Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group

Jamie K. Waselenko, MD; Thomas J. MacVittie, PhD; William F. Blakely, PhD; Nicki Pesik, MD; Albert L. Wiley, MD, PhD; William E. Dickerson, MD; Horace Tsu, MD; Dennis L. Confer, MD; C. Norman Coleman, MD; Thomas Seed, PhD; Patrick Lowry, MD; James O. Armitage, MD; and Nicholas Dainiak, MD

Physicians, hospitals, and other health care facilities will assume the responsibility for aiding individuals injured by a terrorist act involving radioactive material. Scenarios have been developed for such acts that include a range of exposures resulting in few to many casualties. This consensus document was developed by the Strategic National Stockpile Radiation Working Group to provide a framework for physicians in internal medicine and the medical subspecialties to evaluate and manage large-scale radiation injuries.

Individual radiation dose is assessed by determining the time to onset and severity of nausea and vomiting, decline in absolute lymphocyte count over several hours or days after exposure, and appearance of chromosome aberrations (including dicentrics and ring forms) in peripheral blood lymphocytes. Documentation of clinical signs and symptoms (affecting the hematopoietic, gastrointestinal, cerebrovascular, and cutaneous systems) over time is essential for triage of victims, selection of therapy, and assignment of prognosis.

Recommendations based on radiation dose and physiologic response are made for treatment of the hematopoietic syndrome. Therapy includes treatment with hematopoietic cytokines; blood transfusion; and, in selected cases, stem-cell transplantation. Additional medical management based on the evolution of clinical signs and symptoms includes the use of antimicrobial agents (quinolones, antiviral therapy, and antifungal agents), antiemetic agents, and analgesic agents. Because of the strong psychological impact of a possible radiation exposure, psychosocial support will be required for those exposed, regardless of the dose, as well as for family and friends. Treatment of pregnant women must account for risk to the fetus. For terrorist or accidental events involving exposure to radioiodines, prophylaxis against malignant disease of the thyroid is also recommended, particularly for children and adolescents.

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For author affiliations, see end of text.

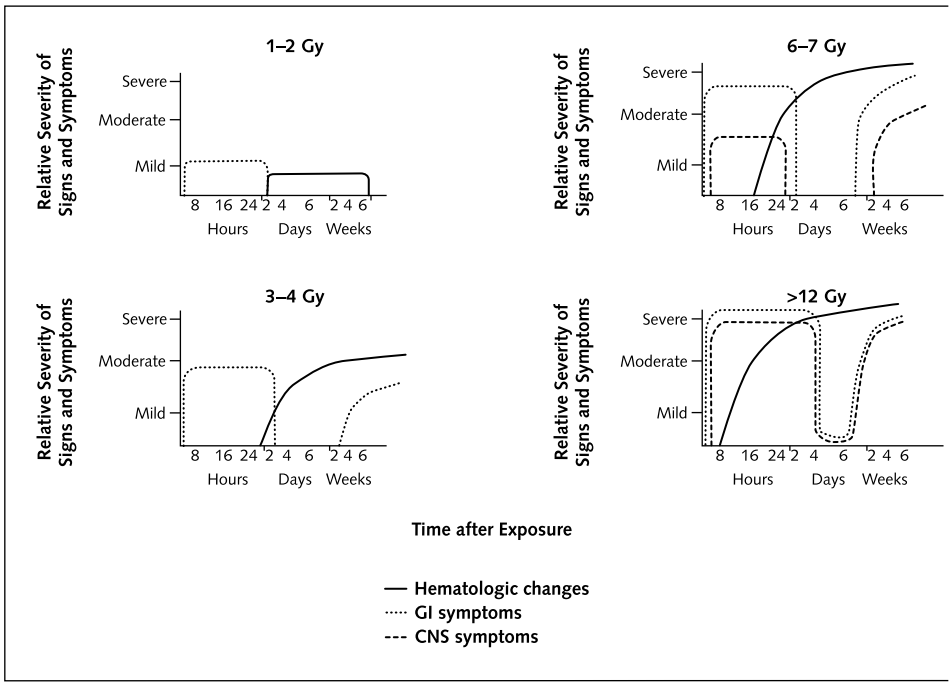
The events of September 11, 2001, confirmed the vulnerability of the United States and other nations to acts of terrorism. While our ability to react to and treat victims of biological terrorism has significantly improved, a terrorist event involving radioactive material remains a threat for which improved preparation is requisite. Several international conferences on treatment of acute radiation injury have been held in the past 2 decades (1–8). The conclusions of these conferences, together with mounting preclinical data showing the benefit of early cytokine use in combination with aggressive clinical support in irradiated animals (9–13), provide valuable information to clinicians faced with treating the acute radiation syndrome.

Scenarios for terrorist acts involving radioactive material have been developed, some of which indicate that mass casualties can occur. However, little information is currently available in the medical literature concerning guidelines for the medical management of large-scale, complex radiation injuries, such as those that might occur in an urban area (14–17). Therefore, this consensus document was created to help physicians who may be involved in evaluation, triage, or medical management of victims with acute radiation injury.

Methods

The Strategic National Stockpile (SNS) convened the SNS Radiation Working Group (Appendix, available at www.annals.org) to address issues of medical management and stockpiling of pharmaceutical agents in case of a significant radiologic event. Participants were selected on the basis of their established expertise in the field. The deliberations of the SNS Radiation Working Group during a series of 4 consensus meetings beginning in August 2002 and 4 additional conference calls were used as a basis to create this document. The group reviewed the available information for cases recorded in the radiation accident registries maintained by the Radiation Emergency Assistance Center/Training Site (REAC/TS), Oak Ridge, Tennessee, and the University of Ulm, Germany (6). This information was supplemented by outcomes of clinical management and therapy for cases reported in the scientific literature. Since no prospective, controlled clinical trials have been conducted in patients with acute radiation injury, the SNS Radiation Working Group reviewed management strategies used in accidental exposures of humans and evaluated results of prospective, controlled studies of acutely irradiated animals. In some cases, recommendations for therapy are based on results of animal studies. For radiologic terrorism events, definitive studies are required in animals to demonstrate impact on mortality and other clinical end points, according to requirements for licensure under the U.S. Food and Drug Administration's Animal Rule. In cases where the members of the SNS Radiation Working Group failed to achieve consensus, the alternatives are presented with relevant reference to the published

Figure 1. **Approximate time course of clinical manifestations.**



Shown are approximate times for hematopoietic, gastrointestinal (*GI*), and central nervous system (*CNS*) symptoms at different ranges of dose of whole-body radiation for exposed, living persons. Hematopoietic changes include development of lymphopenia, granulocytopenia, or thrombocytopenia. Gastrointestinal symptoms include headache, nausea, vomiting, or diarrhea. Cerebrovascular signs and symptoms include headache, impaired cognition, disorientation, ataxia, seizures, prostration, and hypotension. Note that the signs and symptoms of different organ systems significantly overlap at each radiation dose and that cerebrovascular symptoms do not appear until exposure to a high whole-body dose. The relative severity of signs and symptoms is measured on an arbitrary scale. Prepared from data in reference 16.

literature. The Centers for Disease Control and Prevention provided funding to some of the participants for attendance at meetings. This support played no role in the composition, deliberations, or report of the SNS Radiation Working Group. Because new approaches to individual biodosimetry and therapy that will apply to treatment of acutely irradiated persons are likely to emerge, the SNS Radiation Working Group will review scientifically based guidance annually.

Defining the Threat and Public Health Response

The lethality of a nuclear device was demonstrated when a 15-kiloton improvised nuclear device was detonated over Hiroshima, Japan, in 1945, resulting in approximately 150 000 casualties and 75 000 fatalities (18). Virtually all survivors of Hiroshima had estimated exposure of less than 3 Gy (19). Recent review of data suggests that the mean lethal dose of radiation required to kill 50% of humans at 60 days ($LD_{50/60}$) of whole-body radiation is between 3.25 Gy and 4 Gy in persons managed without supportive care and 6 to 7 Gy when antibiotics and transfusion support are provided (20).

Although most radiation injuries in the past 50 years have been due to accidents, society must be prepared for the intentional detonation of nuclear or radiologic devices. Modern nuclear threats can be divided into 5 general categories: 1) an attack on nuclear power plants, 2) a malevolent act using simple radiologic devices, 3) terrorist use of a radiologic dispersal device or "dirty bomb," 4) detonation of an improvised nuclear device, and 5) detonation of a sophisticated nuclear weapon (21). Whereas incidents involving simple devices and radiologic dispersal devices would probably cause a limited number of casualties, those involving improvised nuclear devices and small nuclear weapons would result in mass casualties.

