Title	Acute Radiation Syndrome
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Purpose

This article was written because physicians, healthcare workers, and hospitals will assume the care of individuals involved in an acute radiation exposure whether it is from a terrorist attack, nuclear plant mishap or accidental exposure.

Objectives

1. Describe what Radiation Sickness Is.
2. Describe the difference between acute and chronic radiation sickness.
3. Describe the characteristics of the hematopoietic syndrome.
4. Describe the characteristics of the gastrointestinal syndrome.
5. Describe the characteristics of the cerebrovascular syndrome.
6. Describe the characteristics of the cutaneous syndrome.
7. Define the treatment for acute radiation syndrome.
8. Identify the prognosis for patients with acute radiation syndrome.

DEFINITIONS

Radiation - the release of energy from atoms

Radioactivity - Radioactive decay is the process in which unstable atomic nuclei assume a more stable configuration by emitting particles with kinetic energy (alpha or beta particles) or electromagnetic waves (gamma rays). If a person is exposed to these high-energy particles or electromagnetic waves, energy is deposited into the tissues and can cause injury. (10)

Ionizing (Penetrating) Radiation - energy released from decaying atoms. High-energy particles or electromagnetic waves that have the ability to deposit enough energy to break chemical bonds and produce ion pairs. If living cells receive this energy, cellular function becomes compromised by DNA damage and mutation. (10)(13)

Nonionizing (nonpenetrating) radiation - radiation that lacks the energy to liberate orbital electrons. Nonpenetrating radiation does not pass through your skin. A large dose of nonpenetrating radiation may burn your skin similar to the way severe sunburn does. Examples are microwaves, visible light and infrared light. (10)

Particle radiation - small charged or neutral particles traveling with high energy. Can take the form of alpha particles, beta particles or neutrons.

Radiation waves - include gamma rays and X-rays.

Alpha Particles - alpha emitters tend to be isotopes of uranium. They do not penetrate beyond the stratum corneum of the skin or through clothing. These particles are only a concern when inhaled or ingested such as radon gas.

Beta Particles - can penetrate the body from the outside by a few centimeters. Common isotopes that emit beta particles include carbon-14, cobalt-60 and iodine-131. These are commonly used for X-rays or radiotherapy

Neutrons - penetrate easily through the body and indirectly ionize the cells. High- energy neutrons rarely occur naturally but can be produced in a particle accelerator or in a nuclear reactor as part of the fission process.

Gamma Rays - are high-energy photon waves that penetrate the body (and concrete) easily and travel many meters through the air. Common isotopes are cobalt-60, cesium- 137 and iridium-192.

X-rays - like gamma rays are photon waves but have a longer wavelength and lower energy than gamma rays. (7)

LD50/60 – means lethal dose required to kill 50% of humans at 60 days. (6)

1 Gy = 100 Rads

Chronic Radiation Sickness - chronic radiation sickness may take several days or weeks to develop. The cause can be radioactive fallout from a nuclear explosion or an industrial accident. Therapeutic radiation treatments for cancer can also cause temporary chronic radiation sickness. (13)

Acute radiation sickness - Acute radiation sickness can develop quickly. A person with acute radiation sickness usually has been exposed to large amounts of radiation over a brief period of time, such as in an industrial accident or nuclear bomb explosion. (13)

INTRODUCTION

People everywhere are exposed to radiation daily. In general, most humans on the planet are exposed to 1 to 2 milligray (mGy) a year. This is referred to as "background radiation". Radiation is present all around us: in the air, in the ground and in the water. Some of the most common forms of radiation that people are exposed to may come from natural sources such as cosmic rays and substances in the earth's crust, such as radon. Certain foods such as bananas and Brazil nuts contain more radiation than other foods. Brick and stone homes have higher natural radiation than homes made from other materials such as wood. Levels of natural background radiation can vary greatly from one location to the next. For example, people in the Midwest are exposed to more radiation than residents of the East and West coast because Colorado, for example, has more cosmic rays from the higher altitude and more terrestrial radiation from soils enriched in naturally occurring uranium. (12)

Other exposures come from man-made substances such as waste from nuclear reactors, diagnostic machines such as X-ray, CAT scan or mammogram machines and the use of radioactivity in cancer treatment. There are, however, more serious types of radiation exposures, such as nuclear accidents and atomic weapons use and testing. Intentional sources of radiation exposure could occur if terrorists blew up a nuclear power plant, set off a nuclear bomb or detonated a so-called 'dirty bomb'. A 'dirty bomb' uses conventional explosives to spread radioactive materials, such as radioactive waste from a nuclear power plant or sources

of radiation from a medical facility. (13) These persons who are affected by a single exposure of high levels of ionizing radiation and become very ill are said to have acute radiation syndrome (ARS). As ionizing radiation passes through the body the interaction with tissues cause the transfer of ionizing energy to critical cell systems. (3)

Radiation injury can occur from external irradiation, external contamination with radioactive materials, and internal contamination by inhalation, ingestion, or transdermal absorption with incorporation of radiologic materials into the body's cells and tissues. These three types of exposure can occur in combination and can be associated with thermal burns and traumatic injuries.(6)

Injury from a nuclear detonation varies, depending on the location of the victim relative to the hypocenter and the consequent exposure to different types of energy. Three forms of energy are released from a nuclear detonation:

- heat, accounting for approximately 35% of total energy
- shock or bomb blast, accounting for approximately 50% of total energy
- radiation, accounting for the remaining 15% of total energy.

