REVIEW ARTICLE

Literature Review and Global Consensus on Management of Acute Radiation Syndrome Affecting Nonhematopoietic Organ Systems

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ABSTRACT

Objectives: The World Health Organization convened a panel of experts to rank the evidence for medical countermeasures for management of acute radiation syndrome (ARS) in a hypothetical scenario involving the hospitalization of 100 to 200 victims. The goal of this panel was to achieve consensus on optimal management of ARS affecting nonhematopoietic organ systems based upon evidence in the published literature.

Methods: English-language articles were identified in MEDLINE and PubMed. Reference lists of retrieved articles were distributed to conferees in advance of and updated during the meeting. Published case series and case reports of ARS, publications of randomized controlled trials of relevant interventions used to treat nonirradiated individuals, reports of studies in irradiated animals, and prior recommendations of subject matter experts were selected. Studies were extracted using the Grading of Recommendations Assessment Development and Evaluation system. In cases in which data were limited or incomplete, a narrative review of the observations was made.

Results: No randomized controlled trials of medical countermeasures have been completed for individuals with ARS. Reports of countermeasures were often incompletely described, making it necessary to rely on data generated in nonirradiated humans and in experimental animals. A strong recommendation is made for the administration of a serotonin-receptor antagonist prophylactically when the suspected exposure is >2 Gy and topical steroids, antibiotics, and antihistamines for radiation burns, ulcers, or blisters; excision and grafting of radiation ulcers or necrosis with intractable pain; provision of supportive care to individuals with neurovascular syndrome; and administration of electrolyte replacement therapy and sedatives to individuals with significant burns, hypovolemia, and/or shock. A strong recommendation is made against the use of systemic steroids in the absence of a specific indication. A weak recommendation is made for the use of fluoroquinolones, bowel decontamination, loperamide, and enteral nutrition, and for selective oropharyngeal/digestive decontamination, blood glucose maintenance, and stress ulcer prophylaxis in critically ill patients.

Conclusions: High-quality studies of therapeutic interventions in humans exposed to nontherapeutic radiation are not available, and because of ethical concerns regarding the conduct of controlled studies in humans, such studies are unlikely to emerge in the near future.

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Key Words: countermeasures for ARS, acute radiation syndrome management, treatment of ARS, narrative review of countermeasures for ARS

Acute injury from ionizing radiation may occur after exposure to medical and industrial sources of radioactive material and from accidental or deliberate release of radiological and nuclear materials.[1,2] Although it is prudent to prepare for mass radiation exposure, diverse clinical practices have been used to medically manage individuals who have undergone exposure. A need for harmonization of protocols for the medical management of radiation injuries has been identified in the International Action Plan for Strengthening the International Preparedness and Response System for Nuclear and Radiological Emergencies.[3]

Constructing a consensus approach to the medical management of victims requires preidentifying best practices tools for the treatment of radiation-specific injuries. Such

tools serve to align patient-management protocols within health care delivery systems that include primary and referral hospitals, clinical and biodosimetry laboratories, and public health resources. Moreover, a carefully and fully vetted approach to the medical management of agent-specific threats can help officials identify priorities for future research and better allocate public health assets.

The World Health Organization (WHO) tasked a consultation group in Geneva, Switzerland, with creating a harmonized approach to the medical management of individuals who have undergone radiation exposure. Various sources of guidance already exist to help clinicians who may find themselves responsible for the evaluation, triage, and/or medical management of victims with acute radiation injury.[4,5] Before the Geneva meeting, however, the levels of evidence behind existing recommendations had not been evaluated. Using a tool endorsed by WHO to grade levels of evidence,[6,7] the consultation group weighted the available evidence to decide whether to include available guidance into consensus protocols.

Variations in treatment recommendations made by different groups of subject matter experts from around the world have the potential to create confusion regarding optimal medical management. In Geneva, recognized experts from Europe, North and South America, and Asia convened to evaluate the quality of evidence and to discuss best practices in the medical management of the acute radiation syndrome (ARS) in victims who have been already transferred from the field to a hospital. This document was conceived and created, therefore, as an international consensus approach to ARS management for health care providers, public health officials, and radiation response planners.

A small release of radioactive material once seemed to be the most likely means by which terrorists would exploit radiation. By contrast, experts now believe that the risk of a larger radiological/nuclear incident has increased.[8-10] For this reason, the consultation group assumed that clinicians and public health officials must be prepared to respond to scenarios ranging from smaller radiological incidents involving a few individuals up to larger-scale radiation events requiring the hospitalization of hundreds of patients. For the purpose of this consultancy, mass-casualty scenarios for a nuclear detonation resulting in the hospitalization of thousands or tens of thousands of victims were not considered. Although physicians in some countries may be limited in their ability to adhere to all of the elements of guidance described herein, the recommendations provided are, in general, applicable throughout the world.

METHODS

From March 16 to 18, 2009, a panel of experts met in Geneva to discuss the medical management of patients hospitalized after exposure to high doses of ionizing radiation. Participants were selected on the basis of their established expertise in the field. In addition to subject matter and health policy experts, individuals with knowledge in epidemiologic techniques, statistics, and literature evaluation were invited to attend. Consultation group members were asked to consider and respond to a virtual scenario in which 100 to 200 victims required hospitalization. Protocols for medical triage and prehospital field treatment (occurring before the decision to admit) were intentionally excluded from this discussion, as was consideration of the management of external and internal contamination. Instead, selected participants provided a brief (10-15 minutes), focused aspect of inpatient medical management.

Before the meeting, WHO solicited English-language references from each participant and made them available to all of the conferees. Publications included case series and individual case reports of humans who were exposed accidentally to ionizing radiation; randomized controlled trials and cohort studies of humans who received therapeutic radiation or who may not have been exposed to radiation but who received the indicated treatment; reports of experimental studies in irradiated animals; and prior publications of recommendations of other consensus groups. Additional data were identified during the meeting by searching MEDLINE and PubMed from inception, using search terms that included *radiation* or *radiation toxicity* or *ionizing radiation and therapy* or *treatment* or *gastrointestinal system* or *cutaneous system* or *neurovascular system*. Limits included English language and title/abstract. Reference lists were updated periodically throughout the meeting.

Initial attempts to evaluate the quality of evidence using the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach[12,13] were unsuccessful, owing to incomplete or insufficient documentation of detailed information on therapy in many published reports. Although restricted by the lack of comparator groups in humans, GRADE was successfully applied to the evaluation of medical countermeasures for the management of radiation-associated toxicity to the hematopoietic system (see Part 2 of this article). Treatment options were sequentially discussed by all of the participants. Every attempt was made to encourage discussion to ensure that all sides of controversial topics were critiqued.

Recommendations were based upon an assessment of the published literature that included high-quality studies in experimental animals; human studies, including case reports, uncontrolled and/or inadequately powered studies and reports having limited generalizability; and prior publications presenting the opinions of other expert groups. Quality of evidence and strength of recommendation were determined by consensus during the meeting and by final ranking of each countermeasure by e-mail communication to all of the conferees after the consultancy meeting ended. The criteria included study species, study design, study limitations, dose-response gradients, and confounding variables.

Letter assignments (A, B, C, and D) were made based upon the level of certainty that the magnitudes of benefits and harms of an intervention are known (Table 1). Strong or weak recommendations were made based upon the balance between desirable and undesirable consequences of alternative treatment strategies, quality of evidence, uncertainty about or variability in values and preferences, and impact on resource utilization. The strength of recommendations is summarized in Table 2.

