

Medical Mitigation Strategies for Acute Radiation Exposure During Spaceflight

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The United States Government has recently refocused their space program on manned missions to the Moon by 2018 and later to Mars. While there are many potential risks associated with exploration-class missions, one of the most serious and unpredictable is the effect of acute space radiation exposure, and the space program must make every reasonable effort to mitigate this risk. The two cosmic sources of radiation that could impact a mission outside the Earth's magnetic field are solar particle events (SPE) and galactic cosmic radiation (GCR). Either can cause acute and chronic medical illness. Numerous researchers are currently examining the ability of GCR exposure to induce the development of genetic changes that lead to malignancies and other delayed effects. However, relatively little has been published on the medical management of an acute SPE event and the potential impact on the mission and crew. This review paper will provide the readers with medical management options for an acute radiation event based on recommendations from the Department of Homeland Security (DHS), Centers for Disease Control (CDC), and evidence-based critical analysis of the scientific literature. It is the goal of this paper to stimulate debate regarding the definition of safety parameters for exploration-class missions to determine the level of medical care necessary to provide for the crew that will undertake such missions.

Keywords: space medicine, radiation sickness, acute radiation syndrome.

SINCE YURI GAGARIN first left Earth's surface to the most recent space station experiences, the hazards of working and living in space have become more familiar. The Apollo program ended 30 yr ago and marked the last time a human has left the partial protection of the Earth's magnetic field. Recently, a new goal has been provided to the American space program—to once again leave low-Earth orbit and travel safely to the Moon and then ultimately to Mars. Long-duration exploration-class missions promise to bring a wealth of knowledge and experience, but technological and biophysical hurdles must be overcome before such missions can be safely accomplished.

One of the most important questions that must be answered for these 6-mo to 3-yr long-duration missions is the medical effects of space radiation on crewmembers. Much work has been done examining the chronic and cumulative effects of space radiation (22,72,80,87,88,103). However, relatively little has been done in the way of understanding and defining the necessary medical treatment capabilities that would be required to treat an acute radiation exposure on an extended mission where there is no possibility of aborting the mission and quickly returning to Earth. An evacuation from the International Space

Station (ISS) or perhaps even the Moon to Earth can be done in a timely fashion if the patient is stable. Mars missions present a different medical paradigm, where the ability to quickly return to Earth is impossible. Those aboard the spacecraft must have all the necessary tools with them to limit and medically manage an acute radiation exposure.

The National Research Council, NASA, and other agencies have determined that the study, management, and design of mitigation strategies to prevent radiation-induced damage are critical roadmap questions that must be answered before interplanetary missions can be initiated (19). It is the intent of this paper to describe the clinical manifestations of an acute radiation event during an exploration-class mission and to determine the necessary medical resources required to treat such an event so as to provide an adequate standard of care to exposed crewmembers.

Space Radiation

Radiation has two effects on tissue: excitation and ionization. Excitation occurs when an electron is elevated to a higher energy state but remains within the atom, while ionization results in the release of at least one electron from that atom. Ionizing radiation can be divided into either electromagnetic radiation or particulate radiation (77). Photons are of zero rest mass and travel at the speed of light. Photons energetic enough to ionize biological tissue are ultraviolet rays, X-rays, and gamma rays. In interplanetary space the primary radiation comprises protons, alpha particles, and heavier nuclei called cosmic rays. Neutrons are usually produced through secondary particle interactions in spacecraft materials while electrons are of significance only in the Earth's radiation belts. Galactic cosmic rays (GCR) strike continuously and isotropically and are modulated by the 11-yr solar cycle with minimum intensity around solar maximum (5).

