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Original Research Article

Radiation Accidents and their Management: Review of Therapeutic Principles of Acute Radiation Syndrome

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Fortunately, radiation accidents are of infrequent occurrences, but since they have the potential of large scale events like the nuclear accidents of Chernobyl and Fukushima, preparatory planning for the medical management of radiation accident victims is very important. Radiation accidents can result in different types of radiation exposure for which the diagnostic and therapeutic measures, as well as the outcomes, differ. *The aim of this review* was to provide a framework for physicians and the medical subspecialties to evaluate and manage large-scale radiation injuries. The rationale for the further evaluation of mesenchymal stem cells (MSCs) therapy was stressed to address the current unmet medical needs of acute radiation syndrome (ARS). *Methods:* The most important therapeutic principles with special reference to hematopoietic syndrome and cutaneous radiation syndrome are reviewed. *The results:* The clinical course of ARS depends on the absorbed radiation dose and its distribution. Multi-organ involvement and multi-organ-failure was taken into account. Documentation of clinical signs and symptoms (affecting the hematopoietic, gastrointestinal, cerebrovascular, and cutaneous systems) over time was essential for triage of victims, selection of therapy, and assignment of prognosis. A *conclusion* based on radiation dose and physiologic response was made for treatment of the hematopoietic syndrome. Psychosocial support will be required for those exposed, regardless of the dose, as well as for family and friends. For terrorist or accidental events involving exposure to radioiodine, prophylaxis against malignant disease of the thyroid was also recommended, particularly for children and adolescents. *Recommendations regarding* a multidisciplinary approach built on international cooperation are of the utmost importance and currently the most reasonable strategy to provide the best possible medical care for radiation accident victims. There is a strong need for internationally recognized guidelines for the treatment of severely radiation exposed patients. Further research and experimental studies are necessary to identify prognostic parameters for the estimation of irreversible damage to organs and organ systems and a deeper understanding of the pathophysiology of radiation induced multi-organ failure (MOF).

Keywords: Acute radiation syndrome, Mesenchymal stem cell, Cell therapy, Hematopoietic syndrome, Gastrointestinal syndrome, Radiation injury

INTRODUCTION

Fortunately, radiation accidents are of infrequent occurrences, but since they have the potential of resulting in large scale events, such as the nuclear accidents of Chernobyl and Fukushima, preparatory planning for medical management of radiation accident victims is very important (Dörr and Meineke, 2006). Radiation accidents can result in radiation exposure to only a few up to several hundreds of people, depending on the type of accident and the amount of radiation exposure. Radiation exposure can occur as an external exposure, for instance, from a sealed radiation source, or as internal exposure due to the intake of radionuclides. In a nuclear disaster scenario like the Chernobyl accident, a combination of external and internal radiation exposure could occur. Radiation exposure can also be categorized as either chronic or acute, depending on the period of time of radiation exposure. Another important factor that can affect treatment and outcome is whether the whole body of a person was affected homogeneously or if only localized radiation exposure of a part

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of the body occurred. For each of these different types of scenarios and combinations the expected consequences for the patient, depending on the absorbed radiation dose and distribution as well as diagnostic and therapeutic measures, are different. In the case of whole body exposure, all organs and organ systems are affected and, therefore, multiorgan-involvement and multi-organ-failure has always been taken into account. Additional conventional trauma, such as wounds and burns in people with severe radiation exposure - the so-called radiation combined injury, could worsen the prognosis (DiCarlo et al., 2008).

Management of radiation exposure is difficult, partly because of misinformation on the part of the exposed persons and partly because of current perceptions of medical staff about the effects of exposure. Experience has shown that, in addition to occupational physicians, the complete management of an emergency case involves other professionals such as haematologists, oncologists, plastic surgeons, dermatologists, vascular surgeons, psychiatrists and consultants in other medical specialties including nuclear medicine. However, medical professionals who may be involved in the management of radiation injuries, will start their work from the first few hours or days after an exposure of undefined severity (Bomanji et al., 2014).

There are many aspects to consider when diagnosing and managing radiation exposed patients. Acute versus chronic effects can be differentiated by the latency of manifestation of the radiation effects. Since acute effects require immediate therapeutic intervention, they should be diagnosed at an early stage. Another differentiation could be made between deterministic versus stochastic effects regarding their pathophysiological mechanisms. Deterministic radiation effects, such as the hematopoietic syndrome, occur after a threshold radiation dose is exceeded and the severity will increase with increasing radiation exposure. On the other hand, for stochastic effects like the development of malignant tumors, the probability of their appearance will increase with increasing radiation exposure. Therefore, all efforts must be made to reduce the individual exposure to ionizing radiation and, thus, the absorbed dose (Hall and Giaccia, 2006).