DEFINITION OF TERMS USED FOR CLINICAL RESPONSES TO RADIATION EXPOSURE

ARS occurs after whole-body or significant partial-body irradiation, which typically is at a dose of >1 Gy. Clinical syndromes, including hematopoietic, cutaneous, gastrointestinal, and neurovascular syndromes, may occur either individually or in combination, in response to a whole body absorbed dose. Also known as acute radiation sickness,[11] ARS follows a somewhat predictable clinical course that usually includes a prodromal phase (typically within the first 48 hours after exposure), a latent phase (a brief time period wherein symptoms improve), and a phase of manifest illness (which may last for weeks and, in severe cases, may result in death). The severity of clinical signs and symptoms of ARS correlate in general with the radiation absorbed dose.[11-13]

Radiation-induced multiorgan dysfunction (MOD) and multiorgan failure (MOF) refer to progressive dysfunction of ≥2 organ systems over time.[14-16] MOD/MOF is considered to be a pathophysiologic process rather than a distinct clinical syndrome.[14] It appears to be distinguished from nonradiation MOD caused by sepsis, veno-occlusive disease (eg, sinusoidal obstruction syndrome), and diffuse intravascular coagulation. Radiation-associated MOD develops, in part, as a consequence of a systemic inflammatory response syndrome and, in part, as a consequence of radiation-induced progressive loss of functional cell mass of the vital organs.[15] It has been suggested that treatment of systemic inflammatory response syndrome may prevent the evolution of MOD to subsequent MOF.[14]

Radiation injury may occur in conjunction with thermal burns, chemical injury, and/or mechanical trauma, a condition known as combined injury syndrome. This type of injury may be common for the scenario in question, with data from the 1945 nuclear detonations at Hiroshima and Nagasaki (Japan) showing that deaths were caused by trauma in 60% of cases, burns in 30% of cases, and irradiation in only 10% to 20% of cases.[17] It is reasonable to presume that atomic bomb victims near the epicenter who sustained life-threatening trauma and/or burns also must have sustained radiation injury. Results of preliminary studies in animals suggest that combined injury is expected to have a significantly worse prognosis than radiation injury alone.[18,19] The consultation group unanimously agreed that additional research is needed to determine whether prognosis is altered in this syndrome and, if so, what mechanisms may be responsible for potentiating or inhibiting pathophysiologic processes that affect mortality.

INITIAL APPROACH TO RADIATION-EXPOSED INDIVIDUALS

Because overall mortality correlates well with whole-body dose, an early assessment of radiation dose provides useful information to the treating physician. Individuals receiving a whole-body dose in excess of 10 to 12 Gy virtually never survive longer than 6 months.[12,20,21] By contrast, whole-body doses of 1 to 2 Gy are, in general, survivable. It has been estimated that there is an $LD_{50/60}$ (ie, the mean lethal dose to humans causing 50% mortality at 60 days postexposure) of 3 to 4 Gy in the absence of supportive care and 6 to 7 Gy when supportive care (including fluid and electrolyte replacement, antimicrobial agents, nutrition, and transfusion of blood products) is provided. Individuals who have received a dose of <1 Gy usually have no symptoms and no added early mortality

TABLE 1

Assignments for Quality of Evidence

Assignment	Level	Definition
A	High	The available evidence usually includes consistent results in irradiated or nonirradiated patient or animal populations.
B	Moderate	Available evidence is of moderate quality. It is consistent with beneficial effect on outcomes, but studies in humans and/or animals are suboptimal because of inadequate power, inconsistent findings, or limited generalizability.
C	Low	Available evidence is of low quality. It is insufficient to assess effects on outcomes because of studies in humans and/or animals having inadequate power, inconsistent findings, or limited generalizability.
D	Very low	Available evidence is of very low quality because of a lack of studies or because of studies in humans and/or animals having inadequate power and/or serious flaws in design, measurement techniques, or reproducibility.

TABLE 2

Numerical Representation for Strength of Recommendation Based on Net Benefit*

Assignment	Definition	Implication	Practice
1a	Consultancy strongly recommends this practice with a high certainty of substantial net benefit	Most patients would accept treatment and most clinicians would recommend treatment.	Provide service
1b	The consultancy weakly recommends this practice with a moderate certainty of moderate net benefit.	Although most patients would elect treatment, many would refuse it. Many clinicians would not recommend treatment, but most would recommend treatment.	Probably provide service
2a	Consultancy strongly recommends against this practice since there is a moderate or high certainty of no net benefit.	Most patients would refuse treatment, and most clinicians would not recommend treatment.	Do not provide service
2b	Consultancy weakly recommends against this practice routinely; however, the practice should be considered in individual patients who have a high or moderate certainty of small net benefit.	Although most patients would refuse treatment, many would accept it. Many clinicians would recommend treatment, but most would not.	Provide service only if other considerations support it in an individual patient

*The balance between and undesirable consequences of alternative management strategies.

from radiation per se, although stochastic effects (eg, leukemia, lymphoma, solid tumors) may develop later in life.[22]

In a mass-casualty event, typically clinicians use various pieces of information for the management of patients. This information may include an estimate of the whole- or partial-body absorbed dose, if it is available. Estimates of absorbed dose can be made by several methods, including external (ie, geographic) dosimetry and biological dosimetry. External dosimetry links location of a victim with the levels of radiation measured in his or her immediate environment, at various times after initiation of the incident. Estimation of external contamination may be aided by assaying the surface of the skin using a scintillation counter. Samples of urine, stool, and nasal secretions also may be assayed to assess for internal contamination in individual patients.[4,23]

Biological dosimetry uses laboratory results and clinical signs and symptoms to estimate absorbed dose.[4,20] Cytogenetic analysis (ie, the frequency of chromosome dicentrics in cultured lymphoctyes) is the gold standard for biodosimetry.[24] In addition, the time to onset of emesis and the rate of decline and nadir in the absolute lymphocyte count each may be used to estimate the average whole-body dose[25] and, by extension, survivability of radiation injury among exposed individuals[4,11,12]; however, variability in individual response occurs. For example, more than 45% of individuals receiving an estimated whole-body dose of ≤3 Gy do not experience vomiting.[4] A recent reassessment of reported times to emesis showed a relative error of 200% for prediction of a dose of 2 Gy.[26]

The consultation group recommends that clinicians use as many methods of estimating dose and predicting severity of ARS as they have to design treatment strategies. These methods include careful documentation of a spectrum of observed signs and symptoms in an individual[27] and, where possible, determination of an estimated radiation absorbed dose.[20] Repeat assessments should be made and solicitation of advice from experienced physicians is strongly encouraged.

CLINICAL DECISION MAKING BASED ON DOSIMETRY, SIGNS, AND SYMPTOMS

Clinical decision making requires an understanding of the prognosis of an individual. Physicians may assess the prognosis of irradiated patients, using the presence of certain clinical signs and symptoms (Table 3) and an estimated exposure dose. The advantages of using clinical signs and symptoms as a basis for assisting in clinical decision making include that they are a direct measure of biological effect; they represent the earliest indicator for treatment selection, especially at a whole-body dose in excess of 5 Gy; changes in clinical parameters may be assessed rapidly in real time after exposure; they do not require sophisticated or scarce medical equipment or techniques; cli-

TABLE 3

Grading System for Response Based on Clinical Signs and Symptoms[27]

	Degree			
Symptom	**1**	**2**	**3**	**4**
Neurovascular system				
Nausea	Mild	Moderate	Intense	Excruciating
Vomiting	Occasional (1 time/d)	Intermittent (2-5 times/d)	Persistent (6-10 times/d)	Refractory (>10 times/d)
Anorexia	Able to eat	Intake decreased	Intake minimal	Parenteral nutrition
Fatigue syndrome	Able to work	Impaired work ability	Needs assistance for ADLs	Cannot perform ADLs
Temperature, °C	<38	38-40	>40 for <24 h	>40 for >24 h
Headache	Minimal	Moderate	Intense	Excruciating
Hypotension	Heart rate >100 bpm, blood pressure >100/170 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

ADLs=activities 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.

nicians are, in general, familiar with scoring these signs and symptoms (ie, minimal training is required for their implementation); and they represent cost-effective screening and assessment.

