National Guideline Clearinghouse
www.guideline.gov

Complete Summary

GUIDELINE TITLE

Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group.

BIBLIOGRAPHIC SOURCE(S)

Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, Tsu H, Confer DL, Coleman CN, Seed T, Lowry P, Armitage JO, Dainiak N. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med 2004 Jun 15;140(12):1037-51. [121 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 9, 2007, Erythropoiesis Stimulating Agents (Aranesp [darbepoetin alfa], Epogen [epoetin alfa], Procrit [epoetin alfa]): Changes to the full prescribing information for Aranesp, Epogen, and Procrit to include a new boxed warning, updated warnings, and a change to the dosage and administration sections for all ESAs.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Acute radiation syndrome

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Critical Care
Emergency Medicine
Endocrinology
Family Practice
Gastroenterology
Hematology
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide a framework for physicians in internal medicine and the medical subspecialties to evaluate and manage large-scale radiation injuries

TARGET POPULATION

Individuals exposed to large amounts of radiation who may develop acute radiation syndrome, including children, adolescents, and pregnant women

INTERVENTIONS AND PRACTICES CONSIDERED

Physical Examination

1. Measurement of vital signs (presence of fever, hypotension, and orthostasis)
2. Skin examination (erythema, blistering, onycholysis, edema, desquamation, and petechiae)
3. Neurologic examination (presence of motor or sensory deficits, papilledema, ataxia, and assessment of mental status and cognition)
4. Abdominal examination (presence of pain or tenderness)

Assessment of Radiation Dose Exposure

1. Physical measurements
    - Personal dosimeters (if available)
    - Other radiation monitoring devices
2. Biological measurements
    - Time to onset of nausea and vomiting
    - Measurement of lymphocyte depletion kinetics
    - Chromosome-aberration cytogenetic bioassay (lymphocyte dicentrics assay)
3. Measurement tools under development
    - Premature chromosomes condensation bioassay
    - Messenger ribonucleic acid (RNA) biomarker assessment

Triage and Emergency Care

1. Categorization of patients on the basis of estimated range of radiation exposure and degree of cutaneous, gastrointestinal, and neurovascular symptoms
2. Endotracheal intubation
3. Fluid replacement
4. Surgical Intervention

Hematopoietic Syndrome Management

1. Cytokine therapy and supportive therapy
    - Granulocyte colony-stimulating factor (G-CSF)
    - Granulocyte macrophage colony-stimulating factor (GM-CSF)
    - Pegylated form of G-CSF (pegylated G-CSF or pegfilgrastim)
    - Other: Epoetin and Darbepoetin may be of potential benefit
2. Iron supplementation
3. Packed red blood cell and platelet transfusion with leukoreduction and irradiation
4. Stem cell transplantation

Other Therapies and Management Strategies

1. Antimicrobial agents (quinolones, penicillins, antifungals such as fluconazole, and antivirals such as acyclovir)
2. Antiemetic agents
3. Analgesic agents
4. Anticonvulsant agents
5. Anxiolytic agents (serotonin receptor antagonists)
6. Sedatives
7. Antidiarrheal agents
8. Topical burn creams
9. Prophylaxis against malignant disease of the thyroid (potassium iodide)
10. Prophylaxis against ulceration of the gastrointestinal tract
11. Psychological support and pastoral care
12. Assessment of risk to the fetus in pregnant women
13. Use of isolation precautions by health care providers
14. Use of personal protective equipment by health care providers

MAJOR OUTCOMES CONSIDERED

- Validity and predictive value of biodosimetry methods
- Occurrence of acute radiation syndrome
- Probability of death or survival based on radiation exposure
- Rate of hematopoietic recovery
- Incidence and severity of bacterial, viral, fungal infections
- Rate of reactivation of cytomegalovirus or herpesvirus infections

Top^

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Patient Registry Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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. 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 Strategic National Stockpile (SNS) Radiation Working Group reviewed management strategies used in accidental exposures of humans and evaluated results of prospective, controlled studies of acutely irradiated animals.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Strategic National Stockpile (SNS) convened the SNS Radiation Working Group 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.

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. 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 literature.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

Top^

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The Acute Radiation Syndrome

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

Dose Range, Gy	Prodrome	Manifestation of Illness	Prognosis (without Therapy)
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

GI = gastrointestinal

Management

The table below entitled "Grading System for Response of Neurovascular, Gastrointestinal, and Cutaneous Systems" summarizes the clinical responses for all of these syndromes, and Table 3 in the original guideline document 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).