The Joint Commission on Accreditation of Healthcare Organizations and government leaders have mandated that the health care system develop plans to prepare for response to a radiologic terrorist event. The Hospital Emergency Incident Command System (22) provides a command and coordination approach that is useful for radiation response planning. Emergency plans should clarify authority, command, and control; define organizational responsibilities; develop procedures that integrate efforts of all response agencies; identify logistic support, supplies, and equipment; and assess incident conditions and consequences (23). Given the devastation that would accompany a nuclear detonation, plans should incorporate contingency planning for significant loss of infrastructure and health care personnel in the radiation field and its environs. Contingency planning should include relocation of victims to nearby operational hospitals and medical centers and acti-

vation of regional and state disaster plans that are coordinated with federal agencies. Approaches to radiologic monitoring, triage, and therapy for exposed populations will vary, depending on the number of casualties and resources available on the scene and in emergency treatment centers and hospitals. Although disaster planning is beyond the scope of this document, it is hoped that this clinical guideline defines a need for formalization and coordinated testing of such plans by hospitals and government agencies (see www.ncrp.com).

Barriers to the provision of optimal medical care include limitation of resources, loss of infrastructure, a high volume of victims, and presence of combined injury. Allocation of potentially limited resources should be determined by the number of victims and their long-term prognosis. Estimation of individual radiation dose is recommended for determining survivability of patients in a range of doses that indicate predisposition to the acute radiation syndrome. Treatment recommendations are based on this dose range, which becomes increasingly narrower as the number of casualties increases and with the occurrence of combined injuries.

Essentials of Radiation Exposure and Injury

Radiation injury can occur from external irradiation; external contamination with radioactive materials; and internal contamination by inhalation, ingestion, or transdermal absorption with incorporation of radiologic materials into the body's cells and tissues. These 3 types of exposure can occur in combination and can be associated with thermal burns and traumatic injuries.

Injury from a nuclear detonation varies, depending on the location of the victim relative to the hypocenter and the consequent exposure to different types of energy. Three forms of energy are released from a nuclear detonation: heat, accounting for approximately 35% of total energy; shock or bomb blast, accounting for approximately 50% of total energy; and radiation, accounting for the remaining 15% of total energy. Heat and light cause thermal injury, including flash burns, flame burns, flash blindness (due to temporary depletion of photopigment from retinal receptors), and retinal burns. The blast wave results in fractures, lacerations, rupture of viscera, and pulmonary hemorrhage and edema. Radiation causes the acute radiation syndrome; cutaneous injury and scarring; chorioretinal damage from exposure to infrared energy; and, depending on radiation dose and dose rate, increased long-term risk for cancer, cataract formation (particularly with neutron irradiation), infertility, and fetal abnormalities (that is, growth retardation, fetal malformations, increased teratogenesis, and fetal death). We refer the reader to several excellent in-depth reviews of radiation effects (21, 23–25).

The Acute Radiation Syndrome

Studies in animals and humans exposed to radiation have allowed researchers to describe the acute radiation syndrome, also known as radiation sickness. The acute radiation syndrome occurs after whole-body or significant partial-body irradiation of greater than 1 Gy delivered at a relatively high-dose rate. The most replicative cells are the most sensitive to the acute effects of radiation, particularly spermatocytes, lymphohematopoietic elements, and intestinal crypt cells. The inherent sensitivity of these cells results in a constellation of clinical syndromes that predominates within a predictable range of doses of whole-body or significant partial-body exposure. Clinical components of the acute radiation syndrome include the hematopoietic, gastrointestinal, and cerebrovascular syndromes. The time course and severity of clinical signs and symptoms for the component syndromes at different dose ranges are reviewed in **Figure 1**. Each syndrome can be divided into 4 phases: prodromal, latent, manifest illness, and recovery or death.

Depending on the absorbed dose, symptoms appear within hours to weeks, following a predictable clinical course. The *prodromal phase* of the acute radiation syndrome usually occurs in the first 48 hours but may develop up to 6 days after exposure. The *latent phase* is a short period characterized by improvement of symptoms, as the person appears to have recovered. Unfortunately, this effect is transient, lasting for several days to a month. Symptoms of *manifest illness* then appear and may last for weeks. This stage is characterized by intense immunosuppression and is the most difficult to manage. If the person survives this stage, recovery is likely. Individuals exposed to a supralethal dose of radiation may experience all of these phases

Table 1. **Phases of Radiation Injury***

Dose Range, *Gy*	Prodrome	Manifestation of Illness	Prognosis (without Therapy)
0.5–1.0	Mild	Slight decrease in blood cell counts	Almost certain survival
1.0–2.0	Mild to moderate	Early signs of bone marrow damage	Highly probable survival (>90% of victims)
2.0–3.5	Moderate	Moderate to severe bone marrow damage	Probable survival
3.5–5.5	Severe	Severe bone marrow damage; slight GI damage	Death within 3.5–6 wk (50% of victims)
5.5–7.5	Severe	Pancytopenia and moderate GI damage	Death probable within 2–3 wk
7.5–10.0	Severe	Marked GI and bone marrow damage, hypotension	Death probable within 1–2.5 wk
10.0–20.0	Severe	Severe GI damage, pneumonitis, altered mental status, cognitive dysfunction	Death certain within 5–12 d
20.0–30.0	Severe	Cerebrovascular collapse, fever, shock	Death certain within 2–5 d

* Modified from Walker RI, Cerveny RJ, eds. (21). GI = gastrointestinal.

over a period of hours, resulting in early death. **Table 1** summarizes these responses as a function of dose delivered at a high exposure rate.

The Hematopoietic Syndrome

Irradiation of bone marrow stem and progenitor cells at increasing doses results in exponential cellular death (21). The hematopoietic syndrome is seen with significant partial-body or whole-body radiation exposures exceeding 1 Gy and is rarely clinically significant below this level (21). Mitotically active hematopoietic progenitors have a limited capacity to divide after a whole-body radiation dose greater than 2 to 3 Gy (26). In the ensuing weeks after exposure, a hematologic crisis occurs, characterized by hypoplasia or aplasia of the bone marrow. These changes result in pancytopenia predisposition to infection, bleeding, and poor wound healing, all of which contribute to death.

While most bone marrow progenitors are susceptible to cell death after sufficiently intense radiation doses, subpopulations of stem cells or accessory cells are selectively more radioresistant, presumably because of their largely noncycling (Go) state (27, 28). These radioresistant cells may play an important role in recovery of hematopoiesis after exposure to doses as high as 6 Gy, albeit with a reduced capacity for self-renewal (29). Another critical determinant for reconstitution is inhomogeneity of the dose with sparing of marrow sites that become foci of hematopoietic activity (Appendix, available at www.annals.org).

Lymphopenia is common and occurs before the onset of other cytopenias. A predictable decline in lymphocytes occurs after irradiation. In fact, a 50% decline in absolute lymphocyte count within the first 24 hours after exposure, followed by a further, more severe decline within 48 hours, characterizes a potentially lethal exposure. The predictability of the rate of lymphocytic depletion count has led to the development of a model using lymphocyte depletion kinetics as an element of biodosimetry (30, 31). Patients with burns (32–34) and trauma (35) may develop lymphopenia as a result of these injuries alone. Although currently available predictive models based on absolute lymphocyte count have been validated (and include patients with these injuries), it is important to examine more than one element of biodosimetry whenever possible.

The onset of other cytopenias varies, depending on both dose and dose rate (36). Granulocyte counts may transiently increase before decreasing in patients with exposure to less than 5 Gy (36) (**Appendix Figure 2**, available at www.annals.org). This transient increase before decline, termed an *abortive rise*, may indicate a survivable exposure.

Additional injuries, such as mechanical trauma or burns (the combined injury syndrome), are expected to occur in 60% to 70% of patients after detonation of an improvised nuclear device (19, 21). These injuries significantly complicate the management of patients with the hematopoietic syndrome and significantly lower the $LD_{50/60}$. Prognosis is grave in patients with the combined injury syndrome and radiation exposure (31).

The Gastrointestinal Syndrome

Radiation induces loss of intestinal crypts and breakdown of the mucosal barrier. These changes result in abdominal pain, diarrhea, and nausea and vomiting and predispose patients to infection. At doses exceeding 12 Gy, the mortality rate of the gastrointestinal syndrome exceeds that of the hematopoietic syndrome. Severe nausea, vomiting, watery diarrhea, and cramps occur within hours after high-dose (>10 Gy) irradiation. This is followed by a latent period lasting 5 to 7 days, during which symptoms abate. Vomiting and severe diarrhea associated with high fever make up the manifest illness. Systemic effects may include malnutrition from malabsorption; bowel obstruction from ileus; dehydration, cardiovascular collapse, and electrolyte derangements from fluid shifts; anemia from damage to the intestinal mucosa and microcirculation and subsequent gastrointestinal bleeding; and sepsis and acute renal failure (21).

The Cerebrovascular Syndrome

The cerebrovascular syndrome is less well defined than other syndromes, and its stages are compressed. Individuals presenting with fever, hypotension, and major impairment of cognitive function will most likely have had a supralethal exposure (26). These symptoms may be observed in those receiving more than 20 to 30 Gy of radiation (21). The prodromal phase is characterized by disorientation, confusion, and prostration and may be accompanied by loss of balance and seizures. The physical examination may show papilledema, ataxia, and reduced or absent deep tendon and corneal reflexes. During the latent period, apparent improvement occurs for a few hours and is followed by severe manifest illness. Within 5 to 6 hours, watery diarrhea, respiratory distress, hyperpyrexia, and cardiovascular shock can occur. This rapid decline mimics the clinical course of acute sepsis and septic shock, both of which must be considered. The ensuing circulatory complications of hypotension, cerebral edema, increased intracranial pressure, and cerebral anoxia can bring death within 2 days.