The rapid derivation of an accurate individual dose estimate may be complex. Three individual biodosimetry tools (time after exposure to the onset of nausea and vomiting, rate of decline in absolute lymphocyte count, and cytogenetic analysis) are available to clinicians. Of these tools, only cytogenetic analysis has the ability to account for doses due to heterogeneous external irradiation. Physical objects often serve as barriers to ionizing radiation exposure, partially or completely shielding tissues and organs. Even when there are no barriers between a source and a victim, the body itself serves to attenuate ionizing radiation across a plane of exposure. This means that rarely, if ever, does an individual receive a uniform whole-body dose.

Despite its advantages, several factors constrain the use of cytogenetic analysis. Because there are only a handful of laboratories worldwide capable of performing this test, overall availability is severely limited.[28] Moreover, at present, cytogenetic dosimetry is labor and time intensive, typically requiring 3 to 5 days (or longer where there is a backlog) to process samples completely.[29] By scoring fewer metaphases (eg, 20-50 spreads vs 500-1000 spreads), the time to estimation of approximate dose in a processed sample of peripheral blood may be shortened,[29] although there are no publications describing the shortening of sample process time (ie, collection, separation, and incubation times) to <24 hours (as compared to the 48 hours that is used typically). Therefore, provided that resources are available, results of a cytogenetic analysis may be available sooner when technical modifications are made to the procedures, including sample triage mode metaphase scoring and use of a computer-assisted metaphase-finding system.[30] Finally, whereas cytogenetic dosimetry, with corrections, will usually take account of heterogeneously distributed external doeses, the results it provides may be more applicable to management of hospitalized patients than to triage of victims before hospitalization.

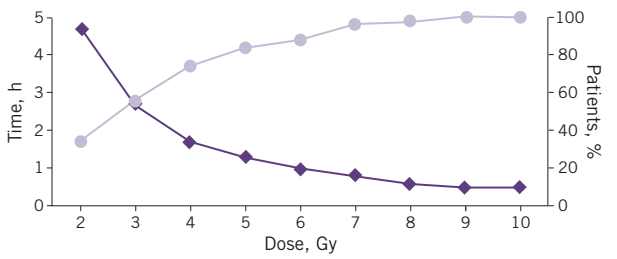
Although there are unique advantages offered by using signs and symptoms as surrogate measures for absorbed dose, health care providers are well advised to bear in mind the inconsistencies in individual response to ionizing radiation. For the second biodosimetry tool, postexposure vomiting, reports in the medical literature note variations in time to onset (particularly at doses of <2 Gy), a false-negative rate of >45% at doses of ≤3 Gy (Figure), and a potentially high false-positive rate at doses >2 Gy. Demidenko et al recently calculated the sensitivity and specificity of dose prediction based on time to emesis.[26] They generated receiver operating characteristic curves to reassess data collected in 108 observations among victims of the Chernobyl nuclear power plant disaster and the γ-ray accidents and criticality accidents populating the Radiation Emergency Assistance Center/Training Site registry.[25] Overall, the relative error for prediction of a dose of 2 Gy by time to emesis was found to be 200%. Table 4 summarizes the sensitivity, specificity, and false-positive rate for time to emesis for 100 hospitalized patients receiving a whole-body dose of >2 Gy. Accordingly, among 100 patients with a dose of 2 Gy, only 35 patients will have emesis, whereas 46 patients with emesis at 4 hours will not have received an exposure dose of >2 Gy (ie, falsely positive).

Although it is unclear why false-positives occur, several explanations are plausible. For example, psychogenic vomiting may masquerade as a radiation-induced symptom in cases in which significant psychosocial trauma has occurred or among individuals with a preexisting or underlying psychiatric disorder. For other clinical findings, the physician must consider the use of commonly prescribed medications that predispose to gastrointestinal bleeding and commonly encountered comorbidities such as gastrointestinal disorders, malignancy, and hematologic disorders, all of which may cause nausea, vomiting, cytopenias, fatigue, and bleeding.

The third biodosimetry tool, measurement of the absolute lymphocyte count, also has strengths and limitations. A relatively wide range of radiation dose is predicted by a single absolute lymphocyte count.[31] When tracked over time, however, a significant decline in the absolute lymphocyte count at 8 to 12 hours after exposure reliably predicts an approximate cumulative whole-body dose.[30-32] Table 5 summarizes dose estimates

FIGURE

Correlation of vomiting with radiation dose.



Percentage of patients experiencing vomiting and time of onset of vomiting among individuals exposed to doses ranging from 2 to 10 Gy. (Reproduced from reference 21.)

TABLE 4

Time to Emesis for 100 Hospitalized Victims After Receiving a >2-Gy Dose[26]

Time, h	Sensitivity, %	Specificity, %	No. False Positives
1	40	98	2
2	66	86	14
3	79	69	31
4	86	54	46

Sensitivity and specificity of time to emesis among individuals exposed to a dose of >2 Gy. (Modified from reference 26.)

TABLE 5

Whole-Body Dose Estimates Based on Absolute Lymphocyte Count[32]

Absolute Lymphocyte Count, per mm^3 (8-12 h postexposure)*	Absorbed Dose, Gy
1700-2500	1-5
1200-1700	5-9
<1000	>10

*A whole-body dose of ≤1 Gy is associated with no depression of the lymphocyte count below the normal range (1500-3500/mm^3).

based on absolute lymphocyte count. Prognosis has been independently predicted by the 24-hour postexposure absolute lymphocyte count[33]: mortality is 100% when the lymphocyte count is <10% of normal, with or without the addition of medical support. Repeat determinations of absolute lymphocyte count over 2-4 days and calculation of rate of decline are required to estimate an absorbed rate of 2-4 Gy.[4]

In consideration of the above evidence, the consultation group unanimously agreed on a multiparameter approach to medical decision making in a radiation mass-casualty event. Health care providers should base individualized treatment decisions on whatever data are available, especially clinical signs and symptoms, but also take into consideration physical dosimetry and individual biodosimetry. Several other groups also have advocated integrating multiple sources of data to optimize the decision making process.[4,5,34,35] Both clinical judgment and technical expertise are required to interpret biodosimetry results appropriately. Clinicians should collaborate with experts in radiation medicine to derive the value of absorbed dose.

ORGAN-BASED MEDICAL MANAGEMENT OF ARS

The following recommendations are made for the medical management of organ-based radiotoxicity, with the caveat that heterogeneous radionuclide distribution and the presence of combined injuries and/or comorbidities may complicate the determination of best practices. For example, individuals receiving a relatively high dose to the lower hemibody may have sufficient marrow reserves for complete recovery, whereas those receiving a relatively low dose but who have mechanical trauma, thermal burns, and/or significant comorbidities such as malignancy and blood dyscrasias may have a low likelihood of survival.

