma occur during the initial day to week after exposure. An acute exudate occurs after 1–3 months, followed by collagen deposition and fibrosis after months to years. Delayed pulmonary involvement may simulate acute respiratory distress syndrome (ARDS) from any cause

with similar morbidity and mortality approaching 100 %. Interstitial pneumonitis accompanied by a restrictive ventilatory defect may lead to death. Management of respiratory failure includes ventilator support with a lung protection strategy, using the lowest possible inhaled oxygen concentration to maintain an arterial oxygen saturation of >90 % [43]. Radiation damage may occur in other organ systems, including the renal, vascular, and cardiac systems. Multiorgan failure (MOF) can be an intermediate- to long-term complication of radiation exposure with significant morbidity and mortality. Vigilance for damage to other organ systems must be maintained throughout medical care. The pathophysiology of MOF is likely complex and remains poorly understood [51]. Its management includes prolonged mechanical ventilation and hemodynamic monitoring [52].

Internal contamination. Internal contamination with radioactive materials is a medical toxicology issue, that is, the management of a poisoning, which is extremely complex. The potential for possible internal contamination with radioactive materials is a matter of emergency, or at least urgent, concern because treatment for internal contamination may need to be initiated *within hours* after the contaminating incident. Following an R/N incident, medical toxicologists and/or the Radiation Emergency Assistance Center/Training Site (REAC/TS; 24/7 emergency phone, 865-576-1005) to assist with management of internal contamination with radioactive materials should be involved.

Summary

A myriad of specialists, especially those well versed in hematologic abnormalities, will be required for any significant ionizing radiation to the whole body or a significant portion thereof because of the potential for injury to circulating WBCs or the bone marrow. In fact, inappropriate management of the HS will almost certainly result in elevated morbidity, if not mortality from the HS itself or damage to other organ systems. The manifestations of immunologic incompetence including the spectrum of infectious diseases must be treated properly in order to improve patient survival. Practitioners must be also vigilant for multiple organ dysfunction/failure secondary to ionizing radiation exposure.

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