For the planning of the medical management of radiation accident victims, it is crucial to estimate the severity of the radiation exposure on the basis of the individual patient's clinical signs and symptoms by means of a clinical dosimetry. After significant acute whole body or partial body radiation exposure, resulting in acute radiation induced health impairments, it is imperative that appropriate therapeutic measures be carried out as soon as possible. When dealing with specific recommendations for countermeasures against radiation-induced health impairments, the main fact is that due to the comparatively low number of radiation victims worldwide, there is a clear lack of controlled studies in this area. Therefore, established and accepted animal models (Williams et al., 2010), as well as recommendations of national and international expert panels and committees in this field (Fliedner et al., 2009; Dainiak et al., 2011), are the main sources of information. Still, there remains uncertainty in many areas, which is the basis for future research (Dörr and Meineke, 2011). The inclusion of cellular therapies in the treatment of battlefield injuries provides a novel and promising approach for addressing long-standing challenges in tissue repair with regard to both structural and functional improvements. Bone marrow-derived mesenchymal stem cells (MSCs), adipose derived stem cells, and endothelial progenitor cells, for example, exhibit a remarkable capacity to adapt to the requirements of the damaged tissue in which the cells integrate. MSC therapy represents a single medical intervention that can simultaneously provide a broad range of therapeutic efficacy, with local activity, at multiple tissue and organ sites. Although ARS is rare, it is a complex and medically challenging disorder that has the potential for large-scale incidence on the battlefield or in conjunction with a domestic terrorist attack. Currently, medical intervention for numerous aspects of ARS is limited to supportive care (Eaton Jr and Varney, 2015).

The aim of this review was to provide a framework for physicians in pediatrics, internal medicine and the medical subspecialties to evaluate and manage large-scale radiation injuries. There is also, stress on the rationale for the further evaluation of mesenchymal stem cells (MSCs) therapy to address the current unmet medical needs of ARS. The most important therapeutic principles with special reference to hematopoietic syndrome and cutaneous radiation syndrome are reviewed.

Acute radiation syndrome (ARS)

Depending on the magnitude of the radiation exposure resulting in significant whole body exposure or partial body exposure, the patient will develop clinically acute radiation effects resulting in ARS (Bomanji et al., 2014). It can occur after exposure to a dose of > 1 Gy (Dainiak et al., 2011). A multidisciplinary team approach is required, involving medical physicians, nuclear medicine physicians, radiation protection officers, plastic and reconstructive surgeons, medical oncologists and haematologists. Treatment has to be individualized according to the nature and grade of the combined injuries. Expert advice from external organizations such as IAEA, Public Health, England or a similar body in individual countries should be sought (Bomanji et al., 2014). Individuals contaminated either externally or internally should be identified and treatment should be started immediately and specifically. If the accident involves only a small number of casualties, medical management is easy to organize, but a large-scale accident involving hundreds of people would place serious demands on hospitals. Medical treatment should be delivered in accordance with the type of trauma and the urgency of each case. The need for emergency treatment is determined initially by the presence of conventional injuries such as trauma, wounds and thermal or chemical burns. From individuals who have suffered radiation exposure, the early clinical symptoms are very helpful for triage and decision making on medical care (Bomanji et al., 2014).

The biological effects of ionizing radiation will start on the cellular level by energy absorption due to several physical effects, such as the Compton process and the photoelectric process for x- or gamma-rays. The most important targets are the DNA-molecules, where direct or indirect actions of radiation could result in lesions, such as base damage, single-strand breaks and double strand breaks. The indirect damage caused by the free radicals and is derived from the ionization or excitation of the water component of the cells (Abaza, 2013). Double-strand breaks are considered the most serious DNA-lesions, since they can result in the cleavage of chromatin and might not be successfully repaired by the cell. The occurrence of DNA-lesions and, especially, of double-strand breaks will increase with increasing radiation exposure and will lead to a higher risk of cell death (Hall and Giaccia, 2006; Bomanji et al., 2014). The underlying pathology of ARS involves physical and chemical damage to DNA, which affects the rapidly dividing cells of the hematopoietic system and the gastrointestinal (GI) tract (Eaton Jr and Varney, 2015).

Table (1): Estimated Threshold Absorbed Doses for Deterministic Effects after Acute Exposure.*

Exposure Health Effect	Organ	Absorbed Dose (Gy)
Temporary sterility	Testis	0.15
Nausea		0.35
Depression of blood cell forming process	Bone marrow	0.5
Reversible skin effects(e.g., early reddening)	Skin	2
Permanent sterility	Ovaries	2.5 –6
Vomiting		3
Temporary hair loss	Skin	3–5
Permanent sterility	Testis	3.5
Skin erythema	Skin	5-6

* For low-linear energy transfer (LET) radiation (x-rays, gamma rays). From NCRP Report No. 138 (1).

Table (2): Early Symptoms of Radiation Injuries and Management Guide (IAEA; Bomanji et al., 2014)

Dose		Clinical Sign		Management
WBE	**LE**	**WBE**	**LE**	
<1	<10	No vomiting	No erythema	Outpatient care with a 5-week surveillance period (skin and blood)
1-2	8-15	Vomiting 2-3h after exposure	Early erythema or abnormal sensation 12-24h after exposure	Surveillance in a general hospital (or outpatient care for 3 weeks followed by hospitalization if necessary)
2-4	15-30	Vomiting 1-2h after exposure	Early erythema or abnormal sensation 8-15h after exposure	Hospitalization under care of a haematologist. In the case of burns, in a surgical department.
>4	>30	Vomiting earlier than 1h after exposure and/or sever symptoms, e.g. hypotension	Early erythema within 3-6h or earlier after exposure of skin and/or mucosa with oedema	Hospitalization to a specialized center for radio-pathology and a fully equipped hematological and surgical unit

LE local exposure; WBE, whole-body exposure

As a result, ARS symptoms are often subclassified into the hematopoietic and GI syndromes, which occur simultaneously at higher exposure levels. As discussed below, the therapeutic benefit of MSC therapy for these individuals could include the facilitation of hematopoietic recovery, enhancement of healing of the GI tract and the skin, and the possible mitigation or treatment of a variety of additional ARS complications (Eaton Jr and Varney, 2015).