Management of Gastrointestinal Syndrome

The classic gastrointestinal (GI) syndrome in humans occurs at whole-body radiation absorbed doses >5 Gy. Destruction of the intestinal epithelial lining causes breakdown of the mucosal barrier that normally separates the contents of the intestinal lumen from the GI tissue, resulting in severe secretory diarrhea, dehydration, and electrolyte imbalance. Whereas progress has been made in the medical management of radiation-induced injury to the bone marrow and immune system, advances in treatments for GI injury have been far fewer. Long-term survival is unlikely in individuals with full-fledged GI radiation syndrome.

Even at lower doses of radiation, the GI tract plays a central role in the pathophysiology of toxicity and clinical outcome.[36,37] This is thought to be caused, in part, by bacterial translocation (passage of bacteria from the intestinal lumen through the defective mucosal barrier and into the bloodstream), which may occur coincident with the period of severe compromise of cell-mediated immunity. Hence, it has been postulated that sepsis from enteric bacteria is a potential cause of death, regardless of radiation dose.

Because of the morbidity and mortality caused by translocation of enteric bacteria and sepsis, the proper use of antibiotics is critical in the management of radiological emergencies. The goal of antimicrobial prophylaxis and therapy is to achieve therapeutic systemic/tissue drug levels, rather than to obtain bowel decontamination. The choice of specific antibiotics for an individual depends on antimicrobial spectra, local resistance patterns, monitoring requirements, toxicities, allergic reactions, and logistics of administration. Antibiotics with adequate activity against Gram-negative and Gram-positive bacteria and without significant toxicities, interactions, or need for monitoring of serum levels are preferred. Fluoroquinolones are recommended as an initial choice for prophylaxis and may be supplemented by a triazole antifungal agent. The expert group acknowledged, however, that no prospective trials have been performed to assess antimicrobial agents for prophylaxis of treatment of GI infections. Therefore, the strength for this recommendation is weak.

Bowel decontamination is not recommended without the concomitant use of systemic antibiotics. Decontamination of the bowel, coupled with systemic antibiotic administration, may be useful in small-volume radiation incidents; however, in a large casualty scenario involving 100 to 200 hospitalized victims, resources may be insufficient to attempt such intervention. Administration of oral antibiotics to patients having a clinical indication for parenteral antibiotics is weakly recommended, provided that resources are available.

Like the other organ systems affected by radiation exposure, the GI tract responds early with prodromal symptoms and after a latent period, with symptoms characteristic of manifest illness. Prodromal-phase symptoms include anorexia, nausea, vomiting, and diarrhea. Time to onset of symptoms is, in general, inversely related to radiation dose, whereas severity is directly related to dose.[38,39] Approximately 10% to 50% of individuals exposed to 1 to 2 Gy experience mild nausea and vomiting within 2 hours of exposure. By contrast, nearly 94% of individuals exposed to 6 to 8 Gy develop severe nausea and vomiting within 30 to 60 minutes.[4,40]

In addition to the replacement of fluids and electrolytes, the mainstays for management of acute GI radiation injury in-

clude administration of antiemetic compounds, antidiarrheal drugs, and antimicrobials. Overall, the clinical experience with the management of GI radiation injury after whole-body exposure is limited. The predominance of evidence for treatment recommendations is derived by inference from reports describing the care of people with unintentional localized radiation exposure and from studies of patients receiving myeloablative radiation and/or chemotherapy in preparation for stem/progenitor cell transplantation.[41-43]

Clinicians should enhance comfort, conserve body fluids and electrolytes, and reduce the risk of aspiration pneumonia in patients with nausea and vomiting. With an optimal antiemetic regimen, adequate control of nausea and vomiting can be expected in >50% of patients. The antiemetic of choice is a serotonin-receptor antagonist, 5-hydroxytryptamine.[4,40,44] The addition of steroids and/or antagonists to substance P (a neurotransmitter involved in the vomiting reflex, vasodilation, and pain sensation), such as aprepitant, is thought by some to be beneficial, although the efficacy of these therapies remains unproven. At biologically equivalent doses, all of the serotonin antagonists appear to have nearly equivalent safety/efficacy profiles and may be used interchangeably. Antiemetics delivered orally appear to be as effective and safe as those administered intravenously.[45-47]

Diarrhea may be controlled with conventional antidiarrheal drugs. Of the 2 most common antidiarrheals, loperamide and diphenoxylate, the former has fewer adverse effects and better efficacy than the latter. Somatostatin analogs (including octreatide, lanreotide, and pasireotide) are more expensive and less readily available but can offer relief in patients with otherwise intractable diarrhea.[48-51] Oral nutritional support is preferred over parenteral nutrition because it promotes the immunological and physiological integrity of the GI tract[52]; however, parenteral support is indicated in patients with adynamic ileus or diffuse bleeding from the GI mucosa.[53,54]

Management of Cutaneous Syndrome

Ionizing radiation damage to the skin is common. The degree of dermatological injury is an important determinant of overall survival of patients with ARS.[55] Based on observations in individuals receiving fractionated radiation therapy, radiation accident victims, atomic bomb victims, and irradiated animals, cutaneous injury usually presents with early and sometimes transient erythema, followed by a symptom-free interval lasting days to weeks.[12,27] During the manifest illness phase, desquamation, blisters, ulcerations, onycholysis, and necrosis may develop in days or weeks after exposure. Evidence suggests that the evolution of radiation-induced skin damage in humans is continuous, as compared with that seen in experimental animals.[27,56,57]

The duration and severity of skin changes are determined by radiation quality, dose, and dose rate.[58-60] Radiation induces the production of cytokines by skin cells; cytokines trigger an inflammatory cascade in the dermis that can result in fibrosis.[61] Moreover, radiation-induced dermatological injury may initiate MOF.[62,63] Bioindicators of poor prognosis include elevated levels of cytokines and other markers that predict for the progression of MOD to MOF.[64,65]

The primary goal of treatment is interruption of radiation-induced inflammation of the dermis. In view of a lack of controlled therapeutic trials, treatment is guided by inference from the standard care for nonradiation-induced skin injury, as recommended by dermatologists and radiotherapists. Anti-inflammatory agents such as topical class II to III steroids (eg, betamethasone, mometasone), topical antibiotics, and antihistamines should be considered. Systemic steroid use is not recommended. Silver sulfadiazine cream with nonadherent dressings may be useful for covering the outer layers of skin during the moist desquamation phase of cutaneous injury.[32,66]

Ulcers, localized necrosis, and severe intractable pain are best treated by surgical excision and skin grafts.[67] Extensive tissue damage requires grafting with artificial skin, split-thickness skin grafts, or donor skin grafts.[68] All necrotic tissue must be removed to maximize the success of engraftment. Once hemostasis is achieved, a split-thickness graft is applied and secured using sutures, staples, or fibrin glue.[69,70] Multiple grafts may be required, and prolonged hospitalization should be anticipated.

Skin flaps are useful when additional reconstructive surgery (for tendon repair, nerve repair, and so forth) is required or when coverage of bone, cartilage, tendons, nerves, or blood vessels is necessary.[67] Flaps also should be used to cover severely scarred areas that are unable to support grafts. Amputation may be required for patients with a necrotic extremity.[71] If the indication is clear, then amputation should take place as soon as possible after medical stabilization is achieved.