Heat and light cause thermal injury, including flash burns, flame burns, flash blindness (due to temporary depletion of photopigment from retinal receptors) and retinal burns. The blast wave results in fractures, lacerations, rupture of viscera and pulmonary hemorrhage and edema.(6) Radiation causes:

- the acute radiation syndrome
- cutaneous injury and scarring
- chorioretinal damage from exposure to infrared energy
- depending on radiation dose and dose rate, increased long-term risk for cancer, cataract formation (particularly with neutron irradiation), infertility, and fetal abnormalities (that is, growth retardation, fetal malformations, increased teratogenesis, and fetal death). (2)

Radiation sickness, known as Acute Radiation Syndrome (ARS), is a serious illness that occurs when the entire body (or most of it) receives a high dose of radiation, usually over a short period of time. Many survivors of the Hiroshima and Nagasaki atomic bombs in the 1940s and many of the firefighters who first responded after the Chernobyl Nuclear Power Plant accident in 1986 became ill with ARS.(1)(3)

People exposed to radiation will get ARS only if:

1. The radiation dose was high (doses from medical procedures such as chest X- rays are too low to cause ARS; however, doses from radiation therapy to treat cancer may be high enough to cause some ARS symptoms),
2. The radiation was penetrating (that is, able to reach internal organs),
3. The person’s entire body, or most of it, received the dose, **and**
4. The radiation was received in a short time, usually within minutes. (1)(5)

Individual radiation dose is assessed by determining the time to onset and severity of nausea and vomiting, decline in absolute lymphocyte count over several hours or days after exposure, and appearance of chromosome aberrations (including dicentrics and ring forms) in peripheral blood lymphocytes. Documentation of clinical signs and symptoms (affecting the hematopoietic, gastrointestinal, cerebrovascular, and cutaneous systems) over time is essential for triage of victims, selection of therapy, and assignment of prognosis. (2) Each syndrome can be divided into four phases:

1. Prodromal
2. Latent
3. Manifest illness
4. Recovery or death.(2)(3)(5)(7)

Prodromal symptoms begin a few hours to four days after exposure. The severity, time of onset, and duration of symptoms relate directly to the dose received, however, the appearance of these symptoms especially nausea and vomiting, can also be induced psychologically. The actual causes of the prodromal symptoms are unknown. The latent period is a brief reprieve from symptoms, when the patient may appear to have recovered. This reprieve may last up to 4 weeks, depending on the dose, and then is likely to be followed by 2-3 weeks of manifest illness. The higher the dose, the shorter the latent phase. At sufficiently high doses the latent phase effectively disappears. The manifest illness stage is the most difficult to manage from a therapeutic standpoint, for this is the maximum state of immunoincompetence that the patient will suffer. If the patient survives the manifest illness stage recovery is almost assured. Therefore, treatment during the first 6 weeks to 2 months after exposure is crucial to ensure recovery from a rapidly received, high dose (less than 5 Gy) of ionizing radiation.(4)(7)(11)

ROUTES OF EXPOSURE

Inhalation - Radiation exposure by inhalation occurs when you breath. radioactive material into your lungs. Radioactive particles can lodge in your lungs and remain there for an extended period of time. As long as these particles remain and continue to decay in your lungs, radiation exposure continues. Although inhaled radioactivity is not likely to result in radiation sickness, tissue damage from inhaled radioactivity eventually can lead to a higher risk of cancer or other diseases. The main sources of inhaled radiation are radon gas and radioactively contaminated dust or smoke. (13)

Ingestion - Exposure to radiation by way of ingestion occurs when you swallow radioactive material. This pathway of exposure releases high energy directly to your tissues, causing cell damage. Although ingested radioactivity isn't likely to result in radiation sickness, tissue damage from ingested radioactivity can eventually lead to a higher risk of cancer. Sources of ingested radiation include contaminated drinking water, plants, milk, fish and meat. Radiation doses from these sources usually are extremely small. (13)

Direct (external) exposure - This route of exposure occurs from a source beaming out and striking your body. Examples of direct exposure include radiation treatments for cancer and radiation from an industrial accident or nuclear explosion. (13)

PHASES OF RADIATION INJURY

A syndrome is a combination of symptoms resulting from a single cause and occurring together so as to constitute a single clinical picture. While any of the four radiation syndromes (hematopoietic, gastrointestinal, cerebrovascular, cutaneous) can cause death, the dose range for each of the four to cause death varies as does the dose required. (11)

THE HEMATOPOIETIC SYNDROME

The hematopoietic syndrome is the result of RBCs, WBCs and platelets being killed by radiation. While mature RBCs and WBCs are somewhat resistant to radiation, the immature stem cells, precursors to WBC's and RBC's are very radiosensitive. After the mature RBC's and WBC's die from natural causes (age) there are no replacement cells. The body becomes depleted in RBC's and WBC's and susceptible to infection. Infection is an important cause of death but may be

controlled in a large part by antibiotics.

The syndrome requiring the lowest dose of radiation is the hematopoietic syndrome. This syndrome requires a dose on the magnitude of 2-8 Gy. This syndrome with proper treatment does not always cause death. The understanding of the hematopoietic syndrome comes from the knowledge of cancer treatments. Patients who are about to receive a bone marrow transplant are given whole body irradiation of these dose levels, although generally given in fractionated doses. The stem cells in the body are the most radiosensitive cells, which is why such a small dose causes damage. Dorsal exposure would maximize damage to this system, because the greatest percentage of active bone marrow lies in the spine, and dorsal regions of the ribs and pelvis. This syndrome is referred to as reproductive death since the body does not show effect until the stem cells attempt division and are unable to do so. Symptoms onset generally occurs within a week and may last up to six weeks. This is the time it will take the stem cells to reach a critical level. The prodromal phase of this illness causes nausea and vomiting that present shortly after irradiation. The latent phase of this syndrome is generally symptom free. This is the time when the prodromal symptoms subside and the real cellular damage begins. This phase will start anytime after exposure and can last up to three weeks. During the latent phase the cells have attempted to repair the damage. The patient then enters the manifest illness. With this phase the patient begins to have chills, becomes fatigued, skin hemorrhages are formed and ulcers are formed in the mouth. These symptoms are all manifestations of the depletion of the stem cells. Infections and fevers will also persist and demonstrate an impairment of the immune system. Patients with this syndrome respond reasonably well to treatment if it is started early. If the patient is given high doses of antibiotics to ward off infection, plenty of fluids to prevent dehydration and given a bone marrow transplant to replace the stem cells lost with irradiation the patient has a chance to survive. (3) (4)