The Cutaneous Syndrome

Cutaneous injury from thermal or radiation burns is characterized by loss of epidermis and, at times, dermis. Injuries to the skin may cover small areas but extend deeply into the soft tissue, even reaching underlying muscle and bone (37). They may be accompanied by profound local edema and place the patient at risk for a compartment syndrome. Patients presenting with burns immediately after exposure have thermal rather than radiation burns. Significant injuries to the integument decrease the $LD_{50/60}$ and amplify the risk for death at any radiation exposure dose. Patients with the hematopoietic syndrome have a more complicated course of the cutaneous syndrome as a result of bleeding, infection, and poor wound healing (37). For a more thorough discussion, readers are directed to

Table 2. **Grading System for Response of Neurovascular, Gastrointestinal, and Cutaneous Systems***

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Neurovascular system				
Nausea	Mild	Moderate	Intense	Excruciating
Vomiting	Occasional (once per day)	Intermittent (2–5 times per day)	Persistent (6–10 times per day)	Refractory (>10 times per 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 beats/min; blood pressure >100/170 mm Hg	Blood pressure <100/70 mm Hg	Blood pressure <90/60 mm Hg; transient	Blood pressure <80/? mm Hg; persistent
Neurologic deficits†	Barely detectable	Easily detectable	Prominent	Life-threatening, loss of consciousness
Cognitive deficits†	Minor loss	Moderate loss	Major impairment	Complete impairment
Gastrointestinal system				
Diarrhea				
Frequency, stools/d	2–3	4–6	7–9	≥10
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Persistent with large amount
Abdominal cramps or pain	Minimal	Moderate	Intense	Excruciating
Cutaneous system				
Erythema§	Minimal, transient	Moderate (<10% body surface area)	Marked (10%–40% body surface area)	Severe (>40% body surface area)
Sensation or itching	Pruritus	Slight and intermittent pain	Moderate and persistent pain	Severe and 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

* Modified from Fliedner TM, Friesecke I, Beyrer K (39). ADL = activity of daily living.
† Reflex status (including corneal reflexes), papilledema, seizures, ataxia, and other motor signs or sensory signs.
‡ Impaired memory, reasoning, or judgment.
§ The extent of involvement is decisive and should be documented for all skin changes.

excellent reviews on the acute radiation syndrome with the cutaneous syndrome (37, 38).

Management

Table 2 summarizes the clinical responses for all of these syndromes, and **Table 3** presents a grading system based on severity of hematologic change. The presence of nausea, vomiting, fatigue, and anorexia may indicate exposure to a significant radiation dose, particularly if onset is within hours of exposure. The physical examination should focus on documentation of vital signs (presence of fever, hypotension, and orthostasis), skin examination (erythema, blistering, onycholysis, edema, desquamation, and petechiae), neurologic examination (presence of motor or sensory deficits, papilledema, ataxia, and assessment of mental status and cognition), and abdominal examination (presence of pain or tenderness).

PSYCHOLOGICAL IMPACT OF RADIATION EXPOSURE

Psychosocial issues must be addressed in the potentially exposed population (40). Since a primary objective of terrorism is to elicit psychological shock, many persons requiring medical treatment will develop psychosocial symptoms even in the setting of no radiation exposure or

Table 3. **Levels of Hematopoietic Toxicity***

Symptom or Sign	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes†	$\geq 1.5 \times 10^9$ 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‡	$\geq 2 \times 10^9$ 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§	$\geq 100 \times 10^9$ 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

* Modified from Dainiak N (24).
† Reference value, $1.4–3.5 \times 10^9$ cells/L.
‡ Reference value, $4–9 \times 10^9$ cells/L.
§ Reference value, $140–400 \times 10^9$ cells/L.

Table 4. **Mass Casualty Scenario for a Nuclear Detonation***

Patient Category	Radiation Dose, *Gy*	Patients, *n*	
		1-kiloton Detonation	10-kiloton Detonation
Combined injuries (minimal to intensive care)	All doses	1000–3000	15 000–24 000
Immediate fatalities	All doses	>7000	>13 000
Radiation fallout			
Expectant care	≥10	18 000	45 000
Intensive care	5–10	19 500	79 400
Critical care	3–5	33 000	108 900
Normal care	1–3	66 000	70 000
Ambulatory monitoring	0.5–1	82 500	139 000
Epidemiologic monitoring	0.25–0.5	106 000	147 000
Monitoring for psychosocial well-being without other injury	<0.25	>150 000	>270 000

* The table depicts projected casualty estimates based on a 1- or 10-kiloton detonation. Assumptions include a city with a population of 2 million people and casualties estimated on the basis of the Hazard Prediction Assessment Capability Program (HPAC), version 3.21 (Defense Threat Reduction Agency, Fort Belvoir, Virginia). Combined injuries consist of radiation injuries in addition to burns or blunt trauma.

very-low-dose exposure. Accordingly, terrorists will exploit an inherent, widespread fear of radiation by the general public to achieve a psychological effect.

Approximately 75% of individuals exposed to nuclear weapon detonations exhibit some form of psychological symptoms, ranging from inability to sleep to difficulty concentrating and social withdrawal (21). Among those at highest risk for significant psychological effects are children, pregnant women, mothers of young children, participants in radiation cleanup, and people with a medical history of a psychiatric disorder (41–43). In addition, exposed individuals and their families and friends have a high rate of post-traumatic stress disorder (44). Symptoms associated with post-traumatic stress disorder include anxiety disorders, depression, and a recurrent sense of re-experiencing the traumatic event. Individuals may exhibit outbursts of anger, an exaggerated startle response, and increased irritability. Post-traumatic stress disorder can be diagnosed when these symptoms persist for more than 1 month (45).

To assess the potential impact on the response system of persons with little or no radiation exposure, we generated a scenario for 1-kiloton and 10-kiloton nuclear detonations (**Table 4**). The number of individuals without exposure (that is, <0.25 Gy) who require psychosocial support is far greater than the number of patients who would be physically injured (**Table 4**). Expeditious triage of the former victims is essential and provision of appropriate treatment in the ambulatory setting is required so that those with survivable injuries can receive supportive care.

Biological Dosimetry

Individual biodosimetry is essential for predicting the clinical severity, treatment, and survivability of exposed individuals and triaging those with minimal or no exposure. The 3 most useful elements for calculating the exposure dose are time to onset of vomiting, lymphocyte depletion kinetics, and the presence of chromosome dicentrics. A radiation casualty management software program, the Biological Assessment Tool, is available at the Armed Forces Radiobiology Research Institute's Web site (www.afrri.usuhs.mil). This tool was developed in collaboration with REAC/TS and others to facilitate medical recording and estimation of individual dose (46). In addition, the International Atomic Energy Agency has developed generic guidelines for recording clinical signs and symptoms for victims of a radiation incident (see www.iaea.org). Using a grading system for the severity of clinical signs and symptoms, the Medical Treatment Protocols team has also developed a quantitative system to assess individual biological response to radiation exposure when results of chromosomal analysis are not yet available (39).

Prodromal signs and symptoms must be recorded throughout the course of medical management after a radiation exposure. Body location of radioactivity and thermal and traumatic injuries, and the degree of erythema, must be recorded on medical cards or flow charts that document signs and symptoms as a function of time after exposure. Dose estimates derived from the use of personnel dosimeters (if available) or other radiation monitoring devices must be recorded as well. These data may then be entered into the Biological Assessment Tool (or similar recording devices) at set triage stations so that an exposure dose can be estimated and the patient can be triaged accordingly.

The rate of decline and nadir of the absolute lymphocyte count over the initial 12 hours to 7 days after exposure is a function of cumulative dose (47). Lymphocyte depletion kinetics predict dose assessment for a photon-equivalent dose range between 1 and 10 Gy with an exposure resolution of approximately 2 Gy. Ideally, a complete blood cell count with leukocyte differential should be obtained immediately after exposure, 3 times per day for the next 2 to 3 days, and then twice per day for the following 3 to 6 days. However, this will require that deployable hematology laboratory capabilities be established and exercised for potential mass-casualty scenarios. It is recommended that 6 (and a minimum of 3) complete blood

Table 5. **Biodosimetry Based on Acute Photon-Equivalent Exposures***

Dose Estimate	Victims with Vomiting	Time to Onset of Vomiting	Absolute Lymphocyte Count†						Rate Constant for Lymphocyte Depletion‡	Dicentrics in Human Peripheral Blood Lymphocytes§	
			Day 0.5	Day 1	Day 2	Day 4	Day 6	Day 8		Per 50 Cells	Per 1000 Cells
Gy	*%*	*h*	←			*×10⁹ cells/L*		→	*k*‡	*n*	
0	–	–	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	–	0.05–0.1	1–2
1	19		**2.30**	**2.16**	**1.90**	**1.48**	1.15	0.89	0.126	4	88
2	35	4.63	**2.16**	**1.90**	**1.48**	0.89	0.54	0.33	0.252	12	234
3	54	2.62	**2.03**	**1.68**	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	**1.90**	**1.48**	0.89	0.33	0.12	0.044	0.504	35	703
5	86	1.27	**1.79**	1.31	0.69	0.20	0.06	0.020	0.63	51	1024
6	94	0.99	**1.68**	1.15	0.54	0.12	0.03	0.006	0.756		
7	98	0.79	**1.58**	1.01	0.42	0.072	0.012	0.002	0.881		
8	99	0.66	**1.48**	0.89	0.33	0.044	0.006	<0.001	1.01		
9	100	0.56	1.39	0.79	0.25	0.030	0.003	<0.001	1.13		
10	100	0.48	1.31	0.70	0.20	0.020	0.001	<0.001	1.26		