Therapeutic approaches to MOD- and MOF-related cutaneous injury include the use of anti-inflammatory agents and topical steroids. Although systemic steroids are not indicated for localized radiation injury,[72] their use should be considered for MOF-related skin dysfunction. Limited experience with the use of other therapeutic options, including pentoxifylline, α-tocopherol, transforming growth factor-β, fibroblast growth factor, interferon-γ, and estradiol has been encouraging.[73-76]

Chronic pain resulting from the compression of cutaneous nerve bundles is a frequent complication of radiation ulcers.[27,71] A novel therapeutic approach using the parenteral or local infusion of autologous, in vitro expanded mesenchymal stem cells (MSCs) was used to treat a patient with intractable pain resulting from a radiation burn.[77] After therapy, the patient experienced significant pain relief. The administration of bone marrow–derived MSCs to macaques and immunodeficient mice has shown a similar effect. Together, these findings provide proof of concept for the use of MSCs in individuals with radiation injury[77-79]; however, concomitant administration of other treat-

ments confounds interpretation of the effect of the MSCs. Controlled studies are required to validate potential benefits and to verify or exclude potential adverse effects such as genomic instability and malignant transformation, both of which were reported in experimental mice receiving bone marrow–derived MSCs.[80] Additional details regarding the potential role of MSCs in the management of the cutaneous syndrome are discussed below.

MSC Treatment of Cutaneous Injury

MSCs are heterogeneous multipotent stem cells with the capacity to differentiate into mesoderm-derived cells.[81] After intravenous infusion, they migrate to injured tissues such as the skin, where they induce cellular and functional recovery and where they exhibit anti-inflammatory and immunoregulatory capacities.[82-86] MSCs usually are obtained from the bone marrow; umbilical cord blood and adipose tissue are alternative sources. In vitro expansion of MSCs in medium containing either fetal calf serum with or without fibroblast growth factor-2 or platelet lysate[87] can generate 1 to 5×10^6 MSCs per kilogram of body weight.

More than 200 patients have safely received autologous or allogeneic MSCs from unrelated donors. In most cases, MSCs have been infused in the context of allogeneic hematopoietic stem cell transplantation. MSCs were first applied in Paris to a 27-year-old Chilean, who, on December 15, 2005, was exposed to an iridium gammagraphy radioactive source (^{192}Ir, 3.3 TBq).[78] Treatment included dosimetry-guided surgery and MSC therapy. A severe radiation burn of the buttock (2000 Gy at the center of the skin lesion) was widely excised (10 cm in diameter), using physical and anatomical dose reconstruction to define the limit of the surgical excision. Secondary extension of radiation necrosis led to a new excision of fibronecrotic tissue. Local cellular therapy was applied using autologous expanded MSCs as a source of trophic factors to promote tissue regeneration. Bone marrow–derived MSCs were expanded using clinical grade, closed culture devices and serum-free medium-enriched human platelet lysate. The clinical outcome was favorable, with resolution of pain and healing of the skin. No recurrence of radiation-induced inflammation was observed after 11 months of follow-up.

Subsequently, 2 additional irradiated victims with deep radiation ulcers were treated in a similar way, with favorable outcomes. Three patients of a series of 23 overirradiated patients with prostate cancer in Épinal, France, were administered MSCs intravenously. In 1 of the treated patients, pain resolved for 4 months and bleeding subsided. Red blood cell transfusions, which were previously administered weekly, were no longer required. When pain reappeared in this patient, a second MSC infusion was administered and the pain resolved. In a second patient, resolution of pain persisted for 6 weeks.

Therapeutic quantities of MSCs are available either commercially or from in vitro expansion of marrow cells prepared from individual donors. Controlled clinical trials are needed to determine the role, if any, of MSC infusion in the management of radiation-associated cutaneous injuries. The potential for genomic instability and malignant transformation[80] must be assessed as well.

Management of Neurovascular Syndrome

Acute, irreversible neurotoxicity occurs at a whole-body dose in excess of approximately 10 Gy.[88,89] Disorientation, ataxia, prostration, and seizures, together with fever (>40°C) and hypotension (<80 mm Hg/palpable), are predictive of a nonsurvivable exposure. Several pathophysiologic processes may contribute to neurovascular collapse, including vascular damage, inflammation, cerebral edema, increased vascular permeability, and perivascular hemorrhage.[15] A brief latent period lasting several hours typically is followed by severe incapacitation, progressing to coma and death within 24 to 48 hours.[90]

At present, supportive care alone is recommended for patients diagnosed as having the neurovascular syndrome. Treatment includes antiemetic therapy (with a serotonin-receptor antagonist), antiseizure medications, mannitol, furosemide, and analgesics (including nonsteroidal anti-inflammatory agents and opiates). The use of corticosteroids such as dexamethasone must be determined individually, based upon the potential benefits and the risk of infection. Depending on resource availability, patients with neurovascular syndrome may receive palliative care at a routine care unit of the hospital.

Management of MOD/MOF

Radiation-induced MOD and MOF result from complex and poorly understood pathophysiologic mechanisms.[14-16] Concurrent injury occurs to multiple organs/organ systems, and complex interactions among cells from damaged and unaffected organs take place. It is believed that early treatment of organ dysfunction may prevent fulminant organ system breakdown. Because the care of patients with MOD/MOF may require multidisciplinary, resource-intensive therapy, including invasive hemodynamic monitoring and prolonged ventilator support,[16] these patients should be managed at institutions staffed by clinicians having experience in providing care to critically ill patients and/or patients with severe immunodeficiency. Excellence in clinical care notwithstanding, a fatal outcome should be expected.

ADDITIONAL ASPECTS OF CLINICAL CARE

General Supportive Care

Depending on the degree of vomiting and/or diarrhea, presence of burns and/or mechanical trauma, and availability of resources, individuals receiving an estimated dose of ≥2 Gy are candidates for hospitalization. At doses exceeding this threshold, the probability of organ specific damage is high, and close clinical monitoring is warranted. Hospitalized patients should be provided with electrolyte and fluid replacement. An adequate intravascular volume and optimal tissue perfusion must be maintained. Monitoring by measurement of central venous

pressure and mixed venous oxygen saturation should be considered. Oxygen delivery should be optimized by the administration of oxygen and the maintenance of cardiac output by fluid administration, and if necessary, by the addition of an inotropic agent.

Antiemetic therapy should be administered when nausea and vomiting are present. Nonsteroidal anti-inflammatory agents should be used with caution because these agents may induce platelet dysfunction in patients who may be destined to develop significant thrombocytopenia, thereby enhancing the risk for life-threatening bleeding. Nutrition should be initiated as early as is feasible. Antiseizure medication is required for individuals experiencing seizure activity. Pain that is secondary to cutaneous injury or other trauma should be managed according to the WHO's pain relief protocol.[91] Because radiation/nuclear incidents have the potential to create fear, anxiety, and depression, every attempt should be made to provide psychological support, sedatives, and anxiolytics, as necessary.

Infection Control and Management

Ionizing radiation suppresses immune function and damages vital organs, placing affected individuals at an increased risk for infection. Because infection is a major cause of mortality after radiation exposure, treating infection is an essential aspect of the care of patients with ARS.

Patients with an absolute neutrophil count of $<0.5 \times 10^9$ cells per liter are at increased risk for opportunistic and nosocomial infections and may benefit from both cytokine (see above discussion) and prophylactic antimicrobial therapy.[4,5,32,40,92] Moreover, individuals with this degree of neutropenia can be presumed to have received a radiation absorbed dose in the range of 2 to 10 Gy, placing them at risk for GI injury and bacterial translocation across the bowel wall.[4] Animal studies indicate that high-dose radiation exposure significantly reduces the number of enteric anaerobic bacteria populating the gut, relative to that of pathogenic aerobes.[66] A primary objective of prophylaxis, therefore, is to address this imbalance by treating individuals with antibiotics that will shift the bacterial population in the gut in favor of anaerobes.[4,40,66] Prophylaxis with a fluoroquinolone having streptococcal coverage is recommended.[4,40,93]

Patients with suspected or established infection should be placed on a treatment regimen that is similar to that of patients with malignancy and neutropenic sepsis. In non-neutropenic patients, use of antibiotics should be reserved for obvious foci of infection secondary to burns, penetrating wounds, and/or abdominal/visceral trauma.[4,40] The antibiotics used may include a carbapenem. Clinicians should base definitive choices for antibiotics on the results of microbiological culture and sensitivity testing, toxicity of selected antibiotics, local patterns of antibiotic resistance, and medical history of allergic reactions.