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Two types of solar events result in large increases in radiation flux, known as solar particle events (SPE). Solar cosmic rays or solar particles arise from sporadic acceleration processes at the sun (solar flares) or in shock waves (coronal mass ejections) in the solar wind (the stream of ionized gas or plasma that flows continuously from the sun). These two types of solar eruption produce energetic particles which are orders of magnitude higher in abundance than the background GCR. The greatest number of events tends to be mainly around solar maximum, but they can occur at any time. The particles travel at a significant fraction of the speed of light and arrive about 8 min after the photons, which signal the magnitude of their acceleration. However, the bulk of the particles undergo a scattering process and the increases are typically spread over a day or two. Events vary greatly in intensity, but increases of 3 to 5 orders of magnitude can occur, so acute lethal effects may be produced in a matter of hours. Fortunately there have only been a few events this severe. The Earth's magnetic field can shield astronauts from solar particles in low Earth orbit apart from the time spent at high latitudes. The much weaker fields of the Moon and Mars are ineffective shields and the exposure is immediate, unlike Earth, where the orbital path must take the vehicle close to the magnetic poles or South Atlantic Anomaly.

Radiation dose measurements use the standard unit Gray (Gy), which is defined as a joule of energy absorbed as ionization and excitation per kg of tissue. A Sievert (Sv) is the absolute dose of radiation in Gy, modified by the relative biological effectiveness (RBE) of a particular form of radiation. For example, for gamma rays, 1.0 Gy = 1.0 Sv; while for a more densely ionizing radiation source that has more biological effect such as a neutron of a particular energy level, 0.1 Gy = 1.0 Sv. To normalize these values, quality factors have been determined for different types of radiation and, in the example above, a quality of 10 would apply for that neutron vs. a quality factor of 1 for gamma rays (47). However, considerable work remains in defining the RBE of different high-energy particles, including those emitted by the Sun during an SPE, and their associated quality factors.

The largest SPE on record for lower energies occurred in August 1972 and has been the subject of significant analysis. Fortunately, this event occurred between Apollo missions and resulted in no casualties. Recent analysis has found the dose rate during this event was significantly higher than previously reported and exceeded the low-dose-rate criteria of both the National Council on Radiation Protection and the United Nations Scientific Committee on the Effects of Atomic Radiation (71). The bone marrow dose that would have been accumulated on the Moon was 0.8 Gy and was well within the range of doses that could cause a serious hazard. Spacesuits (1–5 g · cm⁻² aluminum shielding) would not have mitigated the tissue-damaging effects of this SPE, which might have resulted in significant hematological consequences (i.e., depressed white blood cell count and possible pancytopenia) (71). If the intensity of the 1972 flare had been combined with the

hard spectrum of the February 1956 event, calculations show that a lethal dose would have been absorbed within about 20 h, even with shielding of 16 g · cm⁻² of aluminum (the Space Shuttle provides a maximum of 2 g · cm⁻² of aluminum) (19). While these cases have been called "worse-case scenarios," solar flares have only been measured for a few decades and, therefore, the potential exists for even greater exposure. The uncertainty of these potentially lethal events is of serious concern to the space medical community.

GCR originates outside our solar system, and is predominantly high-energy protons, alpha particles, and heavy nuclei, particularly iron. Of the radiation fluence encountered by astronauts during a trip to Mars, 80–90% will come from protons. However, GCR radiation is not thought to produce acute injury, but rather exerts its effects chronically. While shielding can be quite effective against other forms of radiation, high-energy GCR can pass through conventional thickness shielding. Additionally, when GCR ions collide with shielding material, a release of secondary particles and radiation occurs and could potentially be more dangerous than the original particle (93).

Radiation can exert its damaging effects through multiple mechanisms. It causes the breaking of double-stranded DNA and proliferating cells such as those in the immune system; bone marrow and less differentiated cells that line the gastrointestinal tract are particularly radiosensitive due to their high turnover. Chromosome alterations in lymphocytes can be seen through multiple techniques and can, in fact, be used to estimate the dose (Sv) that has been absorbed for long-duration missions (23,30,35–37). Radiation can also interact with H₂O, resulting in the production of free oxygen radicals. Free radicals can readily interact with DNA and other molecules, causing cell damage and death.