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, 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 (table 1) (Mettler, 2008; Dainiak et al., 2011).

As radiation injury is characterized by a latent period, all important treatments of the non radiation components of combined radiation injury should be carried out during the first 2–3 weeks. Later efforts will be necessary for the treatment of bone marrow and skin radiation injuries. The decision on hospitalization in cases of whole-body exposure or local

exposure depends on the presence of particular early clinical signs, (table 2) (Bomanji et al., 2014).

The classical initial symptoms of acute radiation syndrome occur during the so-called *prodromal phase*. Prodromal symptoms include: anorexia, nausea, vomiting, diarrhea, fluid loss, fever, hypotension, headache and early skin and mucosal erythema (Hall and Giaccia, 2006; Dainiak et al., 2003). These prodromal symptoms could occur, if the possibility of a radiation exposure is not taken into account, be misinterpreted as unspecific symptoms of gastrointestinal or other infectious diseases. For this reason, the possibility of radiation-induced health impairments should always be taken into account, if unspecific symptoms cannot be properly explained. The prodromal phase is followed by the latent phase. In the *latent phase*, symptoms will decrease or even disappear. The length of the latent phase depends on the magnitude of the radiation exposure. After a very high radiation exposure it can also be missing. The latent phase will be followed by the *manifestation phase* (Dörr and Meineke, 2011).

The occurrence and severity of clinical signs and symptoms will depend on the absorbed radiation dose. Depending on the absorbed radiation dose, the manifestation takes place in different organ systems as syndromes of the hematopoietic system, the gastrointestinal system, the skin and the neurovascular system. Hematopoietic syndrome will occur at a lower dose than the other syndromes due to the high radiosensitivity of the hematopoietic system. Even in asymptomatic patients effects on the blood cell counts might be observed. On the other hand, a complete radiation-induced failure of the hematopoietic system requires an ample homogenous whole body exposure for all hematopoietic stem cells in the bone marrow to be irreversibly damaged. With higher radiation exposure, disturbances of the gastrointestinal system, such as destruction of the mucosal layer can take place. A complete loss of the mucosal layer will be fatal. Very high radiation exposure can result in neurological and cardiovascular breakdown causing death within a few days (Dörr and Meineke, 2011). The cutaneous syndrome can occur together with the other syndromes, but cutaneous radiation injury (CRI) could also be the consequence of external exposure to beta-radiation in the absence of other symptoms of ARS (Hall and Giaccia, 2006; Dainiak et al., 2003; Dörr and Meineke, 2011).

All differentiated cells and stem cell pools of the organism will be affected from acute homogeneous whole body radiation exposure resulting in multi-organ involvement (MOI) and even multi-organ failure (MOF). Pathophysiological aspects of radiation-induced MOI include systemic inflammatory response syndrome (SIRS) and consequences of cell loss due to radiation damage (Fliedner et al., 2005). Therapeutic efforts are to be taken to stabilize the homoeostasis and to reconstitute the function of organs and organ systems. A new strategy would be an early therapeutic intervention in order to prevent MOF already in the stage of SIRS. The pathophysiological mechanisms behind this development are still poorly understood (Meineke and Fliedner, 2005; Dörr and Meineke, 2011).

Radiation injury may occur in conjunction with thermal burns, chemical injury, and/or mechanical trauma, a condition known as a *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. It is reasonable to presume that atomic bomb victim 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. 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. (Dainiak et al., 2011).

Therapeutic Principles in Clinical Management of Patients with ARS

Clinical management of patients with ARS is characterized by dealing with radiation induced impairments of different organ functions, MOI or even MOF. In the early stages of the accident situation, reliable information about physical dosimetry and results from biodosimetric methods are not always immediately available. Therefore, the estimation of radiation effects and the patient's prognosis will be based on clinical signs and symptoms as described in the METREPOL system (Fliedner et al., 2001). Instead of making therapeutic decisions only based on information on the absorbed radiation dose, the patient's clinical status will be categorized into response categories (RC) 1 to 4. According to the METREPOL system, organ specific checklists will be used for the grading of radiation effects in the four most important organ systems, such as the neurovascular system (N), the hematopoietic system (H), the cutaneous system (C) and the gastrointestinal system (G). Different levels of the severity of organ system specific clinical signs and symptoms will then result in RC, for example, from H1 to H4 for the hematopoietic system. The organ specific grading will then lead to a resulting RC for the individual patient. These RC describes the degree of radiation-induced damage, but also include prognostic aspects. The definition of the four RC are as follows: RC 1 for mild damage, RC 2 for moderate damage, RC 3 for severe damage and RC 4 for serious or fatal damage (table 3) (Fliedner et al., 2001; Dörr and Meineke, 2011). As soon as reliable information about the physical dose or results from biodosimetry is available, the data should be included in therapeutic decision making and sufficient medical management. It is the prediction of expected radiation-induced impairments of organs or organ-systems that is important for this management, Tables (4-6) (Dörr and Meineke, 2011).

Management of Hematopoietic Syndrome

One of the most critical and most vulnerable organ systems to radiation exposure is the hematopoietic system, since the limited lifespan of blood cells requires continuous cell divisions of hematopoietic stem cells in the bone marrow. The impairment of the hematopoiesis will result in pancytopenia of various degrees with consecutive increased risk of infection, hemorrhage and anemia. General medical management consists of barrier nursing conditions, sufficient and immediate therapy of infections or even prophylactic administration of antibiotic, and antimycotic and antiviral substances (Fliedner et al., 2001; Waselenko et al., 2004). Since renal function is of great importance for maintaining homoeostasis, findings concerning the effectiveness of angiotensin converting enzyme inhibitors and angiotensin II type 1 receptor antagonists in reducing the incidence and severity of chronic renal and lung injuries have to be taken into account (Ghosh et al., 2009; Williams and McBride, 2011; Dörr and Meineke, 2011).

