

Management of Ionizing Radiation Injuries and Illnesses, Part 4: Acute Radiation Syndrome

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Financial Disclosures: None reported.

Support: This work was partly performed under Contract # DE-AC05-06OR23100 between ORAU and the US DOE. REAC/TS is a program of the Oak Ridge Institute for Science and Education, which is operated for the US DOE by ORAU.

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Submitted May 13, 2013; revision received October 18, 2013; accepted November 13, 2013.

To provide proper medical care for patients after a radiation incident, it is necessary to make the correct diagnosis in a timely manner and to ascertain the relative magnitude of the incident. The present article addresses the clinical diagnosis and management of high-dose radiation injuries and illnesses in the first 24 to 72 hours after a radiologic or nuclear incident. To evaluate the magnitude of a high-dose incident, it is important for the health physicist, physician, and radiobiologist to work together and to assess many variables, including medical history and physical examination results; the timing of prodromal signs and symptoms (eg, nausea, vomiting, diarrhea, transient incapacitation, hypotension, and other signs and symptoms suggestive of high-level exposure); and the incident history, including system geometry, source-patient distance, and the suspected radiation dose distribution.

J Am Osteopath Assoc. 2014;114(9):702-711
doi:10.7556/jaoa.2014.138

In September 1987 in Goiânia, Brazil, 2 men found a capsule containing 1375 Ci of cesium-137 (¹³⁷Cs) in a radiation teletherapy unit in an abandoned cancer treatment center.¹ They took the capsule home, broke it open, and removed some of the glowing blue cesium chloride powder. They sold pieces of the capsule to a junkyard owner, who shared the powder with friends, neighbors, and family members over the next few days. A friend of the junkyard owner took additional powder out of the capsule, brought it home, and gave it to his family. The junkyard owner's brother also took some of the powder home and put it on the kitchen table. His 6-year-old daughter played with the fragments while eating a sandwich.

Many of the individuals exposed to the powder began to have nausea and vomiting, diarrhea, dizziness, and fatigue, and some had skin manifestations. The wife of the junkyard owner grew suspicious that the glowing powder was the source of the illness. She and one of the junkyard workers took a bag of the capsule remnants to a clinic, placed it on the desk of one of the physicians, and told him that it was "killing her family." The concerned physician put the bag outside his clinic and called the Tropical Diseases Hospital. One of the physicians at the hospital had become concerned about the skin lesions he was seeing in his patients lately. The physicians at the hospital called the state Department of the Environment of Goiás State, who sent a visiting physicist to the area 3 weeks after the source capsule was breached to investigate. He confirmed widespread radioactive contamination.

Ionizing radiation (IR) injuries and illnesses are not commonly taught in medical school curricula. Radiation oncologists, medical oncologists, surgical oncologists, and some Department of Defense medical personnel may be more familiar with these conditions;

however, their experience with injuries and illnesses due to acute whole-body (or large partial body) exposures may be lacking. Further, these specialists may not recognize atypical presentations of acute radiation syndrome (ARS) in these patients. Cases of local or partial body exposure are more common and yet are still rare.² Currently, few physicians would be able to recognize the IR symptom complex and be aware of the initial treatments.

The aim of this article is to help increase physician knowledge and recognition of ARS by reviewing the basics of the pathophysiologic process, clinical signs and symptoms, laboratory findings, dose estimation, and treatment planning of ARS.

Pathophysiologic Process of ARS

Ionizing radiation damages the molecules that make up the cells of the various tissues of the body. The effects on cells and cellular structures occur in several ways. The energy released from an ionization can break atomic bonds directly or indirectly. Indirect ionization results from the hydrolysis of water, which releases highly reactive free radicals that cause breakage of the bonds and other damage.³

The major target in cells is DNA. The damage may be a single-stranded DNA break or a double-stranded DNA break, with the latter being more difficult to repair and often resulting in chromosomal aberrations and mutations.³ Double-stranded DNA breaks often lead to cellular death. Ionizing radiation may also alter the cell cycle by arresting it, delaying it, or delaying replication with the aberrant chromosomal material. The cell often detects these anomalies and then commits cellular suicide by apoptosis. Cellular death by apoptosis is not accompanied by an inflammatory process, whereas mitotic death and necrosis are associated with an inflammatory response.