Mitigation Strategies for an Acute Radiation Exposure in Space

Primary and Secondary Prevention

Primary prevention could include the selection of astronauts who are inherently more resistant to the effects of space radiation. We do not currently have that capability, and will likely not possess the ability in time for the proposed Moon or Mars missions. There is a theoretical advantage to selecting astronauts who have lower cumulative career radiation exposure levels to keep the probability of radiation-induced disease low or at least comparable to other hazards. Unfortunately, with large acute exposures, these strategies are likely to have little mitigating effect.

Secondary prevention relies on minimizing radiation damage given the fact that crewmembers will be exposed. This can be accomplished using various strategies that include more effective shielding, an early warning system that can direct the crewmembers into a heavily shielded safe-haven module, using propulsion systems that can minimize the travel time during the interplanetary portion of the mission, and the administration of radioprotective compounds. The beginnings

TABLE I. SYMPTOMS OF ACUTE RADIATION EXPOSURE.

Dose (Sv)	Symptoms	Outcome	Syndrome
0–0.25	None	—	—
0.25–1	Mild nausea and loss of appetite	Bone marrow damage, lymph node and spleen damaged	Bone Marrow
1–3	Mild to severe nausea, loss of appetite, infection	Same as above, recovery probable	Bone Marrow
3–6	Severe nausea and diarrhea, hemorrhaging, skin peels	Death occurs with doses greater than 3.5 Sv untreated	Gastrointestinal
6–10	Above symptoms, seizures	Death	CV/CNS
Above 10	Incapacitation	Death	CV/CNS

Sv = Sievert; CV = cardiovascular; CNS = central nervous system.

of an advanced early-warning satellite system are currently on orbit, monitoring solar activity and ejected energetic particles (28,64–66). Further work is required to more effectively detect and monitor SPEs.

It is also possible to medically prevent some symptoms of radiation-induced damage. Amifostine is a sulfhydryl-containing compound that protects tissues against ionizing radiation damage by scavenging radiation-induced free radicals (29). Several randomized trials involving radiation exposure have shown significantly reduced damage to oral, esophageal, and rectal mucosa, reduced bladder toxicity, and decreased incidence of neutropenic fever and post-irradiation pneumonitis in patients receiving subcutaneous amifostine (2,4,7,52–54). The DHS recommends amifostine to first-line medical responders before arrival at a radiological emergency (25). The potential advantage of this drug is that it only needs to be administered minutes before exposure, which makes it useful for mitigating radiation damage. Further work is required to determine whether amifostine can improve morbidity and reduce mortality from large radiation doses (55).

Tertiary Prevention: Medical Management of an Acute Radiation Exposure

Despite the best engineering efforts, crewmembers aboard current space vehicles are still at risk of serious medical complications from an acute radiation event. Mission planners and engineers, medical scientists, and physicians must perform trade studies to determine which equipment and medications are absolutely necessary to be taken on a long-duration mission to minimize vehicle mass, power, volume restraints, and maximize treatment capabilities.

When examining human data regarding radiation exposure, patients can usually be divided into two cohorts. The first cohort is defined by patients who are ill and are receiving therapeutic radiation for a serious underlying medical condition. The other cohort is defined by those individuals who were previously healthy and have received an accidental industrial or military exposure (nuclear detonation or spill), which often requires radioactive decontamination. Exposure of astronauts in space has aspects in common with both of these populations, with healthy individuals being irradiated by a noncontaminating source.

Acute radiation syndrome (ARS) is caused by irradiation of the whole body (or a significant portion of it),

resulting in a spectrum of syndromes that have been used for prognosticating outcomes. These syndromes should not be considered as distinct entities, but rather as a continuum based on the organ system affected, which is in turn based on the radiation dose absorbed. There are three classic syndromes as defined by the Centers for Disease Control (CDC) (14) (Table I): bone marrow syndrome; gastrointestinal syndrome; and cardiovascular/central nervous system syndrome. Each syndrome is comprised of four distinct stages: prodromal period; latent period; manifest illness period; and a period of either recovery or death. The first data about these stages were originally derived from Japanese survivors of the atomic bomb and the people living on the Marshall Islands exposed to radioactive fall-out in 1954, and subsequently applied to those affected by the Chernobyl nuclear accident.