Criteria for choice of therapy

Appropriate criteria are as follows (Bomanji et al., 2014)

1. If the lymphocyte count during the first week is within the range of 0.2–0.5 g/l (200–500 cells/μl), spontaneous recovery is possible. Therapy comprises isolation, antibiotics and supportive treatment, including platelet infusion. Growth factors can be used.
2. If the lymphocyte count in the first week is lower than 0.2 g/l, the stem cells are probably irreversibly damaged. Treatments are as above. Additional growth factor therapy is a method of choice.
3. If the lymphocyte count within the first week is less than 0.1 g/l, treatment with growth factors and BMT has to be considered.

Depending on the severity of the hematopoietic syndrome, the main therapeutic principles are replaced with blood products, such as erythrocyte concentrate, the administration of cytokines like granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and the transplantation of hematopoetic stem cells (HSCT) (Dainiak, 2010). The source of hematopoietic stem cells for HSCT can be bone marrow, mobilized peripheral blood-derived stem cells, umbilical cord blood or the fetal liver (Dainiak and Ricks, 2005). The therapeutic use of hematopoietic factors such as GCSF, GM-CSF, erythropoietin (EPO) and thrombopoietin (TPO) has been described in several cases (Hirama et al., 2003; Liu et al., 2008). Since the number of radiation-exposed patients treated with hematopoietic factors is limited and randomized controlled clinical trials cannot be performed after radiation accidents, the main supporting evidence for the effectiveness of hematopoietic factors in ARS is based on experimental animal studies (Dainiak, 2010; Drouet et al., 2008). Since experimental animal studies are of such great importance in the field of radiation effects, they have to meet certain standards to allow a comparison of the results (Williams et al., 2010). The therapeutic use of hematopoietic factors in radiation accident victims will be considered as “off-label use”. But if the development of severe neutropenia in a patient is expected, the administration of G-CSF or GM-CSF in an early stage is recommended (Dainiak et al., 2011; Waselenko et al., 2004). If unrecoverable damage to the hematopoietic stem cell pool is noticed, a decision about the necessity of HSCT has to be made. The diagnosis, whether or not an autologous recovery of the hematopoiesis could be expected, requires specific expertise (Fliedner et al., 2009; Dainiak and Ricks, 2005; Fliedner et al., 2007). The experience from the treatment of patients after several radiation accidents with HSCT showed that the range between the beneficial treatment with HSCT and a very poor prognosis irrespective of whether HSCT is performed or not, is quite narrow, especially if other organ systems are severely affected or MOI already occurred (Dainiak and Ricks, 2005; Drouet and Hérodin, 2010). HSCT will, therefore, not be considered as the most important treatment option in ARS, although it could be essential for an individual patient (Dörr and Meineke, 2011).

Management of Cutaneous Radiation Syndrome

In addition to hematopoietic syndrome, radiation induced damage to the skin plays an important role in diagnosis and treatment of patients with ARS, but also in the case of local radiation injuries. The impairment of the skin could be a real challenge in the clinical management of patients with cutaneous radiation syndrome. The barrier function of the skin will be affected and inflammatory reactions will take place, which eventually might trigger the development of MOF (Müller and Meineke, 2010). Therapeutic principles in the clinical management of patients with cutaneous radiation syndrome include conservative methods, surgical treatment and the administration of anti-inflammatory agents and topical steroids (Dainiak et al., 2011).

Systemic administration of steroids could be considered for MOF-related skin dysfunction (Hirama et al., 2003). A novel therapeutic approach is the parenteral or local administration of mesenchymal stem cells (François et al., 2006). The treatment of a patient with a local radiation injury using local cellular therapy with autologous expanded mesenchymal stem cells to promote tissue regeneration resulted in favorable pain relief and healing progression (Lataillade et al., 2007). As conservative methods, therapeutic measures for pain control, reduction of inflammation, prevention of infection and of further vasculature insult, improvement of circulation, healing acceleration, wound cleaning and minimizing fibrosis will be performed. Surgical treatment and skin grafts might be required if necrosis of various extents occur (Müller and Meineke, 2010; Benderitter et al., 2010).

In order to avoid disturbances of wound healing after exposure to ionizing radiation, all surgical measures within the ARS should be performed as soon as possible (Dörr and Meineke, 2011). New approaches, such as mesenchymal stem cell administration derived from experimental studies in animal models, should be considered in patients with a cutaneous radiation syndrome (Agay et al., 2010; Akita et al., 2010; Ebrahimian et al., 2009; Lange et al., 2011; Yan et al., 2011; Dörr and Meineke, 2011).

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. 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. Time to onset of symptoms is, in general, inversely related to radiation dose, whereas severity is directly related to dose (Dainiak et al., 2011). 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 (Waselenko et al., 2004; Dainiak et al., 2003; Dainiak et al., 2011).

In addition to the replacement of fluids and electrolytes, the mainstays for management of acute GI radiation injury include administration of antiemetic compounds, antidiarrheal drugs, and antimicrobials. Overall, the clinical experience with

Table (3): Grading System for Response Based on Clinical Signs and Symptoms (Fliedner et al., 2001)

	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.