Antifungal and antiviral therapies also are warranted in this population.[4,5,35] Antifungal therapy should be considered to treat infection in febrile patients who do not respond to antibiotics. Prophylactic fluconazole, which reduces overall mortality in immunosuppressed patients, or similar agents may be used to suppress yeast colonization. Posaconazole, which is also active against *Aspergillus*, has been shown to reduce mortality in patients with chemotherapy-induced neutropenia.[94] Alternative antifungals such as voriconazole and amphotericin B may be indicated in patients for whom fluconazole lacks appropriate efficacy.[4,5,40,92] Prophylactic antiviral therapy with valcyclovir or acyclovir is recommended for individuals with a history of infection with herpes simplex virus or with a positive serology for type 1 or 2 herpes simplex virus.[4] In such patients, immunosuppression confers a heightened risk of viral reactivation.

Critical Care Support

Patients with ARS that is complicated by MOD/MOF may require critical care support in an intensive care unit (ICU).[16,95,96] Patients receiving a whole-body dose of 5 to 10 Gy are candidates for care in an ICU.[4,5,97] Individuals receiving 3 to 5 Gy also may require critical care, depending on the nature of organ involvement and resource availability. Because of the paucity of evidence-based protocols for the critical care management of patients with ARS and MOD/MOF, the basis for management recommendations is derived by inference primarily from principles and guidelines for the management of sepsis-related MOF.[14,96,98] For critical care to be successful, injury to the hematopoietic system should be treatable (see Part 2 of this article), radiation-induced injury to nonhematopoietic organs should be reversible and sufficient medical resources should be available. Because such individuals are at an increased risk for infection, they should be cared for in a reverse-isolation room, pending the recovery of the hematopoietic system. Meticulous attention to universal precautions is required to avoid cross-contamination of organisms within the ICU.

Whole-body exposure to a high radiation dose may induce diffuse intravascular coagulopathy and sepsis.[40,97,99] Because of a higher risk of bloodstream infection, caution should be taken regarding the prolonged use of devices used for invasive monitoring. Rapid replacement of fluids, electrolytes, and blood products is required for irradiated victims presenting with significant burns, hypovolemia, hypotension, and/or shock. Because massive amounts of fluids may be mobilized in the skin and lungs, particularly in a patient with significant cutaneous involvement, close monitoring of intake and output with appropriately matched fluid replacement is necessary.[96,100]

The lung reacts to radiation exposure in distinct, time-dependent phases.[101] For days to weeks, edema and infiltration with leukocytes occur. Later, the number of goblet cells increases, leading to the thickening of pulmonary secretions. An acute exudative phase occurs after 1 to 3 months, which is associated with sloughing of the endothelium and epithelium. Collagen deposition and fibrosis develop in months to years.

Pulmonary complications of a significant exposure include radiation-induced pneumonitis, lung-volume reduction, and pulmonary contusion from blunt trauma associated with a blast injury.[102-104] Atelectasis, pulmonary edema, and pulmonary hemorrhage were reported among Japanese atomic bomb victims, with changes typical of acute respiratory distress syndrome and/or organizing pneumonia.[105,106] Fatal interstitial pneumonitis accompanied by a restrictive ventilatory defect with low diffusing capacity was noted among previously irradiated bone marrow transplant recipients.[107,108] Patients developing acute lung injury and respiratory failure require intubation and treatment with a lung-protective strategy. Prone positioning, a high positive end-expiratory pressure/low tidal-volume strategy, and use of the lowest concentration of inhaled oxygen to achieve an oxygen saturation of >90% are recommended in the therapy of persistent acute respiratory distress syndrome.[105,106,109-111]

The administration of parenteral corticosteroids may be effective in reducing mortality from septic shock.[111,112] A similar approach has been used in patients with radiation-associated shock and MOD/MOF[113,114]; however, in the absence of a specific medical indication, intravenous steroids are not recommended. The use of protocols for sedation of critically ill patients on ventilation reduces the duration of mechanical ventilation and ICU and hospital stay.[115] Daily interruption/lightening of continuous infusion sedation with awakening and retitration may be appropriate for a mechanically ventilated patient with ARS.

Selective decontamination of the digestive tract has resulted in a reduced rate of respiratory tract infections among patients admitted to the ICU.[116-118] Results of a recent study in an ICU population indicate that selective oropharyngeal decontamination achieves a level of reduction in mortality similar to selective digestive tract decontamination (SDD).[119] SDD also has been used in radiation victims.[95,120-122] On the basis of this experience, decontamination of the digestive tract is recommended for ICU patients with ARS. It is recommended that careful consideration be given to the administration of selective oropharyngeal decontamination to minimize the risk of selection for antibiotic-resistant organisms that is of theoretical concern in patients receiving parenteral antibiotics as part of the SDD regimen.

Stress ulcer prophylaxis using an H_2 blocker or a proton pump inhibitor should be administered to critically ill patients to prevent upper gastrointestinal bleeding.[123-125] The benefit of preventing upper GI bleeding should be weighed against the potential effect of increased gastric pH on the development of ventilator-associated pneumonia. The results of observations in patients receiving therapeutic bone marrow transplantation suggest that chronic renal insufficiency may result from irradiation at bilateral renal doses exceeding 4 to 5 Gy.[123] Data from preclinical and clinical studies suggest that the incidence of chronic renal failure is reduced by the administration of prophylaxis with inhibitors of angiotensin-converting enzyme or antagonists of angiotensin II receptor.[124] The molecular basis for these beneficial effects is unknown, and the applicability of these treatments to prevention of subsequent MOF is unclear.[124]

The consultancy group concurs with the recommendations of the American Association of Clinical Endocrinologists and the American Diabetes Association to maintain an average blood glucose concentration of 140 to 180 mg/dL for the majority of patients with diabetes mellitus in most critical care units and of 110 to 140 mg/dL for selected diabetic patients in critical care units having added expertise in diabetes management.[125] Other supportive therapies that may be useful include the use of recombinant human-activated protein C for patients with MOF or patients with a high Acute Physiology and Chronic Health Evaluation II score[126] and hemodialysis for patients with significant renal impairment.[127]

Management of Diabetes Mellitus After Exposure to Ionizing Radiation

No published information was found regarding the impact of radiation exposure on the clinical course of diabetes mellitus. Circumstantial evidence for tight glucose control among nonirradiated patients with diabetes mellitus in the ICU appears to be strong.[128] Although studies in the ICU setting have demonstrated improved mortality among patients in whom tight blood glucose control (<150 mg/dL) was achieved, results of recent analyses of studies of tight glucose control among ICU patients suggest that mortality is increased, largely caused by hypoglycemia.[129,130] When blood glucose is maintained at <120 mg/dL, mortality was significantly higher than when it was maintained between 140 and 180 mg/dL.[131,132] Recommendations have been made jointly by the American Association of Clinical Endocrinologists and the American Diabetes Association to maintain an average blood glucose concentration of 140 to 180 mg/dL for the majority of patients in most critical care units and of 110 to 140 mg/dL for selected patients in critical care units having added expertise in diabetes management.[129] The consultancy group concurs with these recommendations and acknowledges the need for prospective randomized controlled trials in critically and noncritically ill diabetic patients with ARS.

