Abstract:
This article is part of a collaborative effort by experts in the field of emergency preparedness to complete an overview begun by the late Michael Shannon, MD, MPH, on the current challenges and future directions in pediatric disaster readiness. This particular article, "Preparation for Terrorist Threats: Radiation Injury," will address pertinent clinical management issues relating to radioactive agents and the unique vulnerabilities and care needs of children as potential victims of such terrorism.

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Preparation for Terrorist Threats: Radiation Injury

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Mitigating the effects of radiation injury, whether at the political or patient care level, is one of the highest priorities for those that are entrusted with the responsibility of taking care of our children. Radiologic and nuclear threats come from a variety of sources including nuclear detonation, radiologic dispersive devices (dirty bombs), radiologic exposure devices (concealed source), and industrial and shipping accidents (power plant releases, food and medical irradiators). Ionizing radiation injures tissues through energy transfer. Potential exposure outcomes include cell death, cell malfunction, and delayed effects. In cell malfunction, the cell survives but is altered and is incapable of self-repair, potentially causing tissue and organ malfunction. With delayed effects, the cell's genetic material is altered, which creates the potential for subsequent malignancy and birth defects.

The amount of radiation absorbed by the body determines how sick a patient will be. Biodosimetry is the laboratory or clinical methodology used to measure or estimate the exposure dose and is used for triage as well as the development of definitive treatment plans. Emerging biodosimetric technologies may further refine triage and dose assessment strategies. A key component of current radiation countermeasures research is the development of biodosimetry tools including bioassays to evaluate the extent of radiation exposure and injury. Particular attention to pediatric appropriate biomarker research is needed.

The current treatment goals for radiation sickness are to prevent further radioactive contamination, treat damaged organs, reduce symptoms, and manage pain. Internal decontamination targets material that has been inhaled, ingested, and deposited and typically requires medical and/or surgical removal (usually done after initial stabilization). Examples of these medical countermeasures (MCMs) include radionuclide chelating (decorporation) agents that reduce the body burden of an isotope (ie,

diethylenetriamine pentaacetic acid, Prussian blue) and blocking agents that reduce organ uptake of an isotope (potassium iodide).

Survival is possible with mild-moderate exposures (0.5-3.5 Gy) with higher exposures increasing the likelihood of death. With 3.5 Gy, there is approximately a 50% mortality 30 days postexposure. The Radiation Event Medical Management Web site (http://www.remm.nlm.gov/) produced by the Department of Health and Human Services/Office of the Assistant Secretary for Preparedness/National Library of Medicine is an excellent resource for the diagnosis and management of acute radiation syndrome (ARS). The Radiation Event Medical Management's algorithms are very comprehensive for adults and for children; they provide an excellent foundation for a pediatric approach to acute radiation injury.

Low levels of radiation (such as that occurring through natural background radiation and medical diagnostic procedures) are routinely managed by the body's normal repair mechanism. When large radiation exposures occur over short periods, the body's ability to manage the damage can be overwhelmed, leading to a spectrum of clinical changes that are collectively known as ARS. These clinical symptoms occur in stages during a period of hours to weeks after whole-body radiation exposure, as injury to various tissues and organs is expressed. Acute radiation syndrome may involve hematologic, gastrointestinal, cutaneous, and neurovascular systems. Long-term exposure outcomes may also include renal failure and pulmonary fibrosis. Secondary malignancies may appear decades later.

Acute radiation syndrome typically encompasses 4 phases:

Prodromal phase: this is a nonspecific response to acute high-dose radiation exposure. The earlier the onset of nausea, vomiting, and malaise, the greater the exposure dose of radiation. Time to emesis (TE) correlates with dose absorbed: TE less than 4 hours suggests a whole body dose of 3.5 Gy (350 rad) and a TE less than 1 hour suggests a whole body dose of 65 Gy. This phase can occur without later "manifest illness" (see below) if the dose is low enough.

Latent phase: after recovery from the prodromal phase, there will be a length of time during which the exposed individual will be relatively symptom free. The duration of the phase is hours or days. Declining absolute lymphocyte count is best predictor of whether further injury may manifest itself.

Manifest illness: this presents with the clinical symptoms of major the organ system(s) injured, with the time of onset decreasing as the exposure dose is increased. The 3 major organ systems are affected relatively acutely: hematopoietic system, gastrointestinal system, and the central nervous system.

Recovery/death: chronic renal failure and pulmonary fibrosis may follow.[1]

The *hematopoietic syndrome* begins to manifest after radiation exposures of 1.5 to 2.0 Gy in children and can take weeks to manifest. The hematopoietic syndrome is composed of neutropenia, lymphopenia, thrombocytopenia, and anemia. There is consensus that agents that could prevent or reduce the severity of neutropenia, thrombocytopenia, and anemia should be administered to those victims that have received 2 to 6 Gy. Currently, there are no exposure screening mechanisms to delineate a need for the above treatment; therefore, any patient displaying the signs of ARS could be a candidate for treatment.