All of these processes may occur with IR exposure, resulting in a hyperinflammatory and a hypercytokinemic-like syndrome. Systemic inflammatory response syndrome and multiorgan dysfunction often result in

multiorgan failure in all organ-irradiated systems and death.⁴⁻⁷ A continuum of changes occur so that there is ongoing damage to all of the affected organ systems simultaneously.⁸ The ARS subsyndromes—hematopoietic, gastrointestinal (GI), neurovascular, and cutaneous subsyndromes—represent the “classic” presentation of damage to the given organ system and at the doses where changes are typically seen. This article focuses on the former 3 subsyndromes.

The radiosensitivity of the various cell types and their life cycles help determine the clinical presentation of IR injury and ARS. The Bergonié-Tribondeau law, which is the basis of radiosensitivity and radiation oncology, states that characteristics that determine the radiosensitivity of cells include rapid cell division or mitotic activity; undifferentiation; and active proliferation for longer periods.³ Examples of these radiosensitive cells are hematopoietic progenitor cells, epidermal germinal epithelial cells, GI epithelial cells, and endothelial cells primarily in smaller blood vessels in the microvasculature. This property explains why these organ systems are targets for IR injury and result in the subsyndromes of ARS.

All cells exposed to IR can be damaged to varying degrees. This process is best visualized as a spectrum beginning with decrements in lymphocyte counts, then polymorphonuclear counts, then platelets, and, finally, red blood cells (RBCs). Lymphocytes are the exception to the law of Bergonié-Tribondeau. Lymphocytes may be the most sensitive cell type in the human body and, therefore, the decrease and rapidity of decrease in lymphocyte count is an excellent indicator of dose. The higher the IR dose, the more rapid and severe the decrease in lymphocytes. Threshold doses are those at which the classic presentations of ARS subsyndromes are typically seen. The damage to other exposed organ systems is also occurring, and we may not see the textbook manifestations until a threshold dose is reached. These deterministic effects are directly proportional to the dose (ie, the higher the dose, the more severe the effects).

In addition to cellular radiosensitivity, other factors ranging from the radiation dose to an individual's age may determine the effects of IR (*Figure 1*).³

Symptoms of ARS

One of the earliest effects of IR exposure to the whole body or to a large portion of the whole body is a prodromal period of nonspecific signs and symptoms such as nausea, emesis, fatigue, fever, and anorexia. As in the example from Goiânia, Brazil, patients may be unaware of their exposure to radioactive materials. Thus, physicians need to maintain a high index of suspicion when seeing multiple patients with similar patterns of these symptoms. The prodrome may be followed by a latent phase in which patients have a decrease or absence of symptoms. In the manifest illness phase of ARS, the signs and symptoms of damage to a particular cell type or organ will fully exhibit the disease. The severity of the prodrome period is proportional to the dose received and, therefore, the degree of illness manifestation.

The persistence of emesis and diarrhea along with fever are poor prognosticators. The presence of emesis may be used as an initial indicator of dose (*Table 1*), although it is more accurate when used with other parameters. Acute radiation syndrome presents as a complex of its aforementioned subsyndromes. Although hematopoietic, GI, neurovascular, and cutaneous ARS are recognized as the traditional subsyndromes of ARS, an ongoing spectrum of damage occurs in all affected organ systems; there is no isolated damage to one system without some effect on another.⁹ The classic presentations of the subsyndromes, however, appear at certain dose thresholds (*Table 2*). Injury to the skin may be as deadly or more so than the other subsyndromes.⁵ Several entities have assigned grading systems to the subsyndromes to assist in the triage and treatment of these patients.^{8,9}

The median lethal dose that can be expected to result in fatalities in 50% of an untreated population within 60

days is approximately 4 Gy (400 rad). Aggressive medical care, including the use of prophylactic antibiotics, antibiotics for specific foci of infection, and cytokines, can be expected to increase the median lethal dose, thereby pushing the survival curve to the right. In some cases that might otherwise be fatal, including whole-body radiation doses or doses to large portions of the body of 8 to 9 Gy (800-900 rad), aggressive treatment might allow the patient to survive. Whole-body doses greater than approximately 10 Gy (1000 rad) are almost universally fatal (*Figure 2*).