Initial Assessment and Management

In the acute management of radiation injury in space there are two critical aspects of treatment. The first is to provide acute physiological support and the second is to accurately determine the level of exposure so that future complications can be anticipated. The DHS has developed guidelines for the treatment of mass Earth-based casualties following an acute radiation exposure and some of these recommendations have been adapted for a potential exposure during spaceflight (25).

One important acute management challenge is how to prevent or reverse hypovolemia secondary to fluid loss due to emesis and diarrhea, symptoms common to all syndromes. If there is evidence of clinical dehydration, intravenous fluid containing normal saline should be administered to replace the fluid deficit (60). Oral rehydration therapy has been shown to significantly reduce mortality worldwide from diarrheal diseases by allowing fluids and other molecules through the part of the gastrointestinal tract (GI) tract that is functional (85). However, with extensive emesis or GI injury secondary to radiation, this may not be effective, at which point intravenous fluid will be the only means of rehydrating the patient. If diarrhea does not resolve and is refractory to fluid replacement, drug therapy should be considered. Clinical trials have demonstrated the effectiveness of octreotide acetate (a long-acting somatostatin analogue) over diphenoxylate hydrochloride plus atropine sulfate and loperamide, drugs commonly used as therapies for acute radiation-induced diarrhea (12,34,104).

Several studies, including multicenter, randomized double-blind trials have examined the efficacy of antiemetics in the treatment of radiation-induced emesis. In the prevention of emesis, 5-hydroxytryptamine 3-receptor receptor antagonists were shown to be superior to placebo, prochlorperazine, and metoclopramide (31,73,74,89). There appears to be little difference between individual drugs of the 5-hydroxytryptamine 3-receptor class in terms of efficacy and tolerability, although the best studied is ondansetron, and it is, therefore, recommended for use (57). Once emesis has been suppressed sufficiently, oral rehydration therapy can be employed. Intravenous and intraosseous access should be considered for extreme cases of prolonged emesis, but balanced against the adverse effects of these modalities in a thrombocytopenic and/or neutropenic patient.

Some signs of hypotension will be masked in weightlessness, making the determination of volume status more difficult. Accurate recording of intake/output volumes are important for an objective and quantitative measure of volume status. Other objective findings are BP and heart rate, with decreases and increases expected, respectively, with moderate and severe hypovolemia (moderate: 10–20 mmHg drop in systolic pressure; severe: > 20 mmHg). Mucous membranes may be good initial indicators of volume status, but with radiation-induced mucous membrane changes, their utility may be questionable. A depressed level of consciousness will be seen in severe hypovolemia and requires immediate volume resuscitation. On Earth, the jugular venous pressure represents a column of blood in the vena cava that is dependent on the pressure in the right atrium. During spaceflight, 1–2 L of fluid shifts from the legs to the head within the first 24 h, resulting in jugular venous distention for all crewmembers; together with a paradoxical decrease in central venous pressure, the bedside determination of jugular venous pressure in weightlessness is not currently feasible (10,91). If the patient is hypotensive following a radiation exposure, it will be challenging to determine whether the shock is hypovolemic, cardiogenic, or distributive. Cardiogenic shock can occur after a large radiation exposure and distributive shock can occur during infection/sepsis. Therefore, cardiac echocardiography should be considered to help determine volume status and cardiac function (6). Such volume distinctions can be challenging even in the setting of a terrestrial critical care unit. The use of ultrasound to determine cardiac function combined with careful clinical examination and calculation of absorbed dose will be critical in this determination (41,61).