Table 4: Selected Methods for Estimating Radiation Dose. (Dainiak et al., 2003)

Dosimetry	**Method**	**Utility**
Biological	-Whole-body counting -Chromosomal aberrations (dicentrics, ring forms) -Lymphocyte depletion kinetics -Interphase aberrations (PCC, okadaic acid/kinase) -Electron spin resonance (dental enamel)	-Not generally available, impractical. -The "gold standard." Typically requires 4–5 days processing time. -Inexpensive but requires 2–4 days for decline at doses of 4–6 Gy and 4–6 days at 2–4 Gy -Under development -Permanent record of exposure but requires removal of tooth
Clinical	Symptoms and signs	Practical but loses sensitivity at low doses.

Table 5: Phases of Radiation Injury* (Waselenko et al., 2004)

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

* Modified from **Walker RI and Cerveny, RJ**, eds. GI = gastrointestinal.

Table (6): Whole-Body Dose Estimates Based on Absolute Lymphocyte Count (Flynn and Goans, 2006; Parker and Parker, 2007)

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)

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 (Schmoll et al., 2006; Dainiak et al., 2011). 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 (Waselenko et al., 2004; Dainiak et al., 2003; Abdelsayed, 2007).

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 (Roila et al., 2006; Kris et al., 2006). 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 (Dainiak et al., 2011).

A preclinical experimental study regarding the therapeutic intervention in the gastrointestinal tract showed promising results. Administration of the somatostatin analog SOM230 significantly increased the survival rate when started 48 hours after radiation exposure (Fu et al., 2011; Dörr and Meineke, 2011). Somatostatin analogs (including octreatide, lanreotide, and pasireotide) are more expensive and less readily available but can offer relief in patients with otherwise intractable

diarrhea (Dainiak et al., 2011). Oral nutritional support is preferred over parenteral nutrition because it promotes the immunological and physiological integrity of the GI tract (Hermsen et al., 2009) however, parenteral supports is indicated in patients with adynamic ileus or diffuse bleeding from the GI mucosa (McClave et al., 2009; Dainiak et al., 2011). Other possible radiation countermeasures include cytokines, growth factors and antioxidants, which are able to scavenge free radicals and modulate cell death signaling or cell cycle progression (Dumont et al., 2010; Dörr and Meineke 2011).

On the other hands, 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 (Hauer-Jensen et al., 2008). 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 of 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 (Dainiak et al., 2011).

Management of Neurovascular Syndrome

Acute, irreversible neurotoxicity occurs at a whole-body dose in excess of approximately 10 Gy (Dainiak et al., 2011). Disorientation, ataxia, prostration, and seizures, together with fever (>40°C) and hypotension (<80 mm Hg/palpable), are predictive of a non-survivable exposure. Several pathophysiologic processes may contribute to neurovascular collapse, including vascular damage, inflammation, cerebral edema, increased vascular permeability, and perivascular hemorrhage (Gourmelon et al., 2005). A brief latent period lasting several hours typically is followed by severe incapacitation, progressing to coma and death within 24 to 48 hours. 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 (Dainiak et al., 2011).

Management of MOD/MOF

Radiation-induced MOD and MOF result of complex and poorly understood pathophysiologic mechanisms (Meineke and Fliedner, 2005). 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 ventilatory support, (Jackson et al., 2005) 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 (Dainiak et al., 2011).

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 an 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. Non-steroidal 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. Anti-seizure 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. 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 (Dainiak et al., 2011).

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 and prophylactic antimicrobial therapy (Waselenko et al., 2004; Gorin et al., 2006; Flynn and Goans, 2006; Dainiak et al., 2003). 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 (Waselenko et al., 2004). 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. 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 (Waselenko et al., 2004; Dainiak et al., 2003; Berger et al., 2006). 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 (Waselenko et al., 2004; Dainiak et al., 2003). 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 (Waselenko et al., 2004; Gorin et al., 2006; Dainiak et al., 2007). 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 (Cornely et al., 2007). Alternative antifungals such as *voriconazole* and *amphotericin B* may be indicated in patients for whom fluconazole lacks appropriate efficacy (Waselenko et al., 2004; Gorin et al., 2006; Dainiak et al., 2003). 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 (Waselenko et al., 2004). In such patients, immunosuppression confers a heightened risk of viral reactivation (Dainiak et al., 2011).

Palliative Care

Clinicians and public health authorities have a strong ethical obligation to provide palliative care to patients who have received non-survivable 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 (Qaseem et al., 2008). High-quality palliative care should be provided even in the context of limited resources (Dainiak et al., 2011).

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, (Pastel, 2002) 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 has developed policies to minimize uncertainty, stress, and anxiety among victims, relatives, friends, and the public (IAEA, 2011).

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. 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. The 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 (Dainiak et al., 2011)

Summary and Future Directions

The development of acute radiation effects in radiation accident victims depends on the nature and the extent of radiation exposure. Since reliable information about the radiation exposure from physical dosimetry and results from biodosimetric methods are usually not available in accident situations, the estimation of radiation effects can be performed on the basis of clinical signs and symptoms as described in the METREPOL system. Multi-organ involvement, systemic inflammatory response syndrome and even MOF have to be considered in the clinical management of radiation accident victims. Since the hematopoietic system is most vulnerable to ionizing radiation, diagnostic and therapeutic measures dealing with the hematopoietic syndrome are most important. General measures are barrier nursing conditions, sufficient and immediate therapy of infections, or even prophylactic administration of antibiotic, antimycotic and antiviral substances. The main specific therapeutic principles are replacement with blood products, the administration of cytokines like G-CSF and GM-CSF, and the transplantation of hematopoietic stem cells. In addition to hematopoietic syndrome, radiation induced damage to the skin plays an important role in diagnostics and treatment of patients with ARS and eventually might trigger the development of MOF. New approaches are based on the administration of stem cells, such as mesenchymal stem cells, in the case of cutaneous radiation syndrome and localized radiation injuries. Since radiation-induced multi-organ involvement or multi-organ failure will be associated with a poor prognosis in the patient, early therapeutic intervention for preventing the development of MOI and MOF seems to be one of the most important aspects for further research.