Hematopoietic Subsyndrome

The classic presentation of hematopoietic ARS is seen at doses greater than 1 Gy and manifest earlier and more severe with higher doses. Although specific clinical signs and symptoms of radiation exposure are not seen for 1 to 2 weeks, evidence of damage to circulating blood cells or to bone marrow can be seen on complete blood cell (CBC) count with white blood cell (WBC) differential at 0.75 to 1.0 Gy (75-100 rad). Peripheral circulating lymphocytes decrease within the first 12 to 48 hours. The higher the dose of IR, the faster the drop in lymphocytes and the lower the nadir. Lymphocyte depletion kinetics may also be used to help guide treatment and prognosis.^{10,11}

The decreasing absolute lymphocyte count (ALC) is demonstrated in the Andrews curves in *Figure 3*. Mild hematopoietic ARS is characterized by a relatively slow drop of the ALC to a nadir of approximately 1500 cells/mm³ at 48 hours (normal ALC, 2500 cells/mm³). As the dose increases, the slope of the curve becomes steeper and the nadir lowers. Mild injury is considered to result from an acute whole-body dose of approximately 1 to 2 Gy (100-200 rad); moderate injury, 2 to 4 Gy (200-400 rad); severe injury, 4 to 6 Gy (400-600 rad); and very severe injury, 6 to 8 Gy (600-800 rad). Lymphocyte depletion kinetics can be used to predict the speed at which granulocyte counts will drop, in particular neutrophils or the absolute neutrophil count (ANC). With large whole-

Radiation Factors	
Dose	
Dose rate	
Volume of tissue irradiated	
Type and quality of radiation	
Patient Factors	
Presence of other medical conditionsa (eg, homozygosity for ataxia telangiectasia mutation gene, autoimmune disease, diabetes [although some debate exists], previous history of diagnostic or therapeutic irradiation)	
Individual susceptibility	
Age	

Figure 1.

Factors other than cellular radiosensitivity that may determine the effects of ionizing radiation.

body doses, usually greater than 2 Gy (200 rad), which cause damage to bone marrow, the ANC drops to its nadir in 1 to 2 weeks. The damage to hematologic precursor cells results in progressive neutropenia, thrombocytopenia, and anemia as doses increase. However, these effects are usually not seen in the first 72 hours.¹¹

Platelets and RBCs are more radioresistant because they are terminally differentiated, have no nuclei, and are therefore not mitotically active. It is their precursor cells in the marrow that are sensitive to IR, but because of their life cycle, thrombocytopenia and anemia may not manifest for weeks. Therefore, infusions of platelets or packed RBCs are not required in the first 72 hours unless they are needed to maintain hemostasis and oxygen delivery owing to blood loss and ongoing hemorrhage from concomitant trauma. However, if the patient's estimated dose is greater than 2 Gy, HLA antigen typing should be performed as soon as possible (e-mail communication, W. Navarro, MD, May 2011). Further, if the patient's dose is greater than 2 Gy, colony-stimulating factors (CSFs), filgrastim (a granulocyte CSF), or sargramostim (a granulocyte-macrophage CSF) should be started as

