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CME Topic

Acute Radiation Syndrome: Assessment and Management

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Abstract: Primary care physicians may be unprepared to diagnose and treat rare, yet potentially fatal, illnesses such as acute radiation syndrome (ARS). ARS, also known as radiation sickness, is caused by exposure to a high dose of penetrating, ionizing radiation over a short period of time. The time to onset of ARS is dependent on the dose received, but even at the lowest doses capable of causing illness, this will occur within a matter of hours to days. This article describes the clinical manifestations of ARS, provides guidelines for assessing its severity, and makes recommendations for managing ARS victims.

Key Words: acute radiation syndrome, radiation health effects, radiation injury, radiological emergencies

Few clinicians will ever see a patient with a radiation-induced illness or injury. Moreover, whereas other uncommon illnesses may present with characteristic findings, ionizing radiation injury typically presents without distinguishing signs and/or symptoms. Indeed, there are no pathognomonic physical findings associated with ionizing radiation-induced illness. Acute radiation syndrome (ARS), sometimes known as radiation toxicity or radiation sickness, is an acute illness caused by irradiation of the entire body (or most of the body) with a high dose of radiation over a very short period of time (usually a matter of minutes). In the absence of an obvious exposure (e.g., a therapeutic misadventure, or proximity to a nuclear weapon detonation or an industrial accident) the diagnosis of acute radiation syndrome (ARS) will elude most practicing clinicians. Due to the credible threat of radiological and nuclear terrorism, however, healthcare providers should have a basic understanding of the diagnosis and management of ionizing radiation-induced illness and injury.

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Pathophysiology of ARS

Among cells, sensitivity to radiation varies according to cell cycle length. The rate at which a cell replicates and divides is an important determinant of radiosensitivity. During mitosis, when genetic material is most exposed, cells are most vulnerable to the effects of radiation. Spermatogonia are easily damaged by ionizing radiation. Lymphocytes, erythroblasts, and other hematopoietic cells are also fairly radiosensitive, as are the cells of the gastrointestinal tract. Muscle, bone, and collagen-producing cells are less mitotically active and therefore among the least sensitive to the effects of radiation.[1]

The Classic Syndromes of ARS

Differences in cellular sensitivity to ionizing radiation underlie the classic division of ARS into three syndromes:

Key Points

- Acute radiation syndrome is a continuum of clinical manifestations that includes a prodromal phase that may progress, depending on the radiation dose, to the hematopoietic, gastrointestinal or central nervous/cardiovascular syndromes.
- Observation of sequential declining absolute lymphocyte counts in the first 48 hours after exposure is a rapid and available method to assess radiation dose.
- The management of acute radiation syndrome is mainly supportive, including antibiotics, blood products, and in certain cases, colony stimulating factors and stem cell transplant.

hematopoietic, gastrointestinal, and neurovascular. Damage to increasingly radioresistant cells correlates with the magnitude of the absorbed radiation dose and is a marker of overall syndrome severity. The signs, symptoms, and pathology associated with the three ARS syndromes are not, however, entirely distinct from each other. Instead, adverse effects of radiation exposure overlap, forming a spectrum of disease.[1]

Hematopoietic (Also Known as Bone Marrow) Syndrome

The rapidly dividing hematopoietic stem cells and progenitor cells of the bone marrow are highly sensitive to the effects of ionizing radiation. At absorbed doses between 20 and 200 rad (0.2 – 2 Gy), ionizing radiation produces a mild, brief arrest in cell division and a clinically insignificant decrease in cell counts. (Note: Acute radiation exposure is measured in units of absorbed dose known as rad or gray (Gy) where 1 rad is equal to 0.01 joules of energy deposited per kilogram of tissue. One Gy is equal to 100 rad or 1 joule of energy deposited per kilogram of tissue.) Although some patients may complain of mild nausea or headache following exposure to a dose as low as 35 rad (0.35 Gy), these health effects are transient and do not constitute ARS. Exposures in excess of 200 rad (>2 Gy) produce clinical ARS.[2]