* Depicted above are the 3 most useful elements of biodosimetry. Dose range is based on acute photon-equivalent exposures. The second column indicates the percentage of people who vomit, based on dose received and time to onset. The middle section depicts the time frame for development of lymphopenia. Blood lymphocyte counts are determined twice to predict a rate constant that is used to estimate exposure dose. The final column represents the current gold standard, which requires several days before results are known. Colony-stimulating factor therapy should be initiated when onset of vomiting or lymphocyte depletion kinetics suggests an exposure dose for which treatment is recommended (see Table 7). Therapy may be discontinued if results from chromosome dicentrics analysis indicate a lower estimate of whole-body dose.
† Normal range, 1.4–3.5 × 10^9 cells/L. Numbers in boldface fall within this range.
‡ The lymphocyte depletion rate is based on the model $Lt = 2.45 \times 10^9$ cells/L × e − k(D)t, where *Lt* equals the lymphocyte count (×10^9 cells/L), 2.45 × 10^9 cells/L equals a constant representing the consensus mean lymphocyte count in the general population, *k* equals the lymphocyte depletion rate constant for a specific acute photon dose, and *t* equals the time after exposure (days).
§ Number of dicentric chromosomes in human peripheral blood lymphocytes.

counts with differential be obtained within the initial 4 days after exposure to calculate a slope for lymphocyte decline that can be used to estimate exposure dose. Complete blood counts with differential should then be obtained weekly or twice weekly until a nadir in neutrophil count is defined.

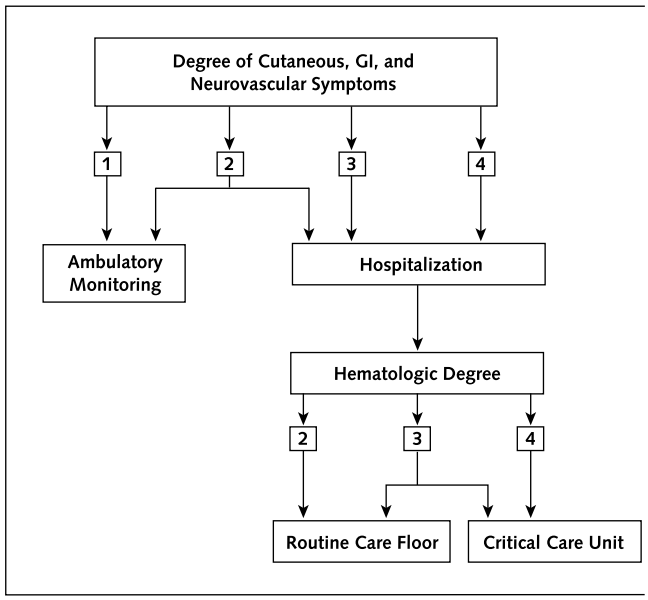
The chromosome-aberration cytogenetic bioassay, primarily the lymphocyte dicentrics assay introduced by Bender and Gooch (48), remains the gold standard for biodosimetry. The International Organization for Standardization recently proposed a standard to certify laboratories for performance of this bioassay (49). Rapid response is required from specialized cytogenetic biodosimetry laboratories in the case of a mass-casualty scenario (50, 51). A peripheral blood sample should be obtained at 24 hours after exposure (or later) in accordance with the policies of a qualified radiation cytogenetic biodosimetry laboratory. Because of incubation times, results will not be available for 48 to 72 hours after the sample has been submitted for analysis. Several cytogenetic biodosimetry laboratories use variations of interphase methods, such as the premature chromosome condensation bioassay, which permits dose assessment at higher doses (>5 Gy photon-equivalent and acute high-dose rate exposures) (52, 53). Although variations of the premature chromosome condensation assay (54) may provide dose estimates in less than 24 hours, this

Table 6. **Priorities in Triage of Patients with and without Combined Injury, Based on Dose of Radiation***

Conventional Triage Categories for Injuries without Exposure to Radiation	Changes in Expected Triage Categories after Whole-Body Radiation		
	<1.5 Gy	1.5–4.5 Gy	>4.5 but ≤10 Gy
Delayed	Delayed	Variable†	Expectant
Immediate	Immediate	Immediate	Expectant
Minimal	Minimal	Minimal‡	Minimal‡
Expectant	Expectant	Expectant	Expectant
Absent	Ambulatory monitoring	Ambulatory monitoring with routine care and hospitalization as needed	

* The military triage system was modified to develop priorities for therapy of individuals with radiation exposure and combined injury (i.e., significant mechanical trauma or burns). Priorities change as a function of radiation dose (range based on acute photon-equivalent exposures). At a whole-body dose <1.5 Gy, triage categories remain the same: 1) delayed treatment for those who are medically stable with significant injury but who may survive until definitive treatment is available; 2) immediate therapy for those with high survivability and significant injury, provided that immediate therapy is available; 3) minimal therapy for medically stable patients with minor injury; and 4) expectant therapy for patients who are seriously injured and in whom survivability is poor. All patients with the combined injury syndrome and an exposure dose >4.5 Gy should be treated expectantly, except for those with minimal or no injury. Patients with radiation injury alone (i.e., without combined injury) should be triaged to the ambulatory setting if dose <1.5 Gy. For those with a higher exposure dose, routine care should include therapy with cytokines, antimicrobial agents, blood transfusion, and frequent outpatient follow-up with laboratory monitoring. Hospitalization may be required, as indicated in Figure 2 and Table 7.
†Triage category depends on the nature and extent of physical injury.
‡ Although other injuries may be minimal, treatment guidelines in Figure 2 and Table 7 should be followed for patients receiving a whole-body radiation dose greater than 3 Gy.

Figure 2. **Approach to triage and therapy for persons exposed to radiation in a limited-casualty scenario.**



A numeric degree of severity is assigned for the cutaneous, gastrointestinal (*GI*), neurovascular, and hematopoietic systems, as defined in **Tables 2** and **3**. The highest degree of toxicity to an organ system indicates the physiologic "response category" (that is, 1, 2, 3, or 4). Modified with permission from reference 24.

method still requires validation. Other methods, such as messenger RNA biomarker assessment using gene profiling technology, are under development (55–58). **Table 5** compares dose estimates based on time to onset of vomiting, reduction in absolute lymphocyte count, and frequency of dicentric chromosomes.

Triage and Emergency Care

The goal of triage is to evaluate and sort individuals by immediacy of treatment needed to do the greatest good for the most people. Triage should include a radiologic survey to assess dose rate, documentation of prodromal symptoms, and collection of tissue samples for biodosimetry. Management of life-threatening injuries takes precedence over radiologic surveys and decontamination.

We present two triage systems. The first system is a modification of the military triage system used in mass-casualty scenarios (**Table 6**). Patients are categorized on the basis of the estimated range of exposure dose and the presence or absence of significant mechanical trauma or burns (that is, combined injury). Individuals requiring surgical intervention should undergo surgery within 36 hours (and not later than 48 hours) after the exposure (21). Additional surgery should not be performed until 6 weeks or later. Depending on the time elapsed after the exposure and availability of resources, patients may be re-triaged to another category. Additional information regarding this triage system is available elsewhere (21).

Alternatively, an individual physiologic "response category" based on grading of clinical signs and symptoms may be used in triage (24, 39) even before individual dose estimates are available to care providers. An initial response category is assigned by determining the degree of toxicity to the cutaneous, gastrointestinal, and neurovascular systems (**Figure 2**). Further categorization of patients based on hematologic degree of toxicity permits triage to an ambulatory setting, admission to a routine-care hospital floor, or admission to a critical care unit. While this system is very useful to the clinician in management of a small-volume radiologic event, it is time-consuming and may be impractical in a large-volume scenario.

Once patients have been triaged by biodosimetry assessment and presence of other injuries, they may be categorized into treatment groups according to general treatment guidelines on the basis of radiation exposure dose (**Table 7**). These guidelines are intended to complement clinical judgment on the basis of signs and symptoms of the exposed individual. Treatment of the acute radiation syndrome is not indicated when exposure dose is very low (<1 Gy) or very high (>10 Gy). Supportive and comfort care is indicated for people with an exposure dose greater than 10 Gy because their prognosis is grave.