CONCLUSIONS

From past experiences, the radiation accidents fortunately are rare events; therefore, the number of patients suffering from

acute radiation effects and ARS is limited. However, current risk analyses of terrorist threats, consider a nuclear scenario as extremely relevant. This certainly would mean that the number of victims would be in a much higher magnitude. Availability of necessary resources could be a limiting factor in the medical management of radiation accident victims. The management of radiation accidents is a very challenging process. Nuclear medicine physicians have to be well organized in order to deliver suitable management in any kind of radiation accident, which includes fast triage of injured persons, prompt diagnosis of radiation casualties and urgent initiation of specific treatment procedures.

On the other hand, stockpiling of essential pharmaceuticals for the treatment of radiation accident victims on a national or international level has to be considered. Prospective studies for the development of therapeutic standards for patients with ARS are extremely limited. Most of the new approaches in therapeutic measures are derived from experimental studies in animal models. Keeping these circumstances in mind, a multidisciplinary approach built on international cooperation is of the utmost importance and currently the most reasonable strategy to provide the best possible medical care for radiation accident victims.

The clinical course, as well as the therapeutic regimen, of each new radiation accident victim should be documented in detail for further analysis. There is a strong need for internationally recognized guidelines for the treatment of severely radiation exposed patients. Further research and experimental studies are necessary to identify prognostic parameters for the estimation of irreversible damage to organs and organ systems and a deeper understanding of the pathophysiology of radiation induced multi-organ failure (MOF).

Abbreviations

ARS: acute radiation syndrome;
CRI: cutaneous radiation injury;
CRS: cutaneous radiation syndrome;
G-CSF: granulocyte colony-stimulating factor;
GM-CSF: granulocyte-macrophage colony-stimulating factor;
Gy: Gray; HSCT: hematopoietic stem cell transplantation;
M-CSF: macrophage – colony stimulating factor;
METREPOL: Medical Treatment Protocols for Radiation Accident;
MOI: multi-organ involvement;
MOF: multi-organ failure;
MSC: mesenchymal stem cells;
RC: response category;
Sv: Sievert;
SIRS: systemic inflammatory response syndrome.

REFERENCES

Abaza A: Radiation effects. In: A. Abaza; editors “Hazards of radiotherapy in pediatric oncology”, 1St edition. LAP LAMBERT Academic Publishing, Germany, 2013; Copyright, OmniScriptum GmbH & Co.KG.

Abdelsayed GG: Management of radiation-induced nausea and vomiting. *Exp Hematol.* 2007; 35 Suppl 1(4):34–36.

Agay D, Scherthan H, Forcheron F, Grenier N, Hérodin F, Meineke V, Drouet M: Multipotent mesenchymal stem cell grafting to treat cutaneous radiation syndrome: development of a new minipig model. *Exp Hematol.* 2010; 38:945-956.

Akita S, Akino K, Hirano A, Ohtsuru A, Yamashita S: Mesenchymal stem cell therapy for cutaneous radiation syndrome. *Health Phys.* 2010; 98:858-862.

Benderitter M, Gourmelon P, Bey E, Chapel A, Clairand I, Prat M, Lataillade JJ: New emerging concepts in the medical management of local radiation injury. *Health Phys.* 2010; 98:851-857.

Berger ME, Christensen DM, Lowry PC, Jones OW, Wiley AL: Medical management of radiation injuries: current approaches. *Occup Med (Lond)*. 2006; 56(3):162–172.

Bomanji JB, Novruzovc F, Vinjam S: Radiation accidents and their management: emphasis on the role of nuclear medicine professionals *Nucl Med Commun.* 2014; 35:995–1002.

Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D : Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; 356(4):348–359.

Dainiak N: Rationale and recommendations for treatment of radiation injury with cytokines. *Health Phys.* 2010; 98:838-842.

Dainiak N and Ricks RC: The evolving role of haematopoietic cell transplantation in radiation injury: potentials and limitations. *BJR* Suppl. 2005; 27:169-174.

Dainiak N, Waselenko JK, Armitage JO, MacVittie TJ, Farese AM: The hematologist and radiation casualties. *Hematology Am Soc Hematol Educ Program* 2003; 473-496.

Dainiak N, Berger P, Albanese J: Relevance and feasibility of multiparameter assessment for management of mass casualties from a radiological event. *Exp Hematol.* 2007; 35 Suppl. 1(4):17–23.