Lymphopenia is common and occurs before the onset of other cytopenias. A predictable decline in lymphocytes occurs after irradiation. In fact, a 50% decline in absolute lymphocyte count within the first 24 hours after exposure, followed by a further, more severe decline within 48 hours, characterizes a potentially lethal exposure. The predictability of the rate of lymphocytic depletion count has led to the development of a model using lymphocyte depletion kinetics as an element of biodosimetry. Patients with burns and trauma may develop lymphopenia as a result of these injuries alone. Although currently available predictive models based on absolute lymphocyte count have been validated (and include patients with these injuries), it is important to examine more than one element of biodosimetry whenever possible.

The onset of other cytopenias varies, depending on both dose and dose rate. Granulocyte counts may transiently increase before decreasing in patients with exposure to less than 5 Gy. This transient increase before decline, termed an abortive rise, may indicate a survivable exposure. (2)

Additional injuries, such as mechanical trauma or burns (the combined injury syndrome), are expected to occur in 60% to 70% of patients after detonation of an improvised nuclear device. These injuries significantly complicate the management of patients with the hematopoietic syndrome and significantly lower the LD50/60. Prognosis is grave in patients with the combined injury syndrome and radiation exposure.(2) Prodromal symptoms may include nausea, vomiting, anorexia, and diarrhea. If severe diarrhea occurs during the first 2 days, the radiation dose may have been lethal. The prodromal phase may last up to 3 days. This is followed by up to 3 weeks of latency, during which the patient will suffer from significant fatigue and weakness. The clinical symptoms of manifest illness appear 21-30 days after exposure, and may last 2 weeks. Severe hemorrhage from platelet loss and infection associated with pantocytopenia from bone marrow suppression are the lethal factors in the hematopoietic syndrome. (4) Overall, the systemic effects that can occur from the hematopoietic syndrome include immunodysfunction, increased infectious complications, hemorrhage, anemia, and

impaired wound healing, which may be due in part to endothelial damage, which significantly depresses the revascularization of injured tissue. (4)

THE GASTROINTESTINAL SYNDROME

This syndrome requires a dose of more than 8 Gy. Although the higher dose is serious and causes some cell death immediately after exposure due to apoptosis, the gastrointestinal syndrome is also considered reproductive death, because of the effect of the radiation on the mucosal lining of the intestine. The gastrointestinal syndrome overlaps the hematopoietic syndrome, but its consequences are more immediate, prompt and profuse onset of nausea, vomiting and diarrhea. (5) These mucosa are made up of villi, which protrude from the lining of the intestine and create more surface area for absorption of nutrients. This syndrome can last from 3 days to many weeks. Survival from this syndrome is rare. (3)

The prodromal phase of this syndrome starts immediately after exposure. Symptoms of nausea, vomiting, diarrhea, loss of appetite and decreased blood pressure occur within hours after irradiation, followed by a much shorter asymptomatic latency period of 5-7 days. Toward the end of this phase the mucosa of the nasal and esophageal passages start to dry out, become swollen and ulcerated leading to difficulty in swallowing and causing dry mouth with a metallic taste. These symptoms will last 3 to 5 days. This passage begins the latent phase which is generally asymptomatic. This phase is similar to the latent phase of the hematopoietic syndrome, meaning the time between irradiation and the expression of the cell damage. The length of the latent phase can be correlated to the dose received. Manifest illness begins with the increase of dehydration, diarrhea, fever, and abdominal pain. These symptoms are due to trauma of the intestinal villi, which consist of four regions. The crypt stem cells, which normally divide with high mitotic activity. (3) The differentiating compartment which is a region farther up the villus where cells are differentiated into functional cells. These differentiated cells migrate to the near tip of the villus, where most of the absorption takes place. These cells will replace the functional cells at the tip of the villus. The very top of the villus is where the functional absorption cells are located and are sloughed off the villi with the passing of the intestinal contents. In an unirradiated system the crypt cells would repopulate these functional cells to replace the discarded ones. This causes the denudation of the intestine.

Cells of the stomach, colon and rectum are soon depleted as well. These occurrences cause the increased dehydration and diarrhea. After the intestinal breakdown, bacteria are able to enter the blood stream through the denuded intestine and cause serious infection because of the destruction of the stem cells in the blood. This causes fever and septicemia in the patient. (3) Although survival of the gastrointestinal syndrome is rare there is a possibility of rescuing a patient when the exposure is less than 10 Gy. Survival would only occur if the intestinal stem cells were not completely destroyed. If the intestinal crypt cells are able to repopulate themselves then proper treatment may help some patients. This requires high levels of antibiotics to control infection and a constant supply of fluids to help with the dehydration. A bone marrow transplant would be needed as well. (3)

Radiation induces loss of intestinal crypts and breakdown of the mucosal barrier. These changes result in abdominal pain, diarrhea, nausea and vomiting and predispose patients to infection. At doses exceeding 12 Gy, the mortality rate of the gastrointestinal syndrome exceeds that of the hematopoietic syndrome. Severe nausea, vomiting, watery diarrhea, and cramps occur within hours after high-dose (>10 Gy) irradiation. This is followed by a latent period lasting 5 to 7 days, during which symptoms abate. Vomiting and severe diarrhea associated with high fever make up the manifest illness. Systemic effects may include:

- malnutrition from malabsorption
- bowel obstruction from ileus

- dehydration
- cardiovascular collapse
- electrolyte derangements from fluid shifts
- anemia from damage to the intestinal mucosa
    - microcirculation
    - gastrointestinal bleeding
- sepsis
- acute renal failure. (4)

THE CEREBROVASCULAR SYNDROME

The cerebrovascular syndrome is less well defined than other syndromes, and its stages are compressed. This syndrome is the least understood and is referred to as a physiological death because the symptoms and ultimate death appear so quickly, usually within 2 days.(3) Individuals presenting with fever, hypotension, and major impairment of cognitive function will most likely have had a supralethal exposure. These symptoms may be observed in those receiving more than 20 to 30 Gy of radiation. 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 five to six 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. (4)

THE CUTANEOUS SYNDROME

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. 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. Significant injuries to the integument decrease the LD50/60 and amplify the risk for death at any radiation exposure dose. Patients with the hematopoietic syndrome have a more complicated course of the cutaneous syndrome as a result of bleeding, infection, and poor wound healing.

The prodromal phase starts within hours with early erythema, heat sensation, and pruritis which lasts 1-2 days. The latent phase begins 1-2 days after exposure with no evidence of injury but note that skin on the face, chest and neck has a shorter latent period than the palms and soles of the feet. The manifest illness stage occurs days to weeks after exposure with a second wave of erythema, increased pigmentation (bronzing), dry or wet desquamation depending on dose, and necrosis. Epilation occurs for a dose > 3 Gy between days 14-21. The third wave of erythema begins 10-16 weeks post exposure, especially beta radiation-late erythema, edema, and increased pain. A bluish discoloration of irradiated skin may be noticeable. The late effects may occur months to years after exposure varying from slight atrophy to constant reoccurring ulcerations with necrosis and deformity. Lymphedema is common. Telangectasis is frequently seen with altered pigmentation and an increased risk for developing skin cancer. (7)

CHRONIC RADIATION EFFECTS

SOMATIC EFFECTS

Chronic exposures are considered low doses of radiation over a relatively long period of time (weeks or years). The effects, if any, do not manifest themselves until years after the exposure. Other than radiation sickness associated with acute exposures, there is no unique disease associated with chronic radiation exposure. A statistical increase exists in the development of harmful effects. The following describes the long term effects that may occur from exposure to ionizing radiation.

Cancer - Ionizing radiation may be shown to exert an almost universal carcinogenic action resulting in tumors in a great variety of organs and tissues. There is evidence that radiation may contribute to the induction of various kinds of neoplastic diseases. The main sites of solid tumors are the breasts in women, thyroid, lung and some digestive organs. These tumors have long latent periods (approximately 10 to greater than 30 years) and occur in larger numbers.

Leukemia - Leukemia (abnormal increase in WBC's) was first noted in radiologists who used radiation in their practices. The incidence of leukemia was much greater for radiologists than other physicians who did not use radiation. Also, atomic bomb survivors within 1500 meters of the blast center showed significantly higher incidence of leukemia than those beyond 1,500 meters.

Leukemia has a much shorter latent period. The incidence of leukemia peaks at three or four years after exposure and returns to normal levels after about 25 years. Leukemia induction is also a function of the type of radiation. In Nagasaki, leukemia induction was not seen in individuals with exposure less than 100 rad, while in Hiroshima, leukemia induction was seen in doses between 20 and 40 rads. The difference being that Hiroshima had a greater neutron dose than Nagasaki.

Cataracts - The lens of the eye is highly susceptible to irreversible damage by radiation. When the cells of the lens become damaged, they lose their transparency and a cataract is formed. Exposures around 200 rad (2 Gy) may produce a cataract, although the signs and symptoms may not be apparent for years after the exposure. The damaging effects of penetrating radiations to the lens of the eye may be cumulative and repeated small doses may result in cataract formation.

Radiation-induced cataracts are produced primarily by neutron and gamma radiation. Radiation-induced cataracts differ from naturally occurring cataracts. Radiation induced cataracts form on a different position on the lens of the eye. Susceptibility to radiation-induced cataract formation seems to be somewhat dependent on age. Radiation is more likely to produce cataracts in younger persons because of the continuous growth of the lens (growing tissues are more radiosensitive).

Extensive irradiation of the eye may result in inflammation of the cornea or in increase in tension within and hardening of the eyeball. These conditions usually become manifest several weeks after the exposure and may terminate in loss of vision.

TRIAGE AND EMERGENCY CARE

The goal of triage is to evaluate and sort individuals by immediacy of treatment needed to do the greatest good for the most people. Triage should include a radiologic survey to assess dose rate, documentation of prodromal symptoms, and collection of tissue samples for biodosimetry. Management of life-threatening injuries takes precedence over radiologic surveys and decontamination. The goal of triage in mass casualty situations is to save as many patients as possible. This often necessitates heart-rendering sacrifices that leave health care personnel at significant risk for post- traumatic stress disorder (PTSD). (7)

In general, treatment of conventional injuries and illness takes precedence over radiation concerns. The quantity of radioactive material that a contaminated individual carries on his or her body is unlikely to present a significant radiation risk to hospital workers. (10)

PRESENTATION OF TWO TRIAGE SYSTEMS

The first system is a modification of the military triage system used in mass- casualty scenarios. Patients are categorized on the basis of the estimated range of exposure dose and the presence or absence of significant mechanical trauma or burns (that is, combined injury). Individuals requiring surgical intervention should undergo surgery within 36 hours (and not later than 48 hours) after the exposure. Additional surgery should not be performed until 6 weeks or later.

Depending on the time elapsed after the exposure and availability of resources, patients may be re-triaged to another category.