Medical Management of the Hematopoietic Syndrome

Treatment of radiologic victims with the hematopoietic syndrome varies with dose estimates, exposure scenarios, and presenting symptoms. Short-term therapy with cytokines is appropriate when the exposure dose is relatively low (<3 Gy). Prolonged therapy with cytokines, blood component transfusion, and even stem-cell transplantation may be appropriate when exposure dose is high (>7 Gy) or when traumatic injury or burns are also present. If there are many casualties, treatment must be prioritized (**Table 7**).

Cytokine Therapy

Today, the only hematopoietic colony-stimulating factors (CSFs) that have marketing approval for the management of treatment-associated neutropenia are the recombinant forms of granulocyte macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and the pegylated form of G-CSF (pegylated G-CSF or pegfilgrastim). Currently, none of these cytokines have been approved by the U.S. Food and Drug Administration for the management of radiation-induced aplasia. The rationale for the use of CSFs in the radiation setting is derived from 3 sources: enhancement of neutrophil recovery in patients with cancer who are treated with CSFs, an apparently diminished period of neutropenia in a small number of radiation accident victims receiving CSFs, and improved survival in irradiated canines and nonhuman primates treated with CSFs.

The value of CSFs in the treatment of radiation-induced myelosuppression of the bone marrow lies in their ability to increase the survival, amplification, and differen-

tiation of granulocyte progenitors. Both GM-CSF and G-CSF activate or prime neutrophils to enhance their function, such as microbicidal activity (60–65). Both have been shown to hasten neutrophil recovery by approximately 3 to 6 days in humans after intensely myelotoxic therapies (66), including bone marrow and stem-cell transplantation (67, 68). In fact, neutrophil recovery times are similar for both early and delayed treatment with G-CSF after transplantation (69–71). In the REAC/TS registry, 25 of 28 patients treated with G-CSF and GM-CSF after radiation accidents appeared to have faster neutrophil recovery. In most instances, these persons received both G-CSF and GM-CSF concurrently for significant periods. However, there was considerable variation in when CSFs were used (often weeks after the incident) and how they were used. Some of these patients also received interleukin-3. A significant survival advantage has been demonstrated in irradiated animals treated with CSFs in the first 24 hours. Laboratory evidence for the efficacy of CSFs after irradiation is summarized in the Appendix (available at www.annals.org).

Table 8 summarizes recommendations for therapy based on radiation exposure dose. In any adult with a whole-body or significant partial-body exposure greater than 3 Gy, treatment with CSFs should be initiated as soon as biodosimetry results suggest that such an exposure has occurred or when clinical signs and symptoms indicate a level 3 or 4 degree of hematotoxicity. Doses of CSFs can be readjusted on the basis of other evidence, such as analysis for chromosome dicentrics. While there may be initial granulocytosis followed by significant neutropenia, CSF treatment should be continued throughout this entire period. The CSF may be withdrawn when the absolute neutrophil count reaches a level greater than 1.0×10^9 cells/L after recovery from the nadir. Reinstitution of CSF treatment may be required if the patient has a significant neutrophil decline ($<0.500 \times 10^9$ cells/L) after discontinuation. Although the benefit of epoetin and darbepoetin has not been established in radiologic events, these agents should be considered for patients with anemia. Response time is prolonged (that is, 3 to 6 weeks), and iron supplementation may be required.

People at the extremes of age (children $<$ 12 years and adults $>$ 60 years) may be more susceptible to irradiation and have a lower $LD_{50/60}$ (26). Therefore, a lower threshold exposure dose (2 Gy) for initiation of CSF therapy is appropriate in such persons and in those who have major trauma injuries or burns (**Table 7**). Individuals receiving an external radiation dose of at least 6 to 7 Gy from an incident involving more than 100 casualties due to detonation of an improvised nuclear device or small nuclear weapon will have a poor prognosis, particularly when additional injury is also present. Depending on the state of the health care infrastructure and availability of resources, it may be prudent to withhold CSF treatment from persons with significant burns or major trauma in a mass-casualty scenario (**Table 6**). Since CSFs are a critical resource that must be given for long durations, particularly in people with multiple injuries such as trauma and burns, difficult triage decisions may mean that CSFs may be preferentially used for people without additional injury because they may have a higher chance of survival (exposure dose of 3 to 7 Gy in adults $<$ 60 years of age and 2 to 7 Gy in children and in adults $\geq$ 60 years of age). The doses of

Table 7. **Guidelines for Treatment of Radiologic Victims***

Variable	Proposed Radiation Dose Range for Treatment with Cytokines	Proposed Radiation Dose Range for Treatment with Antibiotics†	Proposed Radiation Dose Range for Referral for SCT Consideration
	← Gy →		
Small-volume scenario (≤100 casualties)			
Healthy person, no other injuries	3–10‡	2–10§	7–10 for allogeneic SCT; 4–10 if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2–6‡	2–6§	NA
Mass casualty scenario (>100 casualties)			
Healthy person, no other injuries	3–7‡	2–7§	7–10 for allogeneic SCT‖; 4–10 if previous autograft stored or syngeneic donor available‖
Multiple injuries or burns	2–6‖	2–6§‖	NA

* Consensus guidance for treatment is based on threshold whole-body or significant partial-body exposure doses. Events due to a detonation of a radiologic dispersal device resulting in ≤100 casualties and those due to detonation of an improvised nuclear device resulting in >100 casualties have been considered. These guidelines are intended to supplement (and not substitute for) clinical findings based on examination of the patient. NA = not applicable; SCT = stem-cell transplantation.

† Prophylactic antibiotics include a fluoroquinolone, acyclovir (if patient is seropositive for herpes simplex virus or has a medical history of this virus), and fluconazole when absolute neutrophil count is $<0.500 \times 10^9$ cells/L.

‡ Consider initiating therapy at lower exposure dose in nonadolescent children and elderly persons. Initiate treatment with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor in victims who develop an absolute neutrophil count $<0.500 \times 10^9$ cells/L and are not already receiving colony-stimulating factor.

§ Absolute neutrophil count $<0.500 \times 10^9$ cells/L. Antibiotic therapy should be continued until neutrophil recovery has occurred. Follow Infectious Diseases Society of America guidelines (59) for febrile neutropenia if fever develops while the patient is taking prophylactic medication.

‖ If resources are available.

Table 8. **Recommended Doses of Cytokines***

Cytokine	Adults	Children	Pregnant Women†	Precautions
G-CSF or filgrastim	Subcutaneous administration of 5 μg/kg of body weight per day, continued until ANC $>1.0 \times 10^9$ cells/L	Subcutaneous administration of 5 μg/kg per day, continued until ANC $>1.0 \times 10^9$ cells/L	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS; consider discontinuation if pulmonary infiltrates develop at neutrophil recovery
Pegylated G-CSF or pegfilgrastim	1 subcutaneous dose, 6 mg	For adolescents >45 kg: 1 subcutaneous dose, 6 mg	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS
GM-CSF or sargramostim	Subcutaneous administration of 250 μg/m^2 per day, continued until ANC $>1.0 \times 10^9$ cells/L	Subcutaneous administration of 250 μg/m^2 per day, continued until ANC $>1.0 \times 10^9$ cells/L	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS; consider discontinuation if pulmonary infiltrates develop at neutrophil recovery

* ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.
† Experts in biodosimetry must be consulted. Any pregnant patient with exposure to radiation should be evaluated by a health physicist and maternal–fetal specialist for an assessment of risk to the fetus. Class C refers to U.S. Food and Drug Administration Pregnancy Category C, which indicates that studies have shown animal, teratogenic, or embryocidal effects, but there are no adequate controlled studies in women; or no studies are available in animals or pregnant women.

CSFs recommended for use in radiologic incidents are based on the standard doses used in patients who have treatment-related neutropenia (**Table 7**).

Transfusion

Transfusion of cellular components, such as packed red blood cells and platelets, is required for patients with severe bone marrow damage. Fortunately, this complication does not typically occur for 2 to 4 weeks after the exposure, thereby permitting time for rapid mobilization of blood donors. Blood component replacement therapy is also required for trauma resuscitation. All cellular products must be leukoreduced and irradiated to 25 Gy to prevent transfusion-associated graft-versus-host disease in the irradiated (and therefore immunosuppressed) patient. It may be difficult to distinguish transfusion-associated graft-versus-host disease from radiation-induced organ toxicity, which may include fever, pancytopenia, skin rash, desquamation, severe diarrhea, and abnormalities on liver function tests (in particular, hyperbilirubinemia).

Leukoreduction is known to lessen febrile nonhemolytic reactions and the immunosuppressive effects of blood transfusion (72, 73). Moreover, leukoreduction helps protect against platelet alloimmunization and against acquiring cytomegalovirus infections (74, 75). Ideally, life-saving blood products should be leukoreduced and irradiated.

Stem-Cell Transplantation

Matched related and unrelated allogeneic stem-cell transplantations are life-saving and potentially curative treatments in patients with certain predominantly hematologic malignant conditions. A small number of radiation accident victims have undergone allogeneic transplantation from a variety of donors in an attempt to overcome radiation-induced aplasia. The initial experience with this method in an irradiated patient dates back to 1958 (76, 77). Many reports demonstrate transient engraftment with partial chimerism, with nearly all patients experiencing autologous reconstitution of hematopoiesis. However, despite the transient engraftment, outcomes have been poor, largely because of the impact of burns, trauma, or other radiation-related organ toxicity (78–80). In fact, in a recent review of the allogeneic transplant experience in 29 patients who developed bone marrow failure from previous radiation accidents (79), all patients with burns died and only 3 of the 29 lived beyond 1 year. It is unclear whether the transplants affected survival.