Dainiak N, Gent RN, Carr Z, Schneider R, Bader J, Buglova E, Chao N, Coleman CN, Ganser A, Gorin C, Hauer-Jensen M, Huff LA, Lillis-Hearne P, Maekawa K, Nemhauser J, Powles R, Schünemann H, Shapiro A, Stenke L, Valverde N, Weinstock D, White D, Albanese j, Meineke V: Literature Review and Global Consensus on Management of Acute Radiation Syndrome Affecting Nonhematopoietic Organ Systems. *Disaster Med Public Health Prep.* 2011; 5(3): 183–201. Published online 2011 Oct 10. doi: 10.1001/dmp.2011.73

DiCarlo AL, Hatchett RJ, Kaminski JM, Ledney GD, Pellmar TC, Okunieff P, Ramakrishnan N: Medical countermeasures for radiation combined injury: radiation with burn, blast, trauma and/or sepsis. Report of an NIAID Workshop, March 26-27, 2007. *Radiat Res.* 2008; 169:712-721.

Dörr HD and Meineke V: Approprate radiation accident medical management: necessity of extensive preparatory planning. *Radiat Environ Biophys.* 2006; 45:237-244.

Dörr H and Meineke V: Acute radiation syndrome caused by accidental radiation exposure - therapeutic principles. *BMC Medicine* 2011; 9:126 http://www.biomedcentral.com/1741-7015/9/126

Drouet M and Hérodin F: Radiation victim management and the haematologist in the future: time to revisit therapeutic guidelines? *Int J Radiat Biol.* 2010; 86:636-648.

Drouet M, Delaunay C, Grenier N, Garrigou P, Mayol JF, Hérodin F: Cytokines in combination to treat radiation-induced myelosuppresssion: evaluation of SCF + glycosylated EPO + pegylated G-CSF as an emergency treatment in highly irradiated monkeys. *Haematologica* 2008; 93:465-466.

Dumont F, Le Roux A, Bischoff P: Radiation countermeasure agents: an update. *Expert Opin Ther Pat.* 2010; 20:73-101.

Eaton Jr EB and Varney TR: Mesenchymal stem cell therapy for acute radiation syndrome: innovative medical approaches in military medicine. *Military Medical Research* 2015; 2:2-9.

Ebrahimian TG, Pouzoulet F, Squiban C, Buard V, André M, Cousin B, Gourmelon P, Benderitter M, Casteilla L, Tamarat R: Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing. *Arterioscler Thromb Vasc Biol.* 2009; 29:503-510.

Fliedner TM, Friesecke I, Beyrer K, (Eds): Medical Management of Radiation Accidents–Manual on the Acute Radiation Syndrome, Oxford, London, UK: British Institute of Radiology; 2001.

Fliedner TM, Dörr HD, Meineke V: Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of hemopoietic indicators of effect. *BJR* Suppl. 2005; 27:1-8.

Fliedner TM, Graessle D, Meineke V, Dörr H: Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental whole-body radiation exposure: an essential basis for an evidence-based clinical triage. *Exp Hematol.* 2007; 35:8-16.

Fliedner TM, Chao NJ, Bader JL, Boettger A, Case C Jr, Chute J, Confer DL, Ganser A, Gorin NC, Gourmelon P, Graessle DH, Krawisz R, Meineke V, Niederwieser D, Port M, Powles R, Sirohi B, Weinstock DM, Wiley A, Coleman CN: Stem cells, multiorgan failure in radiation emergency medical preparedness: a U.S./European Consultation Workshop. *Stem Cells* 2009; 27:1205-1211.

Flynn DF and Goans RE. Nuclear terrorism: triage and medical management of radiation and combined-injury casualties. *Surg Clin North Am.* 2006; 86(3):601–636.

François S, Bensidhoum M, Mouiseddine M, Mazurier C, Allenet B, Semont A, Frick J, Saché A, Bouchet S, Thierry D, Gourmelon P, Gorin NC, Chapel A: Local irradiation not only induces homing of human mesenchymal stem cells at exposed sites but promotes their widespread engraftment to multiple organs: a study of their quantitative distribution after irradiation damage. *Stem Cells* 2006; 24:1020-1029.

Fu Q, Berbée M, Wang W, Boerma M, Wang J, Schmid HA, Hauer-Jensen M: Preclinical evaluation of Som230 as a radiation mitigator in a mouse model: postexposure time window and mechanisms of action. *Radiat Res.* 2011; 175:728-735.

Ghosh SN, Zhang R, Fish BL, Semenenko VA, Li XA, Moulder JE, Jacobs ER, Medhora M: Renin-Angiotensin system suppression mitigates experimental radiation pneumonitis. *Int J Radiat Oncol Biol Phys.* 2009; 75:1528-1536.

Gorin NC, Fliedner TM, Gourmelon P, Ganser A, Meineke V, Sirohi B, Powles R, Apperley J : Consensus conference on European preparedness for haematological and other medical management of mass radiation accidents. *Ann Hematol.* 2006; 85(10):671–679.

Gourmelon P, Marquette C, Agay D, Mathieu J, Clarencon D: Involvement of the central nervous system in radiation-induced multi-organ dysfunction and/or failure. *BJR* Suppl. 2005; 27:62–68.

Hall EJ and Giaccia AJ: Radiobiology for the Radiologist Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Lippincott Williams & Wilkins; 2006.

Hauer-Jensen M, Kumar KS, Wang J, Berbee M, Fu Q, Boerma M: Intestinal toxicity in radiation-and combined injury: significance, mechanisms, and countermeasures. In: Larche, RA., editor. Global Terrorism Issues and Developments. Hauppauge, NY: Nova Science Publishers; 2008.

Hermsen JL, Sano Y, Kudsk KA: Food fight! Parenteral nutrition, enteral stimulation and gutderived mucosal immunity. *Langenbecks Arch Surg.* 2009; 394(1):17–30.