soon as possible,¹² as should prophylactic antimicrobial drugs. As the patient becomes more neutropenic (<500 cells/mm³), and especially with profound neutropenia (<100 cells/mm³), a careful search for any infection should be conducted and specific foci of infection treated adequately. Serologic testing should be done immediately for herpes simplex virus and cytomegalovirus. If the patient has a positive history of either of these infectious diseases, prophylaxis should be initiated with acyclovir or ganciclovir, respectively. Other antimicrobial drugs should be considered for *Candida* and resistant species of *Candida*, as well as *Aspergillus* and *Pneumocystis jirovecii*. Recommendations may be found in the Infectious Disease Society of America guidelines for febrile neutropenic patients.¹³ Consultation with an infectious disease specialist should always be considered.¹³ The World Health Organization (WHO) Consultancy gives a weak evidence-based recommendation for prophylaxis with a fluoroquinolone.^{12,13} *Streptococcus viridans* bacteremia is another potential infectious disease in these patients. Clinically, patients may exhibit infection, petechiae, epistaxis, bleeding from gums, and hemorrhage. The bone marrow will show aplastic anemia, almost void of cells. Consultation with hematopathology or a bone marrow transplant center such as the Radiation Injury Treatment Network should be considered. Dainiak et al¹² provide an excellent review of recommendations for the use of cytokines and stem cell transplants for the nonhematopathologist.¹²

GI Subsyndrome

The classic presentation of GI ARS is seen at doses greater than 5 to 6 Gy. The initial nausea and emesis of the prodrome are believed by some authorities to be caused centrally.⁷ Regardless, classic GI ARS results from a denuding of the GI epithelium on the intestinal villi. The small intestinal epithelial stem cells reside in GI crypts between microvilli. These crypt cells mature during 7 to 14 days and, as they mature, move toward the tips of the microvilli at the intestinal lumen where they

Table 1.
Acute Radiation Syndrome:
Presence of Emesis May Be Used
as an Initial Indicator of Dose

Time to Emesis, ^a h	Approximate Dose, Gy
<1	4-6
1-2	2-4
>2	<2

^a Time to emesis should only be used as an approximation. It must be validated by lymphocyte depletion kinetics and other biodosimetry methods. Physicians should be aware of possible confusion with psychogenic origin, such as anxiety and fear.

Source: Table VIII. In: International Atomic Energy Agency (IAEA). *Diagnosis and Treatment of Radiation Injuries*. Vienna, Austria: IAEA; 1998:7. *IAEA Safety Reports Series #2*.

will eventually slough off as intestinal contents move across the microvilli. Disorganization occurs as the stem cells try to continue to replace these cells after exposure to IR, resulting in malabsorption, dehydration, diarrhea, translocation of bacteria, bleeding, occasional hematemesis, hematochezia, fluid and electrolyte shifts, hypovolemia, ileus, and renal failure. These sequelae may cause cardiovascular collapse.³ Similar to hematopoietic ARS, the higher the dose, the faster the onset and more severe the symptoms. The WHO Consultancy gives weak evidence-based recommendations, including fluoroquinolone 2 to 4 days after exposure; selective digestive decontamination; prophylaxis with 5HT3 antagonists for estimated exposures greater than 2 Gy; loperamide for diarrhea; enteral nutrition; and prophylaxis with H2 blockers or proton pump inhibitors.¹⁴

Neurovascular Subsyndrome

Neurovascular changes are believed by some to begin early and at low doses.⁵ The classic picture of neurovascular ARS is seen with doses higher than 10 Gy.¹⁵ The timing and severity are dose dependent. The WHO Consultancy lists strong evidence-based recommendations for supportive care, including 5HT3 antagonist, man-

nitol, furosemide, and analgesics.¹⁴ Acute whole-body radiation doses sufficient to cause neurovascular ARS are considered lethal.¹⁴ Historically, patients with signs and symptoms of neurovascular ARS caused by a whole-body radiation dose greater than 10 Gy have survived only a few days after exposure, although there are exceptions.¹⁵ Symptoms of neurovascular ARS include nausea, vomiting, headache, lethargy, irritability, cognitive dysfunction, ataxia, seizures, dysarthria, disorientation, prostration, cerebral edema, and hypotension. Cerebral signs and symptoms begin quickly and may progress too rapidly for a latent phase to develop. At the higher doses, patients may die before signs and symptoms of hematopoietic ARS and GI ARS appear.