Ethical Considerations in Allocating Scarce Resources

A radiation emergency may create panic and social chaos.[93,133] The possibility of shortages of potentially lifesaving resources heightens this concern. A significant radiation event may create circumstances in which not all of the individuals who require certain medical treatments to survive will be able to receive them. When absolute shortages of key resources arise, emphasis should be placed on the mobilization of additional resources, including increasing surge capacity and arrangement for transfer to hospitals and health care facilities that are located outside the incident community.

A transparent, consistent approach to allocation should be taken. The expert group recommends that allocation of scare re-

sources be implemented by "triage teams," in general, senior clinicians who have no direct care duties.[134] These individuals should operate in close collaboration with public health officials. Decisions regarding the assignment of scarce resources (eg, organs for transplantation, vaccines and antiviral agents, mechanical ventilators, critical care beds) must be made within existing legal and ethical constructs. Governments have a responsibility to develop mechanisms that allow civilian triage to occur in radiation emergencies without the fear of legal jeopardy for clinicians, provided that recommended practices are followed. This highlights the importance of an integrated response among health care providers, government agencies, and public health officials.[135]

The consultancy group recommends that patients be prioritized according to predefined allocation criteria and that treatment be provided to as many as possible as defined by the availability of resources. The allocation of resources based on a first-come, first-served basis or based on maximizing the number of survivors regardless of the likely duration of benefit is ethically and practically insufficient. The consultancy group believes that a multiple principle allocation strategy captures more of the ethically relevant factors involved in difficult allocation decisions. Potential allocation criteria include maximizing the number of patients who survive the acute event, the number of life-years saved, and individuals' chances to live through each of life's stages. Numerous principles that may be used to guide allocation decisions should be considered.[136-138] Readers are referred to the extensive literature on ethical decision making in health emergencies.[139-142]

Palliative Care

Clinicians and public health authorities have a strong ethical obligation to provide palliative care to patients who have received nonsurvivable injuries after radiation exposure. The key aspects of basic palliative care include aggressive pain management, control of other physical symptoms such as severe nausea and diarrhea, clear communication, spiritual counseling, and bereavement counseling.[143] High-quality palliative care should be provided even in the context of limited resources.

Psychological Support

Because the psychological effects associated with prior radiation events, including those at Goiânia, Brazil, and Chernobyl, Ukraine, far exceeded the physical health consequences of these emergencies,[144-146] the management of public distress is critical. Health care and mental health providers and rescuers must be prepared to address psychosocial issues arising among irradiated victims. WHO and the International Atomic Energy Agency have developed policies to minimize uncertainty, stress, and anxiety among victims, relatives, friends, and the public.[92,147] It is likely that in an accident requiring the hospitalization of 100 to 200 victims, many additional people with less severe or no exposure will require emotional support. Those at the highest risk for developing significant psychological effects are children, mothers of young children, and individuals with a medical history of a psychiatric disorder.[148,149]

A concise and accurate message should be delivered to radiation victims and the public as soon as possible after a radiological/nuclear event. Frequent updates from trusted sources are required, as information becomes available. Core tenets of psychological first aid include providing for safety, health, and basic needs first, including medical care, shelter, and food. After this, a focus on calming, connecting, and promoting self-efficacy is important. Blaming, victimizing, and catastrophizing should be avoided. Specific tools may be used when dealing with radiation victims, including careful listening, repeating back, and focusing full attention on victims. Patients requiring evaluation by a psychiatrist or psychologist include those with preexisting psychological conditions, those who are inconsolable, and those who have acute fear, grief, or injury rather than chronic illness.

Education and Research

Radiation-specific medical and safety training is required for health care providers to develop a rudimentary understanding of radiation biology and a basic skill set for treating victims of a radiological/nuclear event. Essential information on the use of radiation measurements and clinical guidelines for the medical management of ARS is available to clinicians through several regularly updated sources, including the National Institutes of Health Radiation Event Medical Management Web site from the US Department of Health and Human Services (http://remm.nlm.gov). Excellent information also is available in standard medical textbooks.[150,151] *The Triage, Monitoring and Treatment Handbook*, a technical publication that is appropriate for experts, is available online and in hard copy.[92] Complex guidance documents from governments, professional societies, and international organizations are important, but clinicians with limited radiation expertise may find them difficult to use.[152-155] The utility of such documents for clinicians having no or limited familiarity with radiation injury is questionable. Finally, various software tools (http://www.remm.nlm.gov/remm_SourcesofRadInfo.htm#software) and compact discs are available[156-161] that primarily target specific audiences. The efficacy of some of these tools[155] has not been tested in actual events.

Comprehensive advanced training courses are available to clinicians, including those sponsored by AFRRI (http://www.afrri.usuhs.mil/outreach/meir/meir.htm) Radiation Emergency Assistance Center/Training Site in Oak Ridge, Tennessee (http://orise.orau.gov/reacts/courses.htm), the International Center for Advanced Studies in Health Sciences and Services in Ulm, Germany, and the National Institute of Radiological Sciences in Chiba, Japan. The long-term benefit of intense training for several days or 1 week is unknown. Refresher training exercises may be needed for a greater educational impact. Finally,

simple, just-in-time, evidence-based guidelines available on trusted Web sites may be helpful.

New medical countermeasures are needed to prevent and treat radiation injury. Because ethical considerations preclude the use of randomized trials in humans, information concerning efficacy, adverse effects, and mechanisms of action of such countermeasures must be generated in relevant animal models. Model systems should be developed that are analogous to accidental or intentional exposure to radiation to approximate a human exposure scenario. Cellular and molecular mechanisms for low-dose and moderate- and high-dose radiation effects must be clarified through basic research. National governments should assume responsibility for supporting clinical and basic research in these subject areas. Continued international cooperation regarding the medical management of ARS, MOD/MOF, and potential early and late effects of radiation exposure should be facilitated by WHO.

Response, Training, and Certification

First responders and first receivers at mass-casualty radiation events acquire and maintain specialized knowledge and skills beyond the basic skills they need and use during responses to other mass-casualty events.[162,163] Even individuals who are providing care at facilities that are far from the epicenter of the mass-casualty event need radiation-specific medical and safety training, because the transfer of significant numbers of patients will be required when local facilities are either full, contaminated, or physically damaged.[164]

Providing up-to-date radiation event medical response training is pedagogically challenging. Health care providers have expressed a reluctance to embrace this training for a variety of reasons,[165,166] including that they are already overwhelmed with work, the probability is low that their training will be used and the educational content will be forgotten, medical responses are perceived as futile and personally dangerous, the task is perceived as owned primarily by the national/federal government, and staying home to protect their families is preferred to responding to a radiation event. The pedagogical task is complicated further by a wide range of both baseline content knowledge and preferred learning styles among the diverse professional categories of potential responders.[167]

Multiday civilian and military classroom radiation event medical response training has long been offered by educational institutions, professional societies, and government agencies in various countries.[168-170] Radiation safety principles, including personal protective equipment, suitable personal monitoring devices, and state-of-the-art decontamination techniques also must be practiced. This complex, expensive training typically is time consuming and provided far from home and work by a limited number of experts. Moreover, training is not likely to provide lasting benefits, unless it is repeated regularly and exercised frequently.