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

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
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, degrees 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 >100/70 mm Hg	Blood pressure <100/70 mm Hg	Blood pressure <90/60 mm Hg; transient	Blood pressure <80/? mm Hg; persistent
Neurologic deficits[1]	Barely detectable	Easily detectable	Prominent	Life-threatening, loss of consciousness
Cognitive deficits[2]	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[3]	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

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
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

ADL = activity of daily living.
[1] Reflex status (including corneal reflexes), papilledema, seizures, ataxia, and other motor signs or sensory signs
[2] Impaired memory, reasoning, or judgment
[3] The extent of involvement is decisive and should be documented for all skin changes.

Psychological Impact of Radiation Exposure

Psychosocial issues must be addressed in the potentially exposed population. 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 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. 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. In addition, exposed individuals and their families and friends have a high rate of post-traumatic stress disorder. 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.

To assess the potential impact on the response system of persons with little or no radiation exposure, the guideline developers generated a scenario for 1-kiloton and 10-kiloton nuclear detonations (See Table 4 of original guideline document). 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 (See Table 4 of original guideline document). 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 (http://www.afrri.usuhs.mil/). This tool was developed in collaboration with the Radiation Emergency Assistance Center/Training Site (REAC/TS) and others to facilitate medical recording and estimation of individual dose. In addition, the International Atomic Energy Agency has developed generic guidelines for recording clinical signs and symptoms for victims of a radiation incident (see http://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.

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. Lymphocyte depletion kinetics predicts 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 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, remains the gold standard for biodosimetry. The International Organization for Standardization recently proposed a standard to certify laboratories for performance of this bioassay. Rapid response is required from specialized cytogenetic biodosimetry laboratories in the case of a mass-casualty scenario. 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). Although variations of the premature chromosome condensation assay may provide dose estimates in less than 24 hours, this method still requires validation. Other methods, such as messenger ribonucleic acid (RNA) biomarker assessment using gene profiling technology, are under development. Table 5 in the original guideline document 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.

Two triage systems are presented. The first system is a modification of the military triage system used in mass-casualty scenarios (See table below entitled "Priorities in Triage of Patients with and without Combined Injury, Based on Dose of Radiation"). 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. 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.

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***

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**
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 of the original guideline document.
**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 of the original guideline document should be followed for patients receiving a whole-body radiation dose greater than 3 Gy.

Alternatively, an individual physiologic "response category" based on grading of clinical signs and symptoms may be used in triage 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 of the original document). 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 (see table below entitled "Guidelines for Treatment of Radiologic Victims"). 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.

Guidelines for Treatment of Radiologic Victims*

Variable	Proposed Radiation Dose Range for Treatment with Cytokines (Gy)	Proposed Radiation Dose Range for Treatment with Antibiotics[1] (Gy)	Proposed Radiation Dose Range for Referral for SCT Consideration (Gy)
Small-volume scenario (≤100 casualties)			
Healthy person, no other injuries	3-10[2]	2-10[3]	7-10 for allogeneic SCT; 4-10 if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2-6[2]	2-6[3]	NA
Mass casualty scenario (>100 casualties)			
Healthy person, no other injuries	3-7[2]	2-7[3]	7-10 for allogeneic SCT**; 4-10 if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2-6**	2-6[3]**	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.

[1]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.

[2]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.

[3]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 for febrile neutropenia if fever develops while the patient is taking prophylactic medication.

**If resources are available.

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 (See table above entitled "Guidelines for Treatment of Radiologic Victims").

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 differentiation of granulocyte progenitors. Both GM-CSF and G-CSF activate or prime neutrophils to enhance their function, such as microbicidal activity. Both have been shown to hasten neutrophil recovery by approximately 3 to 6 days in humans after intensely myelotoxic therapies, including bone marrow and stem-cell transplantation. In fact, neutrophil recovery times are similar for both early and delayed treatment with G-CSF after transplantation. 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 of the original guideline document (available from the Annals of Internal Medicine Web site).

The table below entitled "Recommended Doses of Cytokines" 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.

Recommended Doses of Cytokines*

Cytokine	Adults	Children	Pregnant Women**	Precautions
G-CSF or filgrastim	Subcutaneous administration of 5 micrograms/kg of body weight per day, continued until ANC $>1.0 \times 10^9$ cells/L	Subcutaneous administration of 5 micrograms/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

Cytokine	Adults	Children	Pregnant Women**	Precautions
GM-CSF or sargramostim	Subcutaneous administration of 250 micrograms/m^2 per day, continued until ANC >1.0 x 10^9 cells/L	Subcutaneous administration of 250 micrograms/m^2 per day, continued until ANC >1.0 x 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.