Delayed effects of acute radiation exposure that are still considered to be deterministic include late organ effects, such as vascular changes, fibrosis, atrophy, thyroid dysfunction, cataracts, and infertility. The probability of a cancer forming is based on chance and is therefore a stochastic effect. For stochastic effects, as the radiation dose increases, the probability of a cancer developing increases, but the cancer itself does not become “worse.”

Biodosimetric and Multiparameter Dose Estimation

As soon as possible after a radiologic incident, it is important to involve a health or medical physicist familiar with performing incident recreations, which can estimate the radiation dose sustained and thereby guide patient treatment.

An early study by the National Aeronautics and Space Administration performed at Oak Ridge Associated Universities evaluated the radiation dose dependence of the prodromal symptoms of anorexia, nausea, and vomiting.¹⁶ From this work, the effective doses needed to produce a 50% incidence of symptoms were found to be 1.08 Gy for anorexia, 1.58 Gy for nausea, and 2.40 Gy for emesis. A clear trend has been noted whereby the time to emesis decreases with increasing

Table 2.
Classic Presentations of Acute Radiation Syndrome
Subsyndromes at Various Dose Thresholds

Radiation Dose	Signs and Symptoms	Exposure to Presentation, Time
5 rem	Chromosome aberrations first seen	30 min
12 rem	Reduction in sperm count	42 ds
0.75 Gy (75 rad)	Lymphocyte depletion	6 h
1 Gy (100 rad)	Nausea, vomiting	6 h, then 5-7 d
1-6 Gy (100-600 rad)	Hematopoietic syndrome	1-6 h
3 Gy (300 rad)	Temporary epilation	14 d
6 Gy (600 rad)	Erythema	6-48 h, then 2-3 wk
	Pneumonitis	4-6 wk
	Pulmonary syndrome (pulmonary fibrosis, ARDS)	1-6 mo
6-8 Gy (600-800 rad)	Gastrointestinal syndrome	3-4 d
9-10 Gy (900-1000 rad)	Death	Days to weeks
>10 Gy (>1000 rad)	Neurovascular syndrome	Hours to days

Abbreviation: ARDS, acute respiratory distress syndrome.

dose. In addition, a quantitative method to calculate available time to emesis has been published,¹⁷ and analysis of the sensitivity and specificity of the time to emesis as a sole parameter has also been reported.¹⁸ This method is a useful tool, especially in an environment where other methods of testing are not available.

When evaluating patients suspected of sustaining a high radiation dose, serial CBC counts with WBC differentials are needed to evaluate the dose-dependent lymphocyte depletion seen at doses greater than 1 Gy. In the early phase of hematopoietic ARS, neutrophils (N) usually increase, owing to a systemic stress response and resultant demargination from blood vessels, and lymphocytes (L) decrease. The ratio between numbers of N and numbers of L is pertinent for biodosimetric purposes. For initial triage of a patient suspected of having a clinically high radiation dose, the quantity $R = N/L \pm$ is determined, where N is the ANC, L is the ALC, and R is calculated as

the ratio of percentages of 2 cell lines in the CBC count and WBC differential. In a healthy control group of 225 participants, the ratio N/L would be 2.21 ± 0.03 . The question regarding emesis is scored 2 points if yes and 0 points if no. From a preliminary analysis, this test has been found to be generally valid for doses greater than 1 Gy more than 4 hours postincident. A rise in the N/L ratio may be used as another early biological indicator in a radiation incident, generally elevated from the baseline of 2.21 ± 0.05 ($n = 150$ normal controls) within 4 hours postincident and for a dose greater than 1 Gy when nausea is not considered.¹⁹⁻²²

In addition to time to emesis (a clinical biodosimetric parameter) and lymphocyte depletion kinetics (a laboratory biodosimetric parameter),^{22,23} other laboratory parameters can be effective determinants. Serum amylase will be notably elevated if the head and neck area is involved in the irradiated field²⁴ or there is severe abdom-

inal trauma with pancreatic injury. C-reactive protein, as an acute-phase reactant, has been shown in animal studies to be substantially elevated soon after a clinically significant radiation dose.^{17,25,26} Goans et al^{10,11} presented a prediction algorithm to estimate effective whole-body dose within 8 to 12 hours after moderate- and high-level gamma incidents and after criticality accidents. Those authors developed this algorithm to provide health physicists and diagnosing physicians an early approximation of radiation dose so that cytokine therapy, if indicated, could begin early.