Alternatively, an individual physiologic "response category" based on grading of clinical signs and symptoms may be used in triage even before individual dose estimates are available to care providers. An initial response category is assigned by determining the degree of toxicity to the cutaneous, gastrointestinal, and neurovascular systems. Further categorization of patients based on hematological degree of toxicity permits triage to an ambulatory setting, admission to a routine-care hospital floor, or admission to a critical care unit. While this system is very useful to the clinician in management of a small-volume radiologic event, it is time-consuming and may be impractical in a large- volume scenario.

Once patients have been triaged by biodosimetry assessment and presence of other injuries, they may be categorized into treatment groups according to general treatment guidelines on the basis of radiation exposure dose. These guidelines are intended to complement clinical judgment on the basis of signs and symptoms of the exposed individual. Treatment of the acute radiation syndrome is not indicated when exposure dose is very low (<1 Gy) or very high (>10 Gy). Supportive and comfort care is indicated for people with an exposure dose greater than 10 Gy because their prognosis is grave.

DIAGNOSIS

Time to emesis (TE) studies have suggested that time to emesis (TE) is one clinical parameter that can be used to indirectly determine dosage exposure. TE post radiation exposure seems to decrease as dosage increases. For TE less than 1 hour, the whole body dose is estimated to be greater than 4 Gy. For TE between 1 and 2 hours, whole-body dose is estimated to be greater than 3 Gy, and for TE greater than 4 hours, whole-body dose is estimated to be around 1 Gy.

The most useful laboratory test in the setting of acute radiation exposure is the serial complete blood count with differential obtained every 6-12 hours. Lymphocyte count serves as an indicator for prognosis and as an estimate for the dose of radiation. Blood can also be drawn for cytogenetic evaluation. If dicentrics (chromosomes with 2 centromeres) are found, they can be used to indicate extent of radiation exposure. Cytogenetic studies are time-consuming processes that are currently not being used for mass screening.

TREATMENT

No treatment can reverse the effects of radiation exposure. Treatment for radiation sickness is designed to help relieve the signs and symptoms. Doctors may use anti-nausea medicine and painkillers to relieve some symptoms, and use of antibiotics to fight secondary infection. Drugs

approved by the Food and Drug Administration for treatment of radiation contamination from an industrial accident or a 'dirty bomb' include:

- Radiogardase
- Pentetate calcium trisodium (Ca-DTPA)
- Pentetate zinc trisodium (Zn-DTPA)

These drugs are included in the national stockpile of products for use in the event of an emergency. Radiogardase, also known as Prussian Blue, may be used to treat people exposed to radiation containing harmful amounts of cesium-137 or thallium. Ca- DTPA and Zn-DTPA may be used for contamination with radioactive forms of plutonium, americium, and curium. All three drugs work to eliminate the radioactive substances from your body.

Another drug that may be helpful in cases of exposure to high doses of radiation is filgrastim (Neupogen), a drug currently used in people who've received chemotherapy or radiation therapy. The drug stimulates the growth of white blood cells and can help repair bone marrow damage. (13)

Medical Management of the Hematopoietic Syndrome

Treatment of radiologic victims with the hematopoietic syndrome varies with dose estimates, exposure scenarios, and presenting symptoms. Short-term therapy with cytokines is appropriate when the exposure dose is relatively low (<3 Gy). Prolonged therapy with cytokines, blood component transfusion, and even stem-cell transplantation may be appropriate when exposure dose is high (>7 Gy) or when traumatic injury or burns are also present. If there are many casualties, treatment must be prioritized. In cases of internal ingestion or contamination of unknown radioactive material, Some measures (e.g. lavage, charcoal) to decrease absorption may be effective and can be used if not contraindicated. Internal contamination by radioactive iodine can be treated with saturated solution of potassium iodide (SSKI), a blocking agent that reduces uptake of radionuclide in the thyroid. SSKI is most effective when taken within a few hours of exposure.

Chelating agents, such as penicillamine, bind specific radioactive metals causing decreased tissue uptake and increased secretion. Antibiotics should be tailored toward the source of infection. If absolute neutrophil count (ANC) is less than 500 cells/mm3, most experts recommend prophylactic antibiotics including a fluoroquinolone, an antiviral agent, and an antifungal agent.

The use of bone marrow transplant is controversial. Of the thirteen Chernobyl victims who received bone marrow transplants, only 2 survived, one of whom had autologous marrow repopulation. Thus only one survivor was thought to be saved by a bone marrow transplant. Administration of hematopoietic growth factors to stimulate bone marrow post irradiation also remains investigational.

Cytokine Therapy

Today, the only hematopoietic colony-stimulating factors (CSFs) that have marketing approval for the management of treatment-associated neutropenia are the recombinant forms of granulocyte macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and the pegylated form of G-CSF (pegylated G-CSF or pegfilgrastim). Currently, none of these cytokines have been approved by the U.S. Food and Drug Administration for the management of radiation- induced aplasia. The rationale for the use of CSFs in the radiation setting is derived from three sources: enhancement of neutrophil recovery in patients with cancer who are treated with CSFs, an apparently diminished period of neutropenia in a small

number of radiation accident victims receiving CSFs, and improved survival in irradiated canines and nonhuman primates treated with CSFs.