Web sites have provided public access to important, up-to-date official radiation event–response guidance documents. Preparedness and response guidance documents usually are complex and not useful for the average medical responder without expertise in the field of radiation medicine.[171] Print and Internet access to the vast, sophisticated literature on basic and clinical radiation research may be inefficient in teaching nonexpert responders necessary key lessons. Complex software tools also are used for a variety of technical tasks that are related to radiation safety, dosimetry, and response management, but these may not be suitable for some medical responders.[172]

Audience-targeted online and offline e-learning tools have been developed to provide concise, cost-effective, just-in-time, usable, evidence-based training and medical management guidance for responders who are not experts in radiation medicine.[171,173-175] Mobile device versions of some Web-based radiation-response information and e-learning tools also have become available that are of particular interest to first responders in the field.[159-162,176] Using formal, robust e-learning systems, government and private entities have offered key lessons targeted toward specific audiences.[162,177] The lasting efficacy of these tools has not been formally tested. Nevertheless, these tools probably enhance the ease and efficiency of many parts of the learning process. Recently, a comprehensive, multiday advanced training course for physicians based on the Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerised Guidance System concept[27] was held in Europe as a pilot training event. Participant evaluations suggested that the length of time of the training course be reduced to 1 day after a new e-learning component had been completed successfully.[178]

The importance of radiation preparedness training and certification is being acknowledged increasingly by key accrediting authorities. For example, societies for oncology professionals in the United States are actively considering adding questions about radiation mass-casualty response issues to certifying examinations and providing more detailed content in continuing medical education offerings to their members.[179,180] Hospital accreditation in the United States also is being linked increasingly to demonstrations of all-hazards and chemical, biological, radiological, and nuclear–specific emergency preparedness.[5]

Radiation event–response training curricula will require continual revision as new radiation pathophysiology concepts gain acceptance, response operations are revised, and new medical countermeasures are developed. Electronic media will disseminate these changes more efficiently than traditional print media or formal classroom teaching. Robust online software tools that provide global situations awareness and planning also are being used increasingly by individuals who are participating in and managing mass-casualty responses. Linking event management software to vetted

TABLE 6

Summary of Recommendations for Treating 100 – 200 Hospitalized Patients With Whole-Body Exposure to Ionizing Radiation

Syndrome	Recommendation	Strength of Recommendation
Gastrointestinal	Administer fluoroquinolone or similar antibiotic 2-4 d after radiation exposure	Weak (B-1b)
	Provide bowel decontamination and parenteral antibiotics when indicated, if resources permit	Weak (C-1b)
	Administer a serotonin-receptor antagonist prophylactically when suspected exposure is >2 Gy	Strong (A-1a)
	Administer loperamide pro re nata for control of diarrhea	Weak (B-1b)
	Provide nutritional support through enteral route	Weak (B-1b)
Cutaneous	Administer topical class II-III steroids, topical antibiotics and topical antihistamines to radiation burns, ulcers, or blisters	Strong (A-1a)
	Administer systemic steroids for radiation burns, ulcers, or necrosis in the absence of a specific indication for systemic steroid use	Strong against (D-2a)
	Surgically excise and graft radiation ulcers or localized necrosis with intractable pain	Strong (B-1a)
Neurovascular	Provide supportive care with a serotonin receptor antagonist, mannitol, furosemide, and analgesics	Strong (A-1a)
Critical care	Administer fluid and electrolyte replacement therapy and sedatives when significant burns, hypovolemia, and/or shock occur	Strong (A-1a)
	Administer mechanical ventilation with a lung-protective strategy for acute respiratory failure	Strong (A-1a)
	Administer SOD or SDD to decontaminate the digestive tract	Weak (B-1b)
	Maintain average blood glucose of 140-180 mg/dL for majority of critical care patients	Weak (B-1b)
	Administer H_2 blocker or proton pump inhibitor	Weak (B-1b)

medical guidelines may facilitate the provision of medical best practices and patient tracking and follow-up.

The authors of this article, like others before them, recommend strongly that evidence-based medical guidelines, concepts of response operations, countermeasures, and laboratory standard operating procedures be developed and shared internationally whenever possible and be provided in advance to actual responders in a form that can be easily accessed, understood, and used.[181] Optimized, coordinated international responses will assist in the delivery of appropriate, expedited mass-casualty care under even the most difficult circumstances. Electronic software tools of varying types are likely to play an increasing role in enabling responders and planners to remain up to date, evidence based, and effective during mass-casualty radiation events.

IMPLEMENTATION OF NEW MEDICAL PRODUCTS

New knowledge from the fields of inflammation, damage repair, and regenerative medicine are critical in the development of effective medical countermeasures.[181] The development and systematic testing of such countermeasures requires animal model systems for demonstrating the effects of new drugs. Modifications to regulations have been made in an attempt to encourage new drug development via nontraditional pathways.

For example, the US Food and Drug Administration's "animal rule" (21 CFR 314 was enacted in 2002 as a mechanism whereby new drugs may be approved for use in situations in which human efficacy studies are neither ethical nor feasible. The rule provides for efficacy studies in animal models to substitute for human studies with regard to medical countermeasures. Under the provisions of the "animal rule," effectiveness may be derived from adequate and well-controlled studies in animals, without demonstrating efficacy in humans; the effect is demonstrated in >1 animal species that is expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans; the animal study endpoint is clearly related to the desired benefit in humans (enhancement of survival or prevention of major morbidity); a reasonably well-understood mechanism exists for the toxicity of the threat agent and its amelioration or prevention by the countermeasure under study; and safety must be established through the traditional path (animal toxicology and safety in humans).

Accordingly, it is important to develop appropriate animal models that account for the variety of radiation-associated injuries identified in humans and that can predict the human response adequately. It is unclear whether countermeasures approved by the Food and Drug Administration using the "animal rule" will be used to treat radiation injury in countries outside the United States. Engagement in constructive dialogue is needed to maximize the potential for developing countermeasures for use worldwide.

SUMMARY OF RECOMMENDATIONS

The WHO consultancy achieved international consensus on the medical management of ARS. Wherever possible, recommendations were based on quality of evidence, using the GRADE system. A summary of recommendations is presented in Table 6. Depending on the availability of resources and the projected survivability of exposure to radiation, a

strong level of recommendation is made for the management of individuals who meet the treatment criteria with a serotonin-receptor antagonist when the suspected exposure is >2 Gy; topical steroids, topical antibiotics, and topical antihistamines for radiation-induced cutaneous injury; surgical excision and grafting for radiation necrosis of the skin; supportive care for neurovascular toxicity; mechanical ventilation for respiratory failure; and administration of fluids, electrolytes, and sedatives for significant burns, hypovolemia, and/or shock. Although parenteral steroids may be indicated for a specific reason in selected individuals with ARS, a strong level of recommendation is made against their routine use in the absence of a specific medical indication for individuals with ARS who require either critical care or routine medical care in the hospital.

Additional research is needed to identify new therapeutic approaches and to develop novel countermeasures for radiation toxicity. International cooperation among health care providers, scientists, and dosimetrists is required to optimize protocols and treatment outcomes. It is expected that these recommendations will form the basis for future international guidelines on public health response to radiological and nuclear emergencies.

CONCLUSIONS

The medical management of ARS in hospitalized patients optimally involves general internists, subspecialists, and experts in radiation measurement and effects. The integration of clinical information with dosimetry measurements is essential for predicting the severity of injury and assigning prognosis. An objective review of the published literature discloses case series and case reports but no randomized controlled trials in humans. Recommendations for specific countermeasures rely heavily on the results of studies in experimental animals and published guidelines for therapy in nonirradiated individuals. Education and training provide the key to a successful radiation-response effort. Additional research is needed to identify new therapeutic approaches and to develop novel countermeasures for radiation toxicity. International cooperation among health care providers, scientists, and dosimetrists is required to optimize patient outcomes. WHO should continue to facilitate this cooperation.

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