Although there is not a consensus, some laboratory investigators have suggested that serial serum citrulline levels be drawn initially after a radiation exposure incident and then weekly thereafter. Elevations of serum citrulline levels as a measure of enteric biomass have been conducted in humans undergoing radiation therapy, and the molecule has been measured in casualties of radiation incidents. As the GI mucosa sloughs, enteric biomass and serum citrulline level decrease.²⁷

The criterion standard for biodosimetry is the cytogenetic dicentric assay.^{22,28} This technique looks for radiation-induced chromosomal aberrations, called dicentrics. These dicentrics—1 cell that has a chromosome without a centromere and 1 cell that has 2 centromeres—result from the misrepair that occurs during the cell cycle. One limitation of this test is that it relies on using lymphocytes; with doses greater than 5 Gy, there will not be enough lymphocytes to sample. Another similar method of biodosimetry looks for the formation of micronuclei caused by IR. This formation of an extra body from the nucleus is caused by either breaks in the chromosome or by the “lagging” behind of the chromosome during mitosis.²⁹ Both dicentric assay and micronuclei formation assessment have been validated and are enhanced by a technique called premature chromatin condensation. This assay studies the breakage and repair of IR-induced chromosome damage³⁰ and shows potential as an excellent adjunct to dicentric assay and micronuclei formation assessment for doses greater than 5 Gy.^{30,31} Another

promising technique being developed is the γ -H2AX assay, which looks for phosphorylated histone particles released from double-stranded DNA breaks.^{7,30} There is consensus that a multiparameter approach is the most beneficial in assessing dose.

Case Conclusion

Over the next few weeks, more than 112,000 people in Goiânia were monitored for possible ¹³⁷Cs contamination. Of those, 249 persons were externally contaminated and 46 were internally contaminated. The 46 patients with internal contamination were all given oral Prussian Blue, a specific antidote for internal contamination with radioactive cesium. Eleven had already been admitted to the General Hospital of Goiânia, but that hospital did not have the resources to handle the number of patients needing such a high level of care. The most seriously ill were transferred to the Marcilio Dias Naval Hospital in Rio de Janeiro.

It is worth noting that a patient may be exposed to a radiation source but not be contaminated. This means that the patient received a dose but does not have radioactive materials on or in his or her body. Also, a patient who is contaminated with radioactive materials either on or in his or her body can receive a dose from this contamination and then spread it to other places and persons, as with the Goiânia incident. The goal when caring for a contaminated patient is to treat the patient first and then contain or clean up any external contamination, trying to minimize the spread of the material. The measures taken by the Goiânia General Hospital included dividing the ward into a controlled and a free area; limiting visitor stay-times; and prohibiting children and pregnant women from visiting. Furthermore, during the transport of patients, the seats, stretchers, and floors of the vehicles were covered with plastic sheeting (consider this measure as long as it is not a slip or trip hazard), and anyone involved with transporting or handling the patients wore protective gloves.³² When radioactive material has been

internalized (via ingestion, inhalation, absorption, injection, or in an open wound), the addition of medical countermeasures, such as Prussian Blue administration, helps decrease the internal burden and dose.