The number of diagnostic tests aboard the future Mars transport vehicle is likely to be limited. One critical piece of equipment that should be included is a microelectronic cell counter or microscope equivalent, to provide a complete blood count (CBC) with a radiation-specific differential. Lymphocyte populations decline almost immediately after radiation exposure (39,40). Lymphocyte population kinetics follow a simple exponential decay immediately after an effective whole-body exposure and have been used to estimate acute doses (40). A single post-exposure CBC after 8 to

TABLE II. ESTIMATES OF DOSE VERSUS LYMPHOCYTE COUNT 8–12 H POST-EXPOSURE

Dose (Gy)	Lymphocyte count ($\times 10^9$ cells \cdot L $^{-1}$)
< 1	> 2.5
1–5	1.7–2.5
5–9	1.2–1.7
> 10	< 1.0

Gy = Gray; standard unit.

12 h can be used to determine acute exposure as documented by the DHS (Table II) (25).

These studies are not immediately applicable to exposure to heavy nuclei from an SPE, since the dose vs. lymphocyte number curves were calculated using gamma rays and appropriate determination of the RBE of an SPE must first be established in order to better estimate Gray-equivalent dose (71). Since an SPE typically contains high-energy particles, the equivalent biological dose (Sv) will likely be higher than with gamma rays. Given that baseline lymphocyte counts will be known for the crew, a rapid CBC is a critical tool in determining the dose and prognosticating treatment decisions. The DHS advises that rapid clinical assessment by taking careful note of the initiation of symptoms can also be used to estimate dose. For example, 50% of people who present with nausea and emesis will be in the following range of absorbed dose exposure to photons: less than 1 h post-exposure, 6.5 Gy; less than 4 h, 3.6 Gy; greater than 4 h, 0.9 Gy (25).

Bone marrow (BM) syndrome: BM syndrome is thought to occur between doses of 0.7 and 10 Gy, although mild symptoms can occur with as low as 0.3 Gy. These doses are based on X-rays or gamma rays, and equivalent Gy absorbed doses of proton radiation from an SPE are likely to produce a greater biological effect (47,88). The survival rate of patients with this syndrome decreases with increasing dose. Since bone marrow is responsible for the production of all immunological cells (T and B lymphocytes, macrophages, neutrophils, mast cells, eosinophils, and basophils) as well as red blood cells and platelets, deficiencies in these lines result in profound immunosuppression and susceptibility to infection by a wide range of organisms, anemia, and an inability to clot (25). As a consequence, the primary cause of death in this population is due to infection and hemorrhage. Therefore, any medications that can interfere with platelet function, such as acetylsalicylic acid, are contraindicated. Within the first few minutes to a few days, patients will likely develop nonspecific symptoms such as mild-to-moderate nausea, emesis, diarrhea, and edema of the mouth and throat. The patients will often recover from the initial symptoms and a subsequent latent phase begins, lasting from 1 to 6 wk.

Stem cell transplant: Once the biological dose has been estimated and a CBC performed to confirm the dose, the decision of whether to perform an autologous stem cell transplant to restore the blood cell pools must be made within the first few days of exposure. Autologous stem cell transplant is recommended by the DHS after a sufficiently large radiation exposure (25). Stem cell

transplants in hematological malignancies occur after bone marrow destruction by either chemical or radiological means, and are typically done within a day of bone marrow irradiation to minimize the period of vulnerability (24,46).

Preflight mobilization of stem cells can be done after administration of granulocyte-colony stimulating factor (G-CSF), permitting apheresis of CD34⁺ stem cells in the peripheral blood. Cryopreservation allows for the long-term storage of hematopoietic stem cells in 30–70-ml aliquots (5% DMSO in combination with 6% hydroxyethylstarch) at -80°C (33,79). It has been reported that stem cells have been used successfully 11 yr after freezing; 97% of patients receiving stem cells with an average storage time of 2.7 yr achieved a granulocyte count of $> 0.5 \times 10^9$ cells \cdot L⁻¹ at a median of 19 d, indicating that the cells would be stable during current mission designs, although this period is longer than the typical 10- to 12-d recovery (1,3). Based on the literature, at least 1×10^7 CD34⁺ would be required for the autologous transplant (78,82). Additionally, while further experimentation is required, current data indicate frozen cells are protected from the effects of radiation and, therefore, would be expected to survive an acute radiation effect (102). Cardiovascular or central nervous system involvement would indicate that the dose received was fatal, and a stem cell transplant would not be indicated.