Lymphocytes – the blood cell line most sensitive to ionizing radiation – are the first depleted in ARS. Following depletion of lymphocytes, granulocyte and platelet levels will decline over a period of days. Mature red blood cells are cleared from the circulation at a slower rate and over a longer period of time. Rapid-onset anemia solely caused by acute ionizing radiation exposure would be unusual; underlying causes of red cell depletion (such as bleeding) should be sought.[2]

Early-onset adverse health effects associated with the hematopoietic syndrome include nausea and vomiting, headache, fatigue, fever, and transient skin reddening. None of these effects occur as a result of bone marrow radiation exposure but serve as harbingers of more serious adverse health effects. Their severity and rapidity of onset correspond to the radiation dose received.[3]

Later-occurring adverse health effects are a consequence of hematopoietic stem cell loss. Clinicians should anticipate impaired immunity and consequent infection, as well as bleeding and poor wound healing due to low platelet counts. Death – usually due to infection and/or hemorrhage – occurs within weeks to months of high-dose ionizing radiation exposure. Left untreated, approximately half of all people exposed to a dose of more than 350 rad (>3.5 Gy) will die within 60 days.[4,5]

Gastrointestinal (GI) Syndrome

At doses between 600 and 1000 rad (6 – 10 Gy), adverse health effects are more severe and abrupt in onset than are the health effects seen following exposures associated with the hematopoietic syndrome. Occurring within one to two hours of exposure, nausea, vomiting (occasionally severe), anorexia, and crampy abdominal pain are characteristic findings.[4] Curiously, at exposures much above 1000 rad (10 Gy) vomiting is suppressed and not seen as part of the early symptoms.[6] The presence of diarrhea early in the course of the illness is a particularly ominous sign. Death from the gastrointestinal syndrome is most often due to multisystem organ failure, overwhelming sepsis, and complications due to bleeding. Patients generally succumb to absorbed doses of 600 to 1000 rad (or more) within weeks of exposure.[3,4]

Neurovascular Syndrome

Of the three major organ systems included in the spectrum of ARS, the nervous system is generally regarded as the least sensitive to the effects of ionizing radiation. At exposure doses approaching and exceeding 1000 rad (10 Gy), vomiting is suppressed[6]; at the same time, a more global sedation occurs referred to as the "fatigue syndrome." Clinical features of this syndrome include fever and headache and, with increasing dose, altered reflexes, dizziness, confusion and disorientation, ataxia, and loss of consciousness.[4]

At very high doses – 3500 rad (35 Gy) and above – penetrating ionizing radiation damages larger blood vessels resulting in circulatory collapse.[4] Increased intracranial pressure, cerebral vasculitis, and meningitis may be seen. At doses in excess of 5000 rad (50 Gy) victims will succumb within 48 hours or less.[6] The expected bone marrow and gastrointestinal injuries do not have sufficient time to manifest themselves before the victim's demise.

Phases of ARS

Each ARS syndrome follows a predictable course that can be divided into four clinical phases (or stages).[3,4,7,8]

Prodromal Phase

Nausea and vomiting are hallmarks of the prodromal phase. Time to vomiting can range from minutes to days following exposure. More rapid onset suggests a higher absorbed dose. In addition, other nonspecific health effects include fever, headache, parotitis, abdominal cramping, skin erythema, conjunctivitis, and hypotension. Symptoms typically last no more than 48 hours.

Latent Phase

Patients experience apparent clinical improvement for a few hours or even up to a few weeks postexposure as adverse health effects abate. By this time, however, the reservoir of pluripotent stem cells – whose function is to replace cells lost through natural attrition – has been significantly and critically depleted. Adverse health effects associated with cellular loss gradually appear, heralding the next phase of ARS.

Manifest Illness

Adverse health effects that characterize the various syndromes become apparent during the manifest illness phase. Their severity is influenced by such factors as the magnitude of the absorbed dose, the overall body volume irradiated, concomitant infection, trauma, or dermal injury, underlying health status, and age. The manifest illness phase can last from days to months.

Recovery or Death

The recovery process – generally slow – will last for several weeks to years. High quality supportive care can extend the lives of radiation exposure victims. Very high dose radiation exposure will cause death within days; at lower lethal levels of exposure, patients may die within weeks or months.