The value of CSFs in the treatment of radiation-induced myelosuppression of the bone marrow lies in their ability to increase the survival, amplification, and differentiation of granulocyte progenitors. Both GM-CSF and G-CSF activate or prime neutrophils to enhance their function, such as microbicidal activity. Both have been shown to hasten neutrophil recovery by approximately 3 to 6 days in humans after intensely myelotoxic therapies, including bone marrow and stem-cell transplantation. In fact, neutrophil recovery times are similar for both early and delayed treatment with G- CSF after transplantation. In the REAC/TS registry, 25 of 28 patients treated with G- CSF and GM-CSF after radiation accidents appeared to have faster neutrophil recovery. In most instances, these persons received both G-CSF and GM-CSF concurrently for significant periods. However, there was considerable variation in when CSFs were used (often weeks after the incident) and how they were used. Some of these patients also received interleukin-3. A significant survival advantage has been demonstrated in irradiated animals treated with CSFs in the first 24 hours. In any adult with a whole-body or significant partial-body exposure greater than 3 Gy, treatment with CSFs should be initiated as soon as biodosimetry results suggest that such an exposure has occurred or when clinical signs and symptoms indicate a level 3 or 4 degree of hematotoxicity. Doses of CSFs can be readjusted on the basis of other evidence, such as analysis for chromosome dicentrics. While there may be initial granulocytosis followed by significant neutropenia, CSF treatment should be continued throughout this entire period. The CSF may be withdrawn when the absolute neutrophil count reaches a level greater than 1.0 x 109 cells/L after recovery from the nadir. Reinstitution of CSF treatment may be required if the patient has a significant neutrophil decline (<0.500 x 109 cells/L) after discontinuation. Although the benefit of epoetin and darbepoetin has not been established in radiologic events, these agents should be considered for patients with anemia. Response time is prolonged (that is, 3 to 6 weeks), and iron supplementation may be required.

People at the extremes of age (children < 12 years and adults > 60 years) may be more susceptible to irradiation and have a lower LD50/60. Therefore, a lower threshold exposure dose (2 Gy) for initiation of CSF therapy is appropriate in such persons and in those who have major trauma injuries or burns. Individuals receiving an external radiation dose of at least 6 to 7 Gy from an incident involving more than 100 casualties due to detonation of an improvised nuclear device or small nuclear weapon will have a poor prognosis, particularly when additional injury is also present. Depending on the state of the health care infrastructure and availability of resources, it may be prudent to withhold CSF treatment from persons with significant burns or major trauma in a mass- casualty scenario. Since CSFs are a critical resource that must be given for long durations, particularly in people with multiple injuries such as trauma and burns, difficult triage decisions may mean that CSFs may be preferentially used for people without additional injury because they may have a higher chance of survival (exposure dose of 3 to 7 Gy in adults < 60 years of age and 2 to 7 Gy in children and in adults 60 years of age). The doses of CSFs recommended for use in radiologic incidents are based on the standard doses used in patients who have treatment-related neutropenia.

Transfusion

Transfusion of cellular components, such as packed red blood cells and platelets, is required for patients with severe bone marrow damage. Fortunately, this complication does not typically occur for 2 to 4 weeks after the exposure, thereby permitting time for rapid mobilization of blood donors. Blood component replacement therapy is also required for trauma resuscitation. All cellular products must be leukoreduced and irradiated to 25 Gy to prevent transfusion-associated graft-versus-host disease in the irradiated (and therefore immunosuppressed) patient. It may be difficult to distinguish transfusion-associated graft-versus-host disease from radiation-induced organ toxicity, which may include fever, pancytopenia, skin rash,

desquamation, severe diarrhea, and abnormalities on liver function tests (in particular, hyperbilirubinemia). Leukoreduction is known to lessen febrile nonhemolytic reactions and the immunosuppressive effects of blood transfusion. Moreover, leukoreduction helps protect against platelet alloimmunization and against acquiring cytomegalovirus infections. Ideally, life-saving blood products should be leukoreduced and irradiated.

Stem-Cell Transplantation

Matched related and unrelated allogeneic stem-cell transplantations are life-saving and potentially curative treatments in patients with certain predominantly hematologic malignant conditions. A small number of radiation accident victims have undergone allogeneic transplantation from a variety of donors in an attempt to overcome radiation- induced aplasia. The initial experience with this method in an irradiated patient dates back to 1958. Many reports demonstrate transient engraftment with partial chimerism, with nearly all patients experiencing autologous reconstitution of hematopoiesis. However, despite the transient engraftment, outcomes have been poor, largely because of the impact of burns, trauma, or other radiation-related organ toxicity. In fact, in a recent review of the allogeneic transplant experience in 29 patients who developed bone marrow failure from previous radiation accidents, all patients with burns died and only three of the twenty-nine lived beyond one year. It is unclear whether the transplants affected survival.

Similar results were observed in the 1999 radiation accident in Tokaimura, Japan, where two of the three victims were referred for allogenic transplantation. Both patients demonstrated transient evidence of donor-cell engraftment followed by complete autologous hematopoietic recovery before eventually dying of radiation injuries to another organ system or infection. Survival may have been longer than expected in these patients. If resources allow, transplantation should be considered in people with an exposure dose of 7 to 10 Gy who do not have significant burns or other major organ toxicity and who have an appropriate donor. Individuals with a granulocyte count exceeding 0.500 x 109 cells/L and a platelet count of more than 100 x 109 cells/L at 6 days after exposure appear to have evidence of residual hematopoiesis and may not be candidates for transplantation. In the unusual circumstance that a syngeneic donor may be available or previously harvested autologous marrow is available, a stem-cell infusion may be considered in patients with exposures exceeding 4 Gy.

Medical Management of Other Complications and Special Considerations The following treatment recommendations are defined by clinical and laboratory- based triage and observation of the clinical signs and symptoms associated with the acute radiation syndrome.