Optimal engraftment protocols with autologous stem cell transplants are well known. Randomized controlled trials have shown that using G-CSF in patients with autologous bone marrow transplantation reduced the neutropenic days from 27 to 12 d, febrile neutropenia from 10 to 6 d, antibiotic requirements, number of confirmed infections, and duration of hospital stays when compared with placebo alone, demonstrating its relevance to exploration-class missions (21,83,95). Administering G-CSF alone at a dose of $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, initiated in the first 7 d post-irradiation and terminated the day after neutrophil counts are greater than $0.5 \times 10^9 \cdot \text{L}^{-1}$, is the recommended engraftment protocol for spaceflight (9,15,48,92,99,100).

Gastrointestinal (GI) syndrome: GI syndrome will usually occur with a dose between 10 and 100 Gy, though some symptoms may occur at as low as 6 Gy (14). Acute injury is caused by irradiation of mitotically active intestinal crypt cells, impairing the normal cycle of growth and repopulation of GI surface epithelium that occurs every 5 to 6 d. The loss of absorptive surface leads to malabsorptive diarrhea. Depending on the degree of disruption to the mucosal barrier by injury to the surface cells, micro-ulcerations can coalesce to form large lesions. Intracellular tight junctions are disrupted, permitting the passage of bacteria and microbial products into the plasma, potentially resulting in septic shock.

As the absorbed radiation dose increases, patients who already have BM syndrome begin to see involvement of the GI tract. Fever, severe dehydration, almost immediate and intractable nausea, emesis, and bloody diarrhea, followed by a short (< 1 wk) latent period are symptoms that help differentiate GI from BM syn-

drome. These symptoms can be treated, as described above, with octreotide, ondansetron, aggressive fluid replenishment, and acetaminophen. Patients with oral mucositis often have significant pain, requiring the use of morphine for pain control (69). A pain control regimen should begin with the use of acetaminophen, followed by the use of incremental acetaminophen/codeine. Following that, hypodermoclysis morphine may be required.

With increasing time spent in a leukopenic state and with deterioration of the GI mucosa, the likelihood of perforation and severe infection increases dramatically. Infection can lead to secondary peritonitis, an intra-abdominal abscess, and/or a sepsis syndrome. Typically infection is polymicrobial and the pathogens are endogenous. Some early symptoms include abdominal pain, nausea, emesis, fever, and rebound tenderness. When peritonitis becomes localized, an abscess can form, and can present with localized tenderness. The standard of care for intra-abdominal infection is definitive surgical management, including drainage of abscesses, debridement of infected or nonviable tissues, and source management (59,97). Initial ground-based studies in simulated hypogravity have shown promising results using both ultrasound-guided peritoneal drainage and endoscopic surgery, indicating a possible future role for these techniques on exploration-class missions (11,50).

Melena/hematochezia would likely be seen in GI syndrome as a result of GI damage and bleeding along the length of the GI tract (14,25). GI bleeding post-irradiation was observed in the Chernobyl accident, and has been seen after pelvic irradiation (26,32,58). Even with a successful autologous stem cell transplant, there may be a period of time when the damage to the GI tract and thrombocytopenia may combine to produce an uncontrollable GI hemorrhage. An exploration-class spacecraft is likely going to be severely limited in its ability to transport blood products and the only treatment option may be fluid replacement. Endoscopic exploration and injection with adrenaline followed by thermal coagulation is the standard of care for identifiable GI hemorrhage, and may be a technique that can be applied to the space environment (17). Experimental treatments, such as with basic fibroblast growth factor, have been shown to induce GI mucosal regrowth and improvement in mortality in animal models of radiation-induced GI mortality (70). Nonetheless, if the patient survives the initial damage from the GI syndrome, profound bone marrow suppression is still a danger. Survival is possible with aggressive treatment, but unlikely with this syndrome, with death usually occurring within 2 wk (14). Perhaps an initial palliative approach is required for patients presenting with severe GI syndrome.