Assessment and Treatment of ARS

Assessment

Because symptoms are nonspecific, diagnosing ARS in the absence of a history of radiation exposure can be complicated. Measuring an absolute lymphocyte count is the quickest and easiest laboratory test to provide an estimate of exposure.[9] Where possible – and in a large radiation mass casualty event, resources may be constrained – a complete blood count (CBC) should be collected at the time of patient presentation, repeated every 4 hours for the first 8 hours, and then every 6 hours for the next 40 to 48 hours.[10,11] An initially low or progressively falling lymphocyte count is highly suggestive of high dose radiation exposure (See Figure , Classical Andrews Lymphocyte Depletion Curves).[11] The Andrews nomogram provides not only an estimation of whole-body radiation dose but also an approximate measure of illness severity.

Clinicians may also use postexposure time to emesis (assuming an exposure time can be established) to provide an estimate of illness severity. As a general rule, the greater the absorbed dose (up to 1000 rad), the sooner vomiting will begin (Table), although several caveats apply. At absorbed doses of 200 to 300 rad (2 – 3 Gy), fewer than half of all patients will vomit. Thus, even at doses known to cause ARS, not all victims will have emesis. Even at doses of 500 to 600 rad (5 – 6 Gy), between 80% and 90% – though not all – can be expected to vomit. Furthermore, because emesis is a nonspecific finding induced by a variety of conditions, it should be considered a less reliable indicator of radiation dose.[7] Ultimately, formal dosimetry is the most accurate measure of exposure and is necessary to guide management and patient prognosis. Cytogenetic dosimetry, the gold standard, relies on predictable and standardized effects of radiation on deoxyribonucleic acid (DNA) replication in cultured lymphocytes.

Only two laboratories in this country currently perform cytogenetic dosimetry and the results are typically not available for several days.[10]

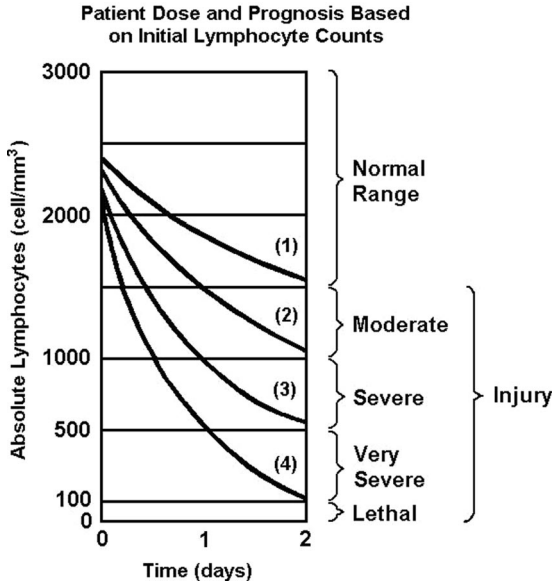

Fig. Classical Andrews lymphocyte depletion curves and accompanying clinical severity ranges. Curves 1 to 4 correspond roughly to the following whole-body doses: curve 1: 3.1 Gy (3,100 rad), curve 2: 4.4 Gy (4,400 rad), curve 3: 5.6 Gy (5,600 rad), and curve 4: 7.1 Gy (7,100 rad). (Modified from Gusev et al.[7,11])

Treatment

Patients with acute, high dose, whole body irradiation will fall into one of three categories: those who recover with minimal intervention; those who require aggressive supportive care, up to and including bone marrow stem cell transplants; and those who – due to the dose they received, concomitant physical trauma, or inadequate clinical resources – will be triaged to receive palliative care. Except for the moribund individual, patient management during the prodromal phase is fairly uniform, regardless of triage category. Obtaining a history and physical examination, removal of external contamination, dose estimation, supportive care (including psychological support of the patient and family), symptomatic treatment, and replacement of fluids and electrolytes should be the earliest goals of medical management. With the onset of the latent phase, medical staff should have at least a crude estimate of absorbed dose and illness severity. Individuals with hematopoietic syndrome should be transferred to tertiary care centers

Table. Estimation of dose related to onset of vomiting (for single acute exposures only)

Vomiting post incident	Estimated dose
<10 min	>8 Gy (800 rad)
<30 min	6–8 Gy (600–800 rad)
<1 h	4–6 Gy (400–600 rad)
1–2 (h)	2–4 Gy (200–400 rad)
>2 h or not at all	<2 Gy (200 rad)

specializing in the care of pancytopenic patients. Physical trauma or burn injury superimposed on radiation exposure predisposes victims to a worse overall prognosis. Individuals with such combined injuries, along with those whose clinical picture suggests an even higher absorbed dose, should be provided with comfort care in order to alleviate pain and suffering.