Supportive Care

Supportive care includes the administration of:

- antimicrobial agents
- antiemetic agents
- antidiarrheal agents
- fluids
- electrolytes
- analgesic agents
- topical burn creams

Experimental work performed more than two decades ago demonstrated the efficacy of supportive care, including the use of systemic antibiotics directed at gram- negative bacteria and transfusion with fresh, irradiated platelets. Careful attention must be given to early fluid resuscitation of patients with significant burns, hypovolemia, hypotension, and multiorgan

failure. Expectant care (treatment for comfort with psychosocial support) is recommended for patients who develop multiorgan failure within hours after exposure, as their radiation dose will have been high (>10 Gy). Resources permitting, routine critical care therapy should be provided to patients who develop multiorgan failure several days to weeks after exposure because their dose will have been in the moderate range. Therapy includes:

- endotracheal intubation
- administration of anticonvulsant agents
- judicious use of parenteral analgesic agents
- anxiolytic agents
- sedatives, as needed

Infections

Susceptibility to infection results from a breech in the integument or mucosal barriers, as well as immune suppression consequent to a decline in lymphohematopoietic elements. Several studies have indicated that administration of antibiotics reduces mortality rates in irradiated dogs in the LD50/30 range. Controlling infection during the critical neutropenic phase is a major limiting factor for successful outcome. In non- neutropenic patients, antibiotic therapy should be directed toward foci of infection and the most likely pathogens. Fluoroquinolones have been used extensively for prophylaxis in neutropenic patients. In patients who experience significant neutropenia (absolute neutrophil count < 0.500 x 109 cells/L), broad-spectrum prophylactic antimicrobial agents should be given during the potentially prolonged neutropenia period. Prophylaxis should include a fluoroquinolone with streptococcal coverage or a fluoroquinolone without streptococcal coverage plus penicillin (or a congener of penicillin), antiviral drugs (acyclovir or one of its congeners), and antifungal agents (fluconazole). Antimicrobial agents should be continued until they are clearly not effective (for example, the patient develops neutropenic fever) or until the neutrophil count has recovered (absolute neutrophil count 0.500 x 109 cells/L). Focal infections developing during the neutropenic period require a full course of antimicrobial therapy. In patients who experience fever while receiving a fluoroquinolone, the fluoroquinolone should be withdrawn and therapy should be directed at gram-negative bacteria (in particular, Pseudomonas aeruginosa), since infections of this type may become rapidly fatal.

Therapy for patients with neutropenia and fever should be guided by the recommendations of the Infectious Diseases Society of America. Use of additional antibiotics is based on treatment of concerning foci (that is, anaerobic cocci and bacilli that may occur in patients with abdominal trauma or infection with gram- positive bacteria such as staphylococcus and streptococcus species in addition to significant burns). Altering the anaerobic gut flora of irradiated animals may worsen outcomes. Therefore, we recommend that gut prophylaxis not be administered empirically unless clinically indicated (for example, in patients with an abdominal wound or clostridium difficile enterocolitis).

Comfort Measures

People with a high exposure dose whose outcome is grim must be identified for appropriate management. Since there is no chance for survival after irradiation with a dose of more than 10 to 12 Gy, it is appropriate for definitive care to be withheld from such individuals. Rather than being treated aggressively, these patients should be provided with comfort measures.

Special Considerations

In pregnant women, the risk to the fetus must be assessed. Persons who have been exposed to radioiodines should receive prophylaxis with potassium iodide. Children and adolescents are particularly prone to developing malignant thyroid disease.

TERATOGENIC EFFECTS

The Law of Bergonie and Tribondeau indicates that the radiosensitivity of tissue is directly proportional to its reproductive capacity and inversely proportional to the degree of differentiation. It follows that children could be expected to be more radiosensitive than adults, fetuses more radiosensitive than children, and embryos even more radiosensitive than fetuses. (11)

Most of the data involving teratogenic effects come from the atomic bomb survivors, which shows evidence of both small head size and mental retardation. The age at which the fetus was exposed was a critical factor in determining the type of effect and the risk.

PRECAUTIONS FOR HEALTHCARE WORKERS

Guidelines have been established for the use of personal protective equipment by health care providers. Providers should use strict isolation precautions, including donning of gown, mask, cap, double gloves, and shoe covers, when evaluating and treating contaminated patients. Outer gloves should be changed frequently to avoid cross- contamination. No health care workers who have adhered to these guidelines have become contaminated from handling a contaminated patient. Radiation detection devices can readily locate contaminants in the hospital facility to allow decontamination to take place. Protective gear should be removed after use and placed in a clearly labeled, sealed plastic container.

Medical management of patients exposed to intentional or accidental radiation is complex and demands many resources. The primary responsibility for optimizing outcome resides with hospital staff and physicians and other health care facilities. Careful documentation of clinical signs and symptoms and estimation of individual radiation dose are required for medical triage. While loss of life in a nuclear detonation may be enormous, the survival benefit afforded those who receive modern supportive care is significant. Effective care requires implementation of well-organized disaster plans. Disaster planning should include contingency planning for a scenario that involves loss of infrastructure.

Guidelines for Management of Pregnancy and Prevention of Thyroid Cancer

All hematopoietic cytokines and many antibiotics are class C drugs. However, any pregnant woman who has been exposed to more than 0.25 Gy of radiation should have an estimate of fetal dose determined. The fetus's dose is often lower than that of the mother, except in the settings of radioiodine exposure (because the fetal thyroid gland is more iodine-avid than the adult thyroid gland) and internal contamination of the maternal urinary bladder (where increased exposure may occur because of proximity of the fetus to radioactivity). Consultation with a health physicist and a maternal-fetal medicine specialist is advised to assess risk to the fetus. The most important factor for ensuring fetal survival is survival of the mother. Pregnant women should receive the same supportive care as that provided to nonpregnant adults. Antibiotic use in pregnant women will require a review of safety in pregnancy. Risks and benefits to the mother and fetus must be explained before therapy is administered.