Electrolyte disturbances, which are likely to be present in GI syndrome, could manifest in several ways, including seizures, arrhythmias, and musculoskeletal problems secondary to changes in sodium, potassium, and calcium levels (38). We currently have the ability to measure simple ions such as sodium and potassium on board the ISS, and it is anticipated that a

more complete metabolic analysis will be possible for future missions. In GI syndrome, dehydration and cell damage result in changes in plasma volume and temporal fluxes in ions such as sodium and potassium, indicating the need for monitoring and management (13,63). Serial electrolyte measurements will guide treatment.

Cardiovascular (CV)/central nervous system (CNS) syndrome: The full syndrome will usually occur with a dose greater than 50 Gy, though some symptoms may occur at as low as 20 Gy (14). With this fatal syndrome, you see the same initial prodromal symptoms as with the BM and GI syndromes. The latent phase has a typical duration in the range of hours and the manifest illness stage is comprised by numerous and ultimately lethal complications. Additional symptoms include nervousness, a burning sensation of the skin, profuse watery diarrhea, a labile BP, cerebral edema, seizures, and coma (44). CV/CNS syndrome is rapidly fatal and is a consequence of high doses of radiation to neurological and muscle cells that are relatively radioresistant. Vasculitis, pericarditis, and meningitis can also occur during this phase. Death within 2 to 7 d is likely due to collapse of the circulatory system as well as increased pressure in the cranial vault secondary to edema (25).

The dose required to achieve rapid CV or CNS involvement indicates a fatal dose. Given that situation, any curative intentions would be futile and may in fact cause discomfort to an expectant patient (49). The patient should be made as comfortable as possible with sedatives and adequate pain control. Palliation is the appropriate medical therapy.

Infection Control

After an acute radiation exposure that damages the bone marrow and GI tract, infective complications are high. Anti-infective treatment can be initiated in a prophylactic manner or during a febrile event. Both possibilities will be discussed.

Anti-infective prophylaxis: The CDC, Infectious Disease Society of America, and American Society of Blood and Marrow Transplantation have thoroughly examined the role of preventing opportunistic infections after stem cell transplants using an evidence-based approach (46). Due to the need for immunosuppression and the potential for graft-vs.-host disease, anti-infectious (antibiotic, antiviral, and antifungal) prophylaxis is required to a much greater degree in allogeneic compared with autologous transplants. As a result only autologous transplants are recommended for exploration-class missions.

The microbiological environment of space vehicles has been studied on orbit. Of the 1150 samples gathered over several years from the Mir space station to study the microbiological flora, 82.5% had microorganisms. A total of 108 species of bacteria and 126 species of fungi were identified (68). Potential pathogens for neutropenic patients included *Staphylococcal* species (55.2% surface samples; 53.2% air samples), *Streptococcal* sp. (5.0% surface, 2.1 air samples), *P. aeruginosa* (1.4% surface; 4.3% air; 20% condensate), *E. coli* (0.2% surface,

1.1% air), *Aspergillus* sp. (39.4% surface; 76.6% air) and *Candida* sp. (3.8% surface; 4.0% of air) (68).

Most post-transplant guidelines do not suggest the routine use of antibacterial prophylaxis in afebrile, asymptomatic patients. Despite these recommendations, a study describing the prescribing practices of American institutions indicated that 60% used bacterial prophylaxis (fluoroquinolone) secondary to fears of potential Gram-negative sepsis (94). However, prophylaxis may be indicated if profound neutropenia is suspected and, therefore, prophylaxis would be indicated during the neutropenic period with an extended spectrum fluoroquinolone (with gram positive activity) (45). Trimethoprim-sulfamethoxazole is recommended for *Pneumocystis carinii* prophylaxis (46,96).