Hirama T, Tanosaki S, Kandatsu S, Kuroiwa N, Kamada T, Tsuji H, Yamada S, Katoh H, Yamamoto N, Tsujii H, Suzuki G, Akashi M: Initial medical management of patients severely irradiated in the Tokai-mura criticality accident. *Br J Radiol.* 2003; 76:246-253.

International Atomic Energy Agency and World Health Organization. Diagnosis and treatment of radiation injuries, safety reports series, No. 2. Vienna: IAEA; 1998.

International Atomic Energy Agency, World Health Organization. [Accessed June 11, 2011]. Generic procedures for medical response during a nuclear or radiological emergency. http://www-pub.iaea.org/MTCD/publications/PDF/EPR-MEDICAL-2005_web.pdf. Published April 2005.

Jackson WL Jr. Gallagher C, Myhand RC, Waselenko JK: Medical management of patients with multiple organ dysfunctions arising from acute radiation syndrome. *BJR* Suppl. 2005; 27:161–168.

Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM: American Society of Clinical Oncology. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol.*2006; 24(18):2932–2947. Epub 2006 May 22. Erratum in: J Clin Oncol. 2006; 24(33):5341-2.

Lange C, Brunswig-Spickenheier B, Cappallo-Obermann H, Eggert K, Gehling UM, Rudolph C, Schlegelberger B, Cornils K, Zustin J, Spiess AN, Zander AR: Radiation rescue: mesenchymal stromal cells protect from lethal irradiation. *PLoS One* 2011; 6:e14486.

Lataillade JJ, Doucet C, Bey E, Carsin H, Huet C, Clairand I, Bottollier-Depois JF, Chapel A, Ernou I, Gourven M, Boutin L, Hayden A, Carcamo C, Buglova E, Joussemet M, de Revel T, Gourmelon P: New approach to radiation burn treatment by dosimetry-guided surgery combined with autologous mesenchymal stem cell therapy. *Regen Med.* 2007; 2:785-794.

Liu Q, Jiang B, Jiang LP, Wu Y, Wang XG, Zhao FL, Fu BH, Istvan T, Jiang E:Clinical report of three cases of acute radiation sickness from a $^{(60)}$Co radiation accident in Henan Province in China. *J Radiat Res.* (Tokyo) 2008; 49:63-69.

McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G; and A.S.P.E.N: Board of Directors; American College of Critical Care Medicine; Society of Critical Care Medicine. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2009; 33(3):277–316.

Meineke V and Fliedner TM. Radiation-induced multi-organ involvement and failure: challenges for radiation accident medical management and future research. *BJR* Suppl. 2005; 27:196–200.

Mettler FA and Upton AC: Deterministic effects of ionizing radiation. In: Mettler, FA; Upton, AC., editors. Medical Effects of Radiation. 3rd ed. Philadelphia: Saunders Elsevier; 2008.

Müller K and Meineke V: Advances in the management of localized radiation injuries. *Health Phys.* 2010; 98:843-850.

Parker DD and Parker JC: Estimating radiation dose from time to emesis and lymphocyte depletion. *Health Phys*. 2007; 93(6):701–704.

Pastel RH: Radiophobia: long-term psychological consequences of Chernobyl. *Mil Med*. 2002; 167 Suppl.(2):134–136.

Qaseem A, Snow V, Shekelle P, Casey DE Jr, Cross JT Jr, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians, Dallas P, Dolan NC, Forciea MA, Halasyamani L, Hopkins RH Jr, Shekelle P: Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2008; 148(2):141–146.

Roila F, Hesketh PJ, Herrstedt J: Antiemetic Subcommitte of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol*. 2006; 17(1):20–28.

Schmoll HJ, Aapro MS, Poli-Bigelli S, Kim HK, Park K, Jordan K, von Pawel J, Giezek H, Ahmed T, Chan CY: Comparison of an aprepitant regimen with a multipleday ondansetron regimen, both with dexamethasone for antiemetic efficacy in high-dose cisplatin treatment. *Ann Oncol*. 2006; 17(6):1000–1006.

Walker RI and Cerveny RJ, eds. Medical Consequences of Nuclear Warfare. Falls Church, VA: Office of the Surgeon General; 1989. Available at www.afrri.usuhs.mil.

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 and Strategic National Stockpile Radiation Working Group: Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Ann Intern Med.* 2004; 140(12):1037-1051.

WHO - Report of the Radio-Nuclear Working Group: Development of Stockpiles for Radiation Emergencies/WHO consultation meeting on Development of Stockpiles for Radiation and Chemical Emergencies. Edited by: Perez M, Carr Z. WHO Headquarters, Geneva, Switzerland; 2007.

Williams JP and McBride WH: After the bomb drops: a new look at radiationinduced multiple organ dysfunction syndrome (MODS). *Int J Radiat Biol.* 2011; 87:851-868.

Williams JP, Brown SL, Georges GE, Hauer-Jensen M, Hill RP, Huser AK, Kirsch DG, Macvittie TJ, Mason KA, Medhora MM, Moulder JE, Okunieff P, Otterson MF, Robbins ME, Smathers JB, McBride WH: Animal models for medical countermeasures to radiation exposure. *Radiat Res.* 2010; 173:557-578.

Yan G, Sun H, Wang F, Wang J, Wang F, Zou Z, Cheng T, Ai G, Su Y: Topical application of hPDGF-A-modified porcine BMSC and

keratinocytes loaded on acellular HAM promotes the healing of combined radiation-wound skin injury in minipigs. *Int J Radiat Biol.* 2011; 87:591-600.