Whole-body counting on the hospital workers involved in the current case revealed negligible internal body damage.³⁴ Of the patients transferred to the Naval hospital, 4 died, including the 6-year-old girl who ate the ¹³⁷Cs-contaminated sandwich. Her intake was estimated to be approximately 27 mCi, the highest cesium intake ever recorded. The external dose sustained by the casualties in this case ranged from 1 to 7 Gy. All of these patients died of resistant *Klebsiella* species. Two female patients died of diffuse and severe hemorrhage to the GI tract and central nervous system, and 2 male patients died of hemorrhagic bronchopneumonias.^{33,34}

Conclusion

The recognition of radiation exposure, whether internal contamination exists, and a determination of the extent of dose is necessary for physicians to effectively treat patients after a radiation incident. Such a diagnosis generally requires the assistance of medical or health physicists. Physicians should use dose estimates to help guide their medical management. To manage medical care and reduce morbidity and mortality, they must be able to recognize IR injuries and illnesses and to understand that frank manifestations of ARS are usually delayed. As with most injuries and illnesses, a medical history is essential for appropriate diagnosis and management. For radiation injuries and illnesses, an incident history is just as important to help determine the extent, magnitude, and symmetry of exposures, which will also help direct medical management. Laboratory diagnostics play an important role in determining extent and magnitude of injury and illness and include serial CBC count with differential, baseline levels of serum amylase and serum citrulline, and cytogenetic biodosimetry as needed. Medical management should include symptomatic care, such as

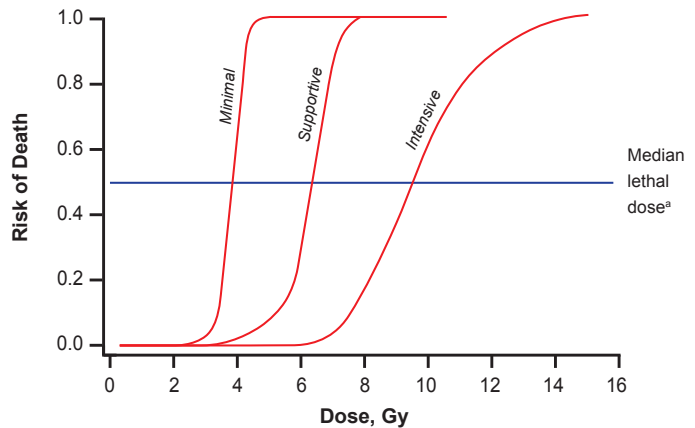


Figure 2. Ionizing radiation doses corresponding with risk of death by minimal, supportive, and intensive care received.
^a Median lethal dose results in fatalities in 50% of an untreated population within 60 days.

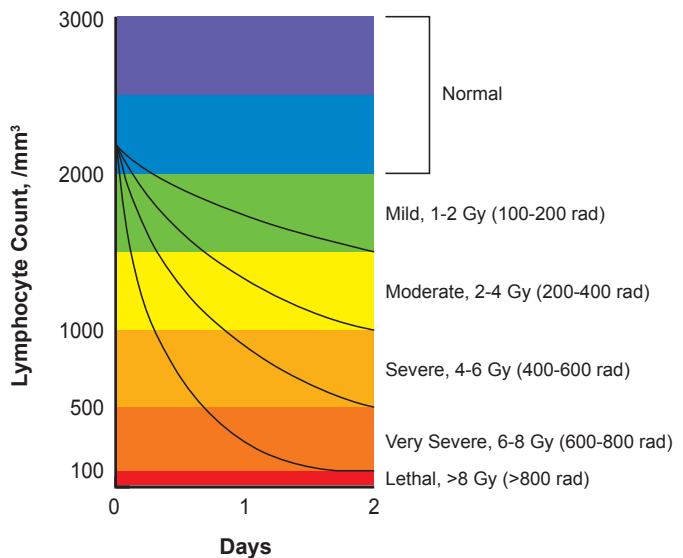


Figure 3. Absolute lymphocyte count is demonstrated by Andrews curves.

fluids; antiemetics; analgesics; blood products as needed for concomitant physical trauma or thermal burns, if present, and as needed for pancytopenia; cytokines to stimulate hematopoietic stem cells to divide, differentiate, and mature; and prophylactic and specific antimicrobials for prevention and management of infections. Hematopathology and infectious disease consultation is needed in most cases.

Author Contributions

Dr Christensen, Iddins, and Goans and Mr Glassman provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drs Christensen, Parrillo, and Goans and Mr Glassman drafted the article or revised it critically for important intellectual content; and Mr Glassman gave final approval of the version of the article to be published.

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