Similar results were observed in the 1999 radiation accident in Tokaimura, Japan (78), where 2 of the 3 victims were referred for allogeneic transplantation. Both patients demonstrated transient evidence of donor-cell engraftment followed by complete autologous hematopoietic recovery before eventually dying of radiation injuries to another organ system or infection. Survival may have been longer than expected in these patients.

If resources allow, transplantation should be considered in people with an exposure dose of 7 to 10 Gy who do not have significant burns or other major organ toxicity and who have an appropriate donor. Individuals with a granulocyte count exceeding 0.500×10^9 cells/L and a platelet count of more than 100×10^9 cells/L at 6 days after exposure appear to have evidence of residual hematopoiesis and may not be candidates for transplantation (81). In the unusual circumstance that a syngeneic donor may be available or previously harvested autologous marrow is available, a stem-cell infusion may be considered in patients with exposures exceeding 4 Gy (**Table 7**).

Medical Management of Other Complications and Special Considerations

The following treatment recommendations are defined by clinical and laboratory-based triage and observation of the clinical signs and symptoms associated with the acute radiation syndrome.

Supportive Care

Supportive care includes the administration of antimicrobial agents, antiemetic agents, antidiarrheal agents, fluids, electrolytes, analgesic agents, and topical burn creams. Experimental work performed more than 2 decades ago demonstrated the efficacy of supportive care, including the use of systemic antibiotics directed at gram-negative bacteria and transfusion with fresh, irradiated platelets (82–86).

Careful attention must be given to early fluid resuscitation of patients with significant burns, hypovolemia, hypotension, and multiorgan failure. Expectant care (treatment for comfort with psychosocial support) is recommended for patients who develop multiorgan failure within hours after exposure, as their radiation dose will have been high (>10 Gy). Resources permitting, routine critical care therapy should be provided to patients who develop multiorgan failure several days to weeks after exposure because their dose will have been in the moderate range. Therapy includes endotracheal intubation; administration of anticonvulsant agents; and the judicious use of parenteral analgesic agents, anxiolytic agents, and sedatives, as needed.

Infections

Susceptibility to infection results from a breech in the integument or mucosal barriers, as well as immune suppression consequent to a decline in lymphohematopoietic elements. Several studies have indicated that administration of antibiotics reduces mortality rates in irradiated dogs in the $LD_{50/30}$ range (84–87). Controlling infection during the critical neutropenic phase is a major limiting factor for successful outcome (85). In non-neutropenic patients, antibiotic therapy should be directed toward foci of infection and the most likely pathogens. Fluoroquinolones have been used extensively for prophylaxis in neutropenic patients (88–91). In patients who experience significant neutropenia (absolute neutrophil count $< 0.500 \times 10^9$ cells/L), broad-spectrum prophylactic antimicrobial agents should be given during the potentially prolonged neutropenia period. Prophylaxis should include a fluoroquinolone with streptococcal coverage or a fluoroquinolone without streptococcal coverage plus penicillin (or a congener of penicillin), antiviral drugs (acyclovir or one of its congeners), and antifungal agents (fluconazole). The efficacy of quinolones in irradiated animal models and guidelines for the use of acyclovir and fluconazole are reviewed in the Appendix (available at www.annals.org).

Antimicrobial agents should be continued until they are clearly not effective (for example, the patient develops neutropenic fever) or until the neutrophil count has recovered (absolute neutrophil count $\geq 0.500 \times 10^9$ cells/L). Focal infections developing during the neutropenic period require a full course of antimicrobial therapy. In patients who experience fever while receiving a fluoroquinolone, the fluoroquinolone should be withdrawn and therapy should be directed at gram-negative bacteria (in particular, *Pseudomonas aeruginosa*), since infections of this type may become rapidly fatal. Therapy for patients with neutropenia and fever should be guided by the recommendations of the Infectious Diseases Society of America (92–94). Use of additional antibiotics is based on treatment of concerning foci (that is, anaerobic cocci and bacilli that may occur in patients with abdominal trauma or infection with gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species in addition to significant burns). Altering the anaerobic gut flora of irradiated animals may worsen outcomes (95). Therefore, we recommend that gut prophylaxis not be administered empirically unless clinically indicated (for example, in patients with an abdominal wound or *Clostridium difficile* enterocolitis).

Gastrointestinal Symptoms

Nausea and vomiting are common in patients exposed to radiation. The time to onset of vomiting has merit as a means of clinical dosimetry (96) but should be interpreted together with other forms of biodosimetric assessment. Given the importance of vomiting onset in determining individual radiation dose, prophylaxis against vomiting is not initially desired and would be impractical given the short time to onset with clinically significant exposures (96). At low exposure doses, vomiting usually abates after 48 to 72 hours; therefore, prolonged antiemetic therapy is not warranted in this situation. Serotonin receptor antagonists are very effective prophylaxis in patients who have received radiation therapy (97–100).

Supportive measures include fluid replacement, antibiotic therapy, and prophylaxis against ulceration of the gastrointestinal tract. Instrumentation of the gastrointestinal tract should be performed judiciously or not at all, since the intestinal mucosa is friable and prone to sloughing and bleeding after mechanical manipulation.

Comfort Measures

People with a high exposure dose whose outcome is grim must be identified for appropriate management. Since there is no chance for survival after irradiation with a dose of more than 10 to 12 Gy (**Table 1**), it is appropriate for definitive care to be withheld from such individuals. Rather than being treated aggressively, these patients should be provided with comfort measures. This includes attention to pain management and general comfort as well as administration of antiemetic and antidiarrheal agents. In this devastating situation, psychological support and pastoral care are essential not only for the patient but also for family and friends, who may experience traumatic grief.

Special Considerations

In pregnant women, the risk to the fetus must be assessed. Persons who have been exposed to radioiodines should receive prophylaxis with potassium iodide. Children and adolescents are particularly prone to developing malignant thyroid disease. Recommendations for treatment of victims who are pregnant and for prevention of thyroid cancer are provided in the Appendix (available at

Table 9. **Sources for Additional Information on Assessment, Triage, and Clinical Management of Radiologic Victims**

Source	Web Site
American Academy of Pediatrics	www.aap.org
American College of Radiology Disaster Planning Task Force, in collaboration with the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine	www.acr.org www.astro.org www.aapm.org
American Medical Association	www.ama-assn.org
Armed Forces Radiobiology Research Institute	www.afrri.usuhs.mil
Centers for Disease Control and Prevention	www.bt.cdc.gov
Health Physics Society	http://hps.org
Radiation Emergency Assistance Center/Training Site	www.orau.gov/reacts
Uniformed Services University of the Health Sciences Center for Disaster and Humanitarian Assistance Medicine	http://usuhs.mil
U.S. Army	www.nbc-med.org
U.S. Department of Homeland Security Working Group on Radiological Dispersal Device Preparedness	www1.va.gov
U.S. Food and Drug Administration	www.fda.gov
U.S. Nuclear Regulatory Commission	www.nrc.gov

www.annals.org). Table 9 lists Web sites providing more detailed information on radiation response.

Precautions for Health Care Workers

Guidelines have been established for the use of personal protective equipment by health care providers, as described elsewhere (23) and on the Oak Ridge Associated Universities Web site (www.orau.gov/reacts). Providers should use strict isolation precautions, including donning of gown, mask, cap, double gloves, and shoe covers, when evaluating and treating contaminated patients. Outer gloves should be changed frequently to avoid cross-contamination. No health care workers who have adhered to these guidelines have become contaminated from handling a contaminated patient. Radiation detection devices can readily locate contaminants in the hospital facility to allow decontamination to take place. Protective gear should be removed after use and placed in a clearly labeled, sealed plastic container.

Conclusion

Medical management of patients exposed to intentional or accidental radiation is complex and demands many resources. The primary responsibility for optimizing outcome resides with hospital staff and physicians and other health care facilities. Careful documentation of clinical signs and symptoms and estimation of individual radiation dose are required for medical triage. While loss of life in a nuclear detonation may be enormous, the survival benefit afforded those who receive modern supportive care is significant. Effective care requires implementation of well-organized disaster plans. Disaster planning should include contingency planning for a scenario that involves loss of infrastructure. Organizing as a nation will be instrumental in order to successfully combat a radiologic threat in the United States and across the globe.

From Walter Reed Army Medical Center and Catholic University of America, Washington, DC; Greenebaum Cancer Center, University of Maryland, Baltimore, Maryland; Armed Forces Radiobiology Research Institute and National Institutes of Health, Bethesda, Maryland; Strategic National Stockpile Program, Centers for Disease Control and Prevention, Office of Emergency Preparedness and Response, Atlanta, Georgia; Oak Ridge Associated Universities, Oak Ridge, Tennessee; National Marrow Donor Program, Minneapolis, Minnesota; University of Nebraska, Omaha, Nebraska; and Yale-New Haven Health System and Yale University School of Medicine, New Haven, Connecticut.