Over the first week to 10 days postexposure – as granulocytes begin to decrease towards a nadir – it is critical to support neutrophil levels. As the number of neutrophils falls, the likelihood of infection increases. Patients most at risk are those with neutrophil counts $<0.5 \times 10^9$ cells/liter. Consultations with infectious disease specialists and hematologists are recommended if febrile neutropenia develops.[2,12] Strict infection control can and should be supplemented as soon as possible by administration of cytokines: granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF). These drugs stimulate neutrophil precursor cells in the bone marrow to divide and produce mature cells. Subpopulations of radioresistant bone marrow stem cells unaffected by ionizing radiation and pools of hematopoietic stem cells spared by shielding provide an intrinsic reservoir for recovery, especially when enhanced by the use of cytokines and intensive supportive care.[13]

Neither G-CSF nor GM-CSF has been approved for use by the US Food and Drug Administration (FDA) as a treatment for radiation-induced neutropenia. Nevertheless, the "non-approved" use of G-CSF (filgrastim or Neupogen®), GM-CSF (Leukine®, Leucotropin®), or the pegylated form of G-CSF (peg-filgrastim or Neulasta®) has been recommended by the Strategic National Stockpile (SNS) Radiation Working Group and by other experts in radiation medicine.[5] The Centers for Disease Control and Prevention (CDC), which has oversight for the SNS, currently holds an Investigational New Drug application with the FDA for the release and use of Neupogen® following a radiation mass casualty event. Bone marrow stem cell transplants can be considered for whole body absorbed doses of 700 to 1000 rad (7 to 10 Gy). The Radiation Injury Treatment Network (http://bloodcell.transplant.hrsa.gov/ABOUT/RITN/index.html) was developed to respond to potential disasters where victims may suffer overwhelming bone marrow damage.

Conclusion

Health care providers may yet be called upon to provide care to victims of acute, high-dose, ionizing radiation exposure following a terrorist radiation event. ARS, a consequence of such an exposure, will be assessed and managed on the basis of a thorough history and physical examination, diagnostic testing, and appropriate resource allocation. Even with proper management, recovery from ARS takes a long time and lifelong medical followup is essential.

Additional Resources

The CDC has produced a broad range of educational products including fact sheets, satellite broadcasts, videos, and CD-ROMs (http://www.bt.cdc.gov/radiation/). The Radiation Event Medical Management (REMM) web portal (http://remm.nlm.gov/), developed under the auspices of the US Department of Health and Human Services, includes guidance for health care providers. Finally, radiation emergency medicine consultation services are provided by the Radiation Emergency Assistance Center/Training Site (REAC/TS). REAC/TS physicians and health physicists are available 24 hours a day, 7 days a week at 865.576.1005 (http://orise.orau.gov/reacts/).

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Acute Radiation Syndrome: Diagnosis and Management

June 2010 CME Questions

1. Which of the following is true regarding acute radiation syndrome (ARS)?
   A. ARS occurs as a result of exposure to high-dose penetrating radiation
   B. ARS occurs as a result of exposure to nonionizing radiation
   C. ARS is divided into two syndromes: gastrointestinal and cardiovascular/neurologic
   D. Clinical ARS develops after exposure to less than 100 rad

2. Which of the following is useful in the diagnosis of acute radiation syndrome?
   A. Prodromal symptoms such as vomiting
   B. Decreasing absolute lymphocyte counts during the first 48 hours after exposure
   C. Cytogenetic dosimetry
   D. All of the above

3. Medical management of acute radiation syndrome includes:
   A. Colony stimulating factors
   B. Blood products (red cells, platelets, etc.) as needed
   C. Symptomatic treatment and supportive care
   D. All of the above

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1. A, 2. D, 3. D

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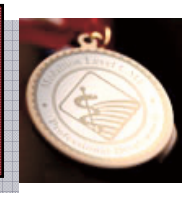

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