People at the extremes of age (children <12 years and adults >60 years) may be more susceptible to irradiation and have a lower $LD_{50/60}$. 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 (see table above entitled "Guidelines for Treatment of Radiologic Victims"). 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 (See table above entitled "Priorities in Triage of Patients with and without Combined Injury, Based on Dose of Radiation"). 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 CSFs recommended for use in radiologic incidents are based on the standard doses used in patients who have treatment-related neutropenia (see table above entitled "Guidelines for Treatment of Radiologic Victims").

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. Moreover, leukoreduction helps protect against platelet alloimmunization and against acquiring cytomegalovirus infections. 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. 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. In fact, in a recent review of the allogeneic transplant experience in 29 patients who developed bone marrow failure from previous radiation accidents, 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, 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. 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 (see table above entitled "Guidelines for Treatment of Radiologic Victims").

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.

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. Controlling infection during the critical neutropenic phase is a major limiting factor for successful outcome. 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. 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 of the original document (available from the Annals of Internal Medicine Web site).

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. 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. Therefore, the guideline developers 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 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. 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.

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 (see table above entitled "Phases of Radiation Injury"), 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 of the original guideline document (available from the Annals of Internal Medicine Web site). Table 9 of the original document 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 and on the Oak Ridge Associated Universities Web site (http://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.

CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for the approach to triage and therapy for persons exposed to radiation in a limited-casualty scenario.

Top^

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Top^

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of patients exposed to radiation

POTENTIAL HARMS

- Graft versus host disease may be a complication following stem cell transplantation.
- 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.
- For use of potassium iodide, caution should be taken in victims who have a personal history of allergy to iodine because severe allergic reactions have been reported.
- All hematopoietic cytokines and many antibiotics are pregnancy class C drugs, 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.
- For precautions of cytokine administration, see the table entitled "Recommended Dosages of Cytokines" in the "Major Recommendations" field.

Top^

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The opinions or assertions contained herein are the private views of the authors and are not necessarily those of the U.S. Army, the Department of Defense, or the Centers for Disease Control and Prevention. Mention of specific commercial equipment or therapeutic agents does not constitute endorsement by the U.S. Department of Defense or the Centers for Disease Control and Prevention; trade names are used only for the purpose of clarification.

Top^

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

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.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

Top^

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety
Timeliness

Top^

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, Tsu H, Confer DL, Coleman CN, Seed T, Lowry P, Armitage JO, Dainiak N. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med 2004 Jun 15;140(12):1037-51. [121 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jun 15

GUIDELINE DEVELOPER(S)

Strategic National Stockpile - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Strategic National Stockpile Radiation Working Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: 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; Nicholas Dainiak, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Potential Financial Conflicts of Interest: Honoraria: T.J. MacVittie (Amgen), J.O. Armitage (Amgen); Stock ownership or options (other than mutual funds): P.C. Lowry (Amgen); Grants received: T.J. MacVittie (Amgen); Patents received: W.F. Blakely.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Annals of Internal Medicine Online Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from Nicholas Dainiak, MD, Department of Medicine, Bridgeport Hospital, 267 Grant Street, Bridgeport, CT 06610; e-mail, pndain@bpthosp.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Appendix to the medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med 2004 Jun 15;140(12):W-64-W67.

Electronic copies: Available from the Annals of Internal Medicine Online Web site in HTML Format and Portable Document Format (PDF).

Print copies: Available from Nicholas Dainiak, MD, Department of Medicine, Bridgeport Hospital, 267 Grant Street, Bridgeport, CT 06610; e-mail, pndain@bpthosp.org.

PATIENT RESOURCES

The following is available:

- Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, Tsu H, Confer DL, Coleman CN, Seed T, Lowry P, Armitage JO, Dainiak N. Summaries for patients. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med 2004 Jun 15;140(12): I-51.

Electronic copies: Available from the Annals of Internal Medicine Online Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on December 2, 2004. This summary was updated by ECRI on December 5, 2005, following the U.S. Food and Drug Administration advisory on Aranesp, Epogen, and Procrit. This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents.

COPYRIGHT STATEMENT

Top^

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines

represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx.

NGC, AHRQ, and its contractor ECRI make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Top^