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Requests for Single Reprints: Nicholas Dainiak, MD, Department of Medicine, Bridgeport Hospital, 267 Grant Street, Bridgeport, CT 06610; e-mail, pndain@bpthosp.org.

Current author addresses are available at www.annals.org.

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Appendix

Institutional and Committee Participants

Armed Forces Radiobiology Research Institute, Bethesda, Maryland (William F. Blakely, PhD; Itzak Brook, MD; William E. Dickerson, MD; John Jacocks, MD; Thomas Seed, PhD; Horace Tsu, MD); Centers for Disease Control and Prevention, Atlanta, Georgia (Susan Gorman, PharmD; Nicki Pesik, MD; James Smith, PhD); U.S. Food and Drug Administration, Washington, DC (David Green, PhD; Patricia Keegan, PhD; Amy Rosenberg, PhD); Fort Dietrich, Frederick, Maryland (Marc Caouette, MD; Ellen Kavanaugh, MD); National Institutes of Health, Bethesda, Maryland (C. Norman Coleman, Helen Smith); National Marrow Donor Program, Minneapolis, Minnesota (Dennis L. Confer, MD); Radiation Emergency Assistance Center/Training Site, Oak Ridge, Tennessee (Patrick Lowry, MD; Robert Ricks, PhD; Albert Wiley, MD, PhD); University of Maryland Greenebaum Cancer Center (Thomas J. MacVittie, PhD); University of Nebraska, Omaha, Nebraska (James Armitage, MD); Walter Reed Army Medical Center, Washington, DC (Jamie K. Waselenko, MD); Yale-New Haven Health System (Bridgeport Hospital) and Yale University School of Medicine, New Haven, Connecticut (Nicholas Dainiak, MD).

Hematopoietic Reconstitution

Hematopoietic reconstitution has been shown to be possible with partial-body radiation exposure of up to 10 to 12 Gy. Recovery may result from proliferation and differentiation of radioresistant stem cells or stem cells that are spared from radiation because the person's physical environment and proximity to the source may afford partial shielding. **Appendix Figure 1** summarizes the medical record of a radiation accident victim. Note that the lowest dose of 1.5 Gy is received in the right posterior pelvis. Hematopoietically active bone marrow predominates in the dorsal areas of the spine, ribs, and pelvis (21). Accordingly, the patient may have areas of viable marrow, and his injury is potentially survivable (26). Indeed, this individual survived the acute injuries and died 17 years later of radiation hepatitis (36).

Persons exposed to a radiation dose of less than 5 Gy may have a transient increase in granulocyte count. This abortive increase is followed by a nadir that occurs between 1 and 4 weeks (**Appendix Figure 2**) (26, 36). A longer time to nadir is seen with an exposure to a low dose or dose rate of radiation, but the duration of the nadir may be prolonged, requiring long-term therapy.

Experimental Evidence of Efficacy of CSFs

Several studies examining the role of G-CSF, GM-CSF, pegylated G-CSF, and a chimeric molecule in an irradiated rhesus macaque model (10, 101–106) demonstrated significant neutrophil enhancement when these agents were administered 1 day after exposure and were continued for 14 to 21 consecutive days. Studies performed in irradiated rhesus macaques also suggested that there is a survival benefit to initiation of G-CSF or GM-CSF therapy within 24 hours of exposure. However, another report suggested that there is no diminished efficacy when cytokine therapy is delayed (101). Therefore, there is no conclusive proof that early (that is, within 24 hours) administration is necessary and sufficient for optimal outcome in mammals. Nevertheless, CSF therapy should be initiated as early as possible for persons who have been exposed to a survivable whole-body dose of radiation and are at risk for the hematopoietic syndrome (>3 Gy but <10 Gy in adults <60 years of age; >2 Gy but <10 Gy in nonadolescent children and in adults ≥ 60 years of age). Those who become significantly neutropenic (absolute neutrophil count $<0.500 \times 10^9$ cells/L) should also receive CSFs.

Pegfilgrastim has recently received marketing approval in the United States and has efficacy similar to that of G-CSF in chemotherapy-induced myelosuppression (107, 108). Preclinical studies in irradiated rhesus macaques demonstrated that neutrophil recovery occurs after a single injection of pegfilgrastim and that the effect is equivalent to that observed with conventional, daily dosing with filgrastim (109).

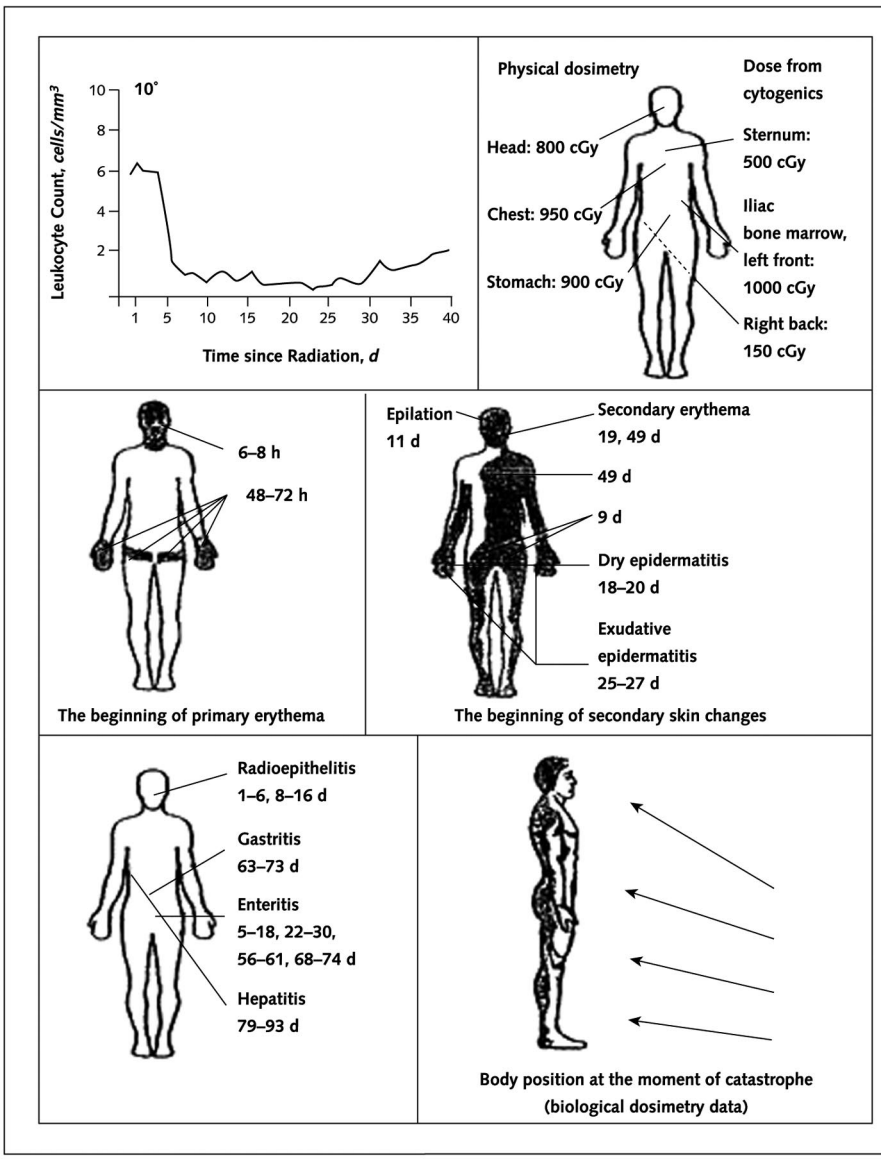
Rationale for Use of Antibiotics

Studies in irradiated mice demonstrated that the gut flora is dramatically altered soon after acute, high-dose exposure. The total mass of aerobes and anaerobes is reduced by several orders of magnitude, while Enterobacteriaceae increase at the expense of vital anaerobic species (95). In addition to breaks in the integrity of the gut wall, a dose-dependent reduction in number of stem cells in intestinal crypts occurs in the first 4 days after radiation (95, 110). Fatal bacteremia may result from bacterial outgrowth and translocation across damaged walls and interstitium of these organisms to the bloodstream. The use of quinolones was effective in controlling systemic endogenous gram-negative infections after radiation (110, 111). Supplementation with penicillin prevented treatment failures due to *Streptococci* infection and in patients with cancer who experienced treatment-related neutropenia (112). Quinolones were also effective in preventing endogenous infections with *Klebsiella* and *Pseudomonas* species (95, 111, 113).

If serologic tests for herpes simplex viruses (HSV-1 and HSV-2) are known to be positive, acyclovir or one of its congeners should be administered. Patients with positive serologic results are at high risk for reactivation of HSV infection during intense immunosuppression and may present with a clinical scenario that mimics radiation stomatitis. While patients undergoing local radiation therapy for head and neck cancer do not show a significant risk for HSV reactivation (114), patients who receive immunosuppressive therapies such as bone marrow transplantation have a high incidence of reactivation (115), which may add to the severity of mucosal injury. If serologic results are not known, it is reasonable to offer HSV prophylaxis on the basis of a medical history of oral or genital herpes infection. Individuals who experience severe mucositis should be assessed for possible reactivation of HSV.