- Lymphopenia: a drop in absolute lymphocyte count of 50% in 24 hours indicates a significant exposure. At the present time, there is no known treatment for lymphopenia, and the recovery of immunity is, in many instances, prolonged and incomplete.
- Neutropenia: the loss of progenitor cells and the unusual kinetics of neutrophil production and release account for the delayed onset of the hematopoietic syndrome.[2] Human granulocyte colony-stimulating factor are glycoproteins that act on hematopoietic cells by binding to specific cell receptors that stimulate proliferation and differentiation as well as some end-cell function (based on the degree of radiation exposure, these cytokines would be initiated prophylactically). Keratinocyte growth factor has been shown to reduce the period of febrile neutropenia secondary to total body irradiation.
- Thrombocytopenia: the loss of progenitor cells with radiation exposure also results in a decrease in platelets. Thrombocytopenia treatment challenges include the need for recurrent platelet transfusions, which can be extremely difficult in the mass casualty setting. Thrombopoietin is a cytokine that has been isolated and identified as the primary growth factor responsible for regulation of megakaryopoiesis and thrombopoiesis. Second-generation thrombopoietin drugs such as

Romiplostim, recently licensed for idiopathic thrombocytopenic purpura, hold promise for the treatment of radiation induced injury.
- Anemia: the long half-life of red cells makes this less of an immediate problem within the hematopoietic syndrome. Two erythropoietin-stimulating agents (epoetin alfa, darbepoetin alfa) have been approved by the Food and Drug Administration for other indications and may be useful in the management of radiation-induced anemia.
- Stem cell transplantation is a consideration with significant exposures. Many recommend following the Radiation Injury Treatment Network-National Marrow Donor Program/American Society for Bone and Marrow Transplantation (RITN-NMDP/ASBMT) guidelines.

The *gastrointestinal system* is affected with doses in the range of 6 to 20 Gy[1] and always occurs in conjunction with hematopoietic injury and is associated with a high mortality rate. The pathophysiology involves disruption of the villous membrane by reducing expression of endothelial thrombomodulin, a transmembrane protein receptor that regulates inflammation and is found on endothelial cells, with resultant diarrhea (fluid losses may be severe enough to cause shock), infection (with membrane integrity lost opportunistic gram-negative organisms invade), and bleeding from injury to the submucosal vasculature.[3,4]

Treatment aims to restore fluid losses as well as treat opportunistic infections in a neutropenic host. Additional treatment modalities include statins, which increase the levels of endothelial thrombomodulin, thus reducing radiation effects and decreasing gastrointestinal injury. Palifermin (recombinant keratinocyte growth factor) has been approved for use in prevention of oral mucositis, and animal studies suggest that it may prevent intestinal mucositis.[3,4]

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

Cutaneous injury from thermal or radiation burns is characterized by loss of epidermis and, at times, dermis. Injuries to the skin may cover small areas but extend deeply into the soft tissue, even reaching underlying muscle and bone.[6] They may be accompanied by profound local edema and place the patient at risk for a compartment syndrome. Patients presenting with burns immediately after exposure have thermal rather than radiation burns. Treatment protocols have not been standardized, but clinicians have used corticosteroids, interferon, pentoxiflylline, α-tocopherol, and superoxide dismutase for treatment of their patients.

Lung injury may manifest 1 to 6 months after exposure to therapeutic doses of radiation to the chest. Acute pneumonitis may occur with symptoms of shortness of breath, cough, and sometimes fever. In patients and animal models, pneumonitis is associated with cell loss in the alveolar lining, alveolar hemorrhage, breathlessness, pulmonary edema, and leukocyte infiltration. Within 3 weeks of radiation exposure, there is an increase in mucous-secreting goblet cells and ciliary dysfunction. Within 3 to 12 weeks, radiation-induced pneumonia occurs. This manifestation of radiation injury is often fatal. If recovery occurs, fibrosis develops, which is the replacement of the normal alveolar architecture with abnormal scar tissue. Pentoxifylline has been found to be effective in mitigating pulmonary toxicity, and the combination of pentoxifylline combined with α-tocopherol has been shown useful for the treatment of radiation-induced fibrosis.[7-10]

Delayed radiation-induced *kidney injury* occurs months to years after exposure to radiation doses of 10 to 20 Gy. The higher the dose, the sooner the onset and progression of injury. In animal models, ultrastructural damage to the glomerular endothelium is evident within approximately a month. Tubular epithelial cells manifest evidence of injury soon after, followed by interstitial scarring. Structural damage and renal function worsen with time. High levels of protein and nitrogen are observed in the urine, and hypertension occurs. Mechanistic studies have suggested the involvement of the renin-angiotensin system in the development of radiation-induced renal effects.[11,12] Treatment may include

suppression of the renin-angiotensin system using angiotensin-converting enzyme inhibitors, angiotensin II receptor antogonists (based on anecdotal evidence of efficacy).

FUTURE PEDIATRIC RESEARCH NEEDS

In the years after the September 11, 2001 terrorist attacks, the federal government in collaboration with academia and industry has prioritized development and stockpiling of MCMs to deal with the consequences of weapons of mass destruction. Unfortunately, for a multitude of reasons, regulatory, fiscal, ethical, and the lack of a pediatric voice, children do not have the same protective resources available for them as the adults in our community do. In addition, many of the MCMs undergoing research and development at this point in time are not being adequately studied to benefit children. To bring attention to this problem and to provide a starting point for resolution, a meeting of government and academic pediatric biodefense experts was held at the Eunice Kennedy Shriver National Institute of Child Health and Human Development on September 8 to 9, 2008. The goals of this meeting were to:

- Identify what additional studies may be needed to help ensure that the current therapeutic agents in the Strategic National Stockpile are properly formulated, dosed, safe, and effective for the care of children and pregnant women.
- Review and provide input into further development of therapeutic countermeasures for children and pregnant women in selective ongoing basic science and clinical biodefense-related research studies.

Visit the National Institute of Child Health and Human Development–Best Pharmaceuticals for Children Act[13] Web site for an overview of the contents of the meeting. Further continuous pediatric input is crucial at all levels of biodefense research and development as well as subsequent deployment of future MCMs. Mechanisms are currently being developed to assist in this process.

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