In the fetus, child, and adolescent, the thyroid gland is a radiosensitive organ that is at risk for malignant transformation. Because the thyroid gland concentrates iodine with great efficiency, exposure to radioiodines results in localization of radioactivity in the thyroid gland. This concentration of radioactivity can result in thyroid cancer, a delayed consequence that may be more aggressive than de novo forms of thyroid cancer. The main route of radioiodine exposure is inhalation by those in the near field and ingestion of contaminated food and drink (particularly milk) for those farther away (in the far field). Thyroid blocking with potassium iodide offers some protection (reduction of radioiodine uptake by 50% when administered

within 4 hours of the exposure) by saturating the thyroid gland with nonradioactive iodine. However, potassium iodide is not a generic antiradiation drug. If radioiodines are not part of the exposure, potassium iodide is not recommended. For example, because of their short half-life of 8.5 days, it is extremely unlikely that radioiodines will be incorporated into a radiologic dispersal device or 'dirty bomb'. In this scenario, potassium iodide will be of no clinical benefit but its potential toxicity (including life-threatening anaphylaxis) will be risked. Therefore, it is recommended that treatment with potassium iodide be avoided in victims of a 'dirty bomb' explosion. Potassium iodide should be administered by mouth (tablets or Lugol solution) as soon as possible after the accident (six hours). Caution should be taken in victims who have a personal history of allergy to iodine because severe allergic reactions have been reported. Thyroid protection for pregnant women exposed to radioiodine is critical for the mother and fetus. In the first trimester with a near-field exposure, stable iodine will protect the mother. Pregnant women with far-field exposure may be able to avoid contaminated foods and milk. The fetal thyroid gland normally does not begin to function until approximately the 12th week of gestation. Thus, pregnant women in the second and third trimesters should receive potassium iodide in both near- and far-field exposures to protect the maternal and fetal thyroid glands.

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Course Exam

1. Radiation waves include gamma rays and X-rays.

   ○ True ○ False

2. People exposed to numerous X-rays and CT scans will become sick with acute radiation syndrome.

   ○ True ○ False

3. LD50/60 is the mean lethal dose required to kill 50% of humans at 60 days.

   ○ True ○ False

4. People exposed to radiation will get ARS only if the radiation dose was high, the radiation was penetrating, the person's entire body, or most of it, received the dose, and the radiation was received in a short time.

   ○ True ○ False

5. The latent period of ARS is when the patient has recovered.

   ○ True ○ False

6. The syndrome requiring the lowest dose of radiation is the hematopoietic syndrome.

   ○ True ○ False

7. The hematopoietic syndrome is referred to as reproductive death since the body does not show effect until the stem cells attempt division and are unable to do so.

   ○ True ○ False

8. Survival from the gastrointestinal syndrome occurs frequently.

   ○ True ○ False

9. The cerebrovascular syndrome is referred to as a physiological death because the symptoms and ultimate death appear quickly, usually within 2 days.

   ○ True ○ False

10. If the patient survives the manifest illness stage in the gastrointestinal syndrome, recovery is almost assured.

    ○ True ○ False

11. Individual radiation dose is assessed by determining the time to onset and severity of nausea and vomiting.

    ○ True ○ False

12. Lymphocytopenia is a late sign of acute radiation syndrome, and results in poor prognosis.

    ○ True ○ False

13. The manifest illness of the gastrointestinal syndrome include, vomiting, severe diarrhea and high fever.

    ○ True ○ False

14. Individuals presenting with fever, hypotension, and major cognitive impairment will most likely survive.

    ○ True ○ False

15. The late effects of the cutaneous syndrome may occur months to years after exposure.

    ○ True ○ False

16. Survival from the hematopoietic syndrome is rare.

    ○ True ○ False

17. Management of life-threatening injuries takes precedence over radiologic surveys and decontamination.

    ○ True ○ False

18. Healthcare workers are at risk for post-traumatic stress disorder during mass casualty situations.

    ○ True ○ False

19. Individuals requiring surgical intervention should undergo surgery within 36 hours after exposure.

    ○ True ○ False

20. Children and adolescents are particularly prone to developing malignant thyroid disease.

    ○ True ○ False

21. Gloves are all that is needed when evaluating and treating contaminated patients.

    ○ True ○ False

22. The most important factor for ensuring fetal survival is survival of the mother.

    ○ True ○ False

23. Certain foods such as bananas and Brazil nuts contain radiation.

    ○ True ○ False

24. The appearance of symptoms of acute radiation syndrome, such as, nausea and vomiting, can also be induced psychologically.

    ○ True ○ False

25. The higher the dose of radiation, the longer the latent phase.

    ○ True ○ False

26. Radiation particles can lodge in your lungs and remain there for extended periods of time, leading to continual radiation exposure.

    ○ True ○ False

27. The lens of the eye is highly susceptible to irreversible damage by radiation.

    ○ True ○ False

28. Radiation induced cataracts differ from naturally occurring cataracts.

    ○ True ○ False

29. Treatment of conventional injuries and illness should be done after decontamination of radiation.

    ○ True ○ False

30. The hematopoietic syndrome is the result of RBC's, WBC's, and platelets being killed by radiation.

    ○ True ○ False

31. Leukemia occurs more frequently in patients exposed to radiation.

    ○ True ○ False

32. With treatment the effects of radiation can be reversed.

    ○ True ○ False

33. A dirty bomb uses conventional explosives to spread radioactive material.

    ○ True ○ False

34. The stem cells are the most radiosensitive cells in the body.

    ○ True ○ False

35. The law of Bergonie and Tribondeau indicates that the radiosensitivity of tissue is directly proportional to its reproductive capacity and inversely proportional to the degree of differentiation.

    ○ True ○ False

36. The use of bone marrow transplant is controversial.

    ○ True ○ False

37. Most patients involved in a radioactive accident suffer from the combined injury syndrome.

    ○ True ○ False

38. Radiation induces loss of intestinal crypts and breakdown of the mucosal barrier.

    ○ True ○ False

39. Papilledema, ataxia, and reduced or absent deep tendon reflexes and corneal reflexes characterize the hematopoietic syndrome.

    ○ True ○ False

40. There is no unique disease associated with chronic radiation syndrome.

    ○ True ○ False