Oral fluconazole, 400 mg/d, lessens the severity of invasive fungal infections and mortality rates in patients undergoing allogeneic bone marrow transplantation (116, 117). Data in patients receiving conventional forms of severely myelotoxic chemotherapy have also demonstrated benefit (59), although conflicting results exist (118, 119). Fluconazole prophylaxis is ineffective

Appendix Figure 1. **Summary of a medical record of a patient injured in a radiation accident.**



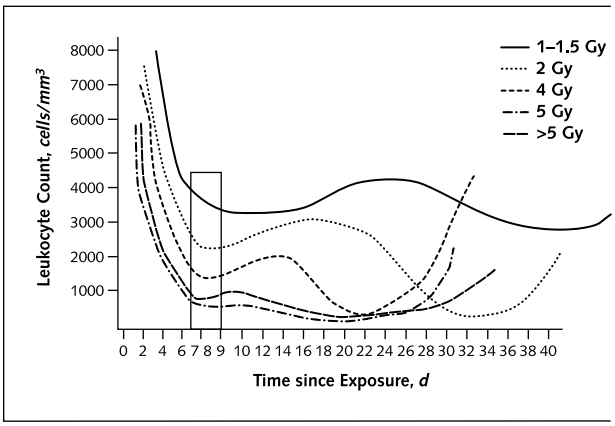
Shown are the absolute leukocyte count (*top left panel*), estimated organ dose (*top right panel*), areas of skin injury (*middle panels*), injury to oral cavity and gastrointestinal system (*bottom left panel*), and body position relative to the radioactive source (*bottom right panel*) as a function of time after the exposure. To convert cells/mm^3 to $\times 10^9$ cells/L, multiply by 0.001. Redrawn with permission from reference 29.

against aspergillus, molds, *Candida krusei*, and resistant *Candida* species.

Prolonged immune suppression from radiation may lead to reactivation of CMV and development of *Pneumocystis carinii* pneumonia. While the incidence of reactivation of CMV in patients with serologic evidence of previous infection after exposure to ionizing radiation is unknown, extrapolation from the marrow transplant literature indicates that the period of greatest risk is within the first 100 days of exposure. If resources allow, the serologic status of CMV should be determined and a sensitive test should be used to assay for reactivation of CMV (that is, antigen assessment or a polymerase chain reaction test) every 2 weeks for 30 days postexposure, up to day 100 in patients with documented previous CMV exposure. Subsequent examination may be necessary based on the clinical scenario because CMV infection may occur later.

An assessment of the absolute CD4 cell count should be considered at 30 days postexposure for patients who have had or currently have radiation-associated lymphopenia. Patients who are highly susceptible to *Pneumocystis carinii* pneumonia have an absolute CD4 cell count less than 0.200×10^9 cells/L. Trimethoprim–sulfamethoxazole should be avoided until the leukocyte count exceeds 3.0×10^9 cells/L or the absolute neutrophil count exceeds 1.5×10^9 cells/L. Alternative therapy includes atovaquone, dapsone, and aerosolized pentamidine. Prophylaxis should continue until the absolute CD4 cell count increases to a level of 0.200×10^9 cells/L or greater. This increase in CD4 cell count may not occur for several months.

Appendix Figure 2. **Leukocyte count based on exposure dose in patients exposed to radiation in Chernobyl.**



Note the abortive rise (transient increase before the fall) in counts of leukocytes, which are primarily composed of granulocytes, in doses less than 5 Gy. Neutropenia may not occur for weeks, especially with lower exposures, and its duration may be prolonged. To convert cells/mm^3 to $\times 10^9$ cells/L, multiply by 0.001. Redrawn with permission from reference 36.

Guidelines for Management of Pregnancy and Prevention of Thyroid Cancer

All hematopoietic cytokines and many antibiotics are class C drugs (**Table** 7). However, any pregnant woman who has been exposed to more than 0.25 Gy of radiation should have an estimate of fetal dose determined. The fetus's dose is often lower than that of the mother, except in the settings of radioiodine exposure (because the fetal thyroid gland is more iodine-avid than the adult thyroid gland) and internal contamination of the maternal urinary bladder (where increased exposure may occur because of proximity of the fetus to radioactivity). Consultation with a health physicist and a maternal–fetal medicine specialist is advised to assess risk to the fetus. The most important factor for ensuring fetal survival is survival of the mother. Pregnant women should receive the same supportive care as that provided to nonpregnant adults. Antibiotic use in pregnant women will require a review of safety in pregnancy. Risks and benefits to the mother and fetus must be explained before therapy is administered.

In the fetus, child, and adolescent, the thyroid gland is a radiosensitive organ that is at risk for malignant transformation. Because the thyroid gland concentrates iodine with great efficiency, exposure to radioiodines (^{131}I, ^{125}I) results in localization of radioactivity in the thyroid gland. This concentration of radioactivity can result in thyroid cancer, a delayed consequence that may be more aggressive than de novo forms of thyroid cancer (120). The main route of radioiodine exposure is inhalation by those in the near field and ingestion of contaminated food and drink (particularly milk) for those farther away (in the far field). Thyroid blocking with potassium iodide offers some protection (reduction of radioiodine uptake by 50% when administered within 4 hours of the exposure) by saturating the thyroid gland with nonradioactive iodine.

However, potassium iodide is not a generic antiradiation drug. If radioiodines are not part of the exposure, potassium iodide is not recommended. For example, because of their short half-life of 8.5 days, it is extremely unlikely that radioiodines will be incorporated into a radiologic dispersal device or "dirty bomb." In this scenario, potassium iodide will be of no clinical benefit but its potential toxicity (including life-threatening anaphylaxis) will be risked. Therefore, it is recommended that treatment with potassium iodide be avoided in victims of a "dirty bomb" explosion.

Dosing guidance for exposures involving radioiodines is reviewed in the **Appendix Table** and is also available online at www.bt.cdc.gov/radiation/ki.asp. Potassium iodide should be administered by mouth (tablets or Lugol solution) as soon as possible after the accident (≤6 hours). Caution should be taken in victims who have a personal history of allergy to iodine because severe allergic reactions have been reported. Thyroid protection for pregnant women exposed to radioiodine is critical for the mother and fetus. In the first trimester with a near-field exposure, stable iodine will protect the mother. Pregnant women with far-field exposure may be able to avoid contaminated foods and milk. The fetal thyroid gland normally does not begin to function until approximately the 12th week of gestation. Thus, pregnant women in the second and third trimesters should receive potassium iodide in both near- and far-field exposures to protect the maternal and fetal thyroid glands.

Appendix Table. **Threshold Dose and Recommended Doses of Potassium Iodide for Different Risk Groups***

Patients	Predicted Thyroid Dose	Daily Dose of Potassium Iodide	130-mg Tablets	65-mg Tablets
	Gy	*mg*	*n*	
Adults >40 y of age	≥5	130	1	2
Adults >18 through 40 y of age	≥0.1	130	1	2
Pregnant or lactating women	≥0.05	130	1	2
Adolescents >12 through 18 y of age†	≥5	65	1/2	2
Children >3 through 12 y of age	≥5	65	1/2	1
Children >1 mo through 3 y of age	≥5	32	1/4	1/2
Birth through 1 mo	≥5	16	1/8	1/4

* Based on reference 121. Potassium iodide tables or Lugol solution must be used within 4 to 6 hours of exposure to block uptake of radioiodines by the thyroid gland. If radioiodines are not part of the exposure, potassium iodide treatment is not indicated. Therapy should be continued for 7 to 10 days or as long as the exposure continues.
† Adolescents approaching adult size (≥70 kg) should receive the full adult dose (130 mg).

Current Author Addresses: Dr. Waselenko: Walter Reed Army Medical Center, 6900 Georgia Avenue, WD78, Washington, DC 20307.
Dr. MacVittie: Greenebaum Cancer Center, University of Maryland, 22 South Greene Street, Baltimore, MD 21201.
Dr. Blakely: Armed Forces Radiobiology Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5603.
Dr. Pesik: Strategic National Stockpile Program, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333.
Drs. Wiley and Lowry: Radiation Emergency Assistance Center/Training Site, Oak Ridge Associated Universities, 150 Vance Road, Oak Ridge, TN 37830.
Drs. Dickerson and Tsu: Armed Forces Radiobiology Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5603.
Dr. Confer: National Marrow Donor Program, 3001 Broadway Street, NE 500, Minneapolis, MN 55413.
Dr. Coleman: National Cancer Institute, National Institutes of Health, Building 10, B3869, Bethesda, MD 20892-1002.
Dr. Seed: Catholic University of America, 620 Michigan Avenue NE, Washington, DC 20064.
Dr. Armitage: University of Nebraska, 987680 Nebraska Medical Center, Omaha, NE 68198.
Dr. Dainiak: Department of Medicine, Bridgeport Hospital, 267 Grant Street, Bridgeport, CT 06610.