Prophylaxis against fungal species is also recommended. Current guidelines suggest the use of fluconazole at a dose of 400 mg · d⁻¹ for autograft recipients with a potential for prolonged neutropenia or neutropenia complicated by GI damage, and should be discontinued once the absolute neutrophil count exceeds 0.5 × 10⁹ · L⁻¹ (94). Fluconazole, while an acceptable alternative to amphotericin B in the treatment of *Candida* infections, is not recommended for *Aspergillus* species (45). Both *Candida* and *Aspergillus* have been found in spacecraft and may pose a serious threat to crewmembers with suppressed immune systems (68,84).

In a large multicenter trial, voriconazole was compared with liposomal amphotericin B, and was shown to be a suitable alternative to amphotericin B preparations for empirical antifungal therapy in patients with neutropenia and persistent fever with fewer side effects (infusion-related reactions and nephrotoxicity), and has also been shown to be a superior treatment for diagnosed *Aspergillus* infection (42,101). Given the high likelihood of *Aspergillus* infection, the use of voriconazole would be recommended to protect against both *Candida* and *Aspergillus* infection.

Prophylactic treatment of cytomegalovirus was not recommended for autologous donors, even if the patient was previously infected with cytomegalovirus (46). To date randomized control trials have not demonstrated that the use of prophylactic acyclovir can prevent herpes simplex virus reactivation; however, acyclovir is still routinely prescribed for 30 d post-transplant to prevent reactivation in herpes simplex virus seropositive patients (46). To avoid the potential of varicella-zoster virus (VZV) spread to immunosuppressed crewmembers, it is recommended that all non-immune crewmembers be vaccinated for VZV before leaving Earth (46). Antivirals for treatment for VZV should only be initiated with the outbreak of symptoms (45). With the recent introduction of a VZV vaccine in early childhood, it is possible that when crew selection occurs for a Mars mission, there may be a choice between astronauts who have natural immunity to VZV and those that have never been infected, although are immunized. In this situation, with all other parameters being equal, it may be of benefit to select crews who have never been exposed, and, therefore, are at no risk for reactivation.

Neutropenic fever: A febrile episode during a state of

profound immunosuppression leaves the patient vulnerable to a wide range of pathogens. As a result, no single empiric therapeutic regimen can be recommended for neutropenic fever, despite the large number of studies performed on antibiotic choices (45). The large number of potential pathogens responsible for neutropenic fever (*Staphylococcal* sp., *P. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *S. pyogenes*, *Enterococci*, *Aspergillus*, and *Candida* being the most common) and different antibiotic resistance patterns seen worldwide make the use of only a single-line antibiotic therapy impossible. Antibiotic sensitivities at the time of the mission and in the community in which the crewmembers reside are important factors in determining appropriate antibiotic selection criteria. Initial assessment of a neutropenic fever of unknown origin should classify the patient as low risk or high risk. Low-risk patients are those that have no focus of infection, no hypotension, recovering neutrophil counts, no co-morbid conditions, and absolute neutrophil and monocyte counts $> 0.1 \times 10^9 \cdot L^{-1}$. These patients should receive oral ciprofloxacin plus amoxicillin-clavulanate for broad-spectrum gram-positive, Gram-negative, and anaerobic coverage (45). If the patient does not meet the requirement of low risk, there are many treatment regimens that are available. The first choice is selection between either intravenous monotherapy or combination therapy. Cefepime, piperacillin/tazobactam, and meropenem have been shown to be equivalent in the treatment of neutropenic fevers as monotherapy, and the addition of either amikacin or vancomycin has not resulted in improved efficacy of empiric treatment (8,16,18,20,27,43,45,67,76,81). Additionally, employing cefepime instead of piperacillin/tazobactam is appropriate; although they are equivalent in efficacy in the treatment of neutropenic fever, cefepime may be more effective at treating Gram-negative infections and piperacillin/tazobactam may be better at gram-positive infections (45). Given that currently, 60–70% of infections are due to gram-positive organisms, piperacillin/tazobactam should be the first choice for intravenous empiric treatment (8,45).

If the high-risk case is complicated by some other factor (extensive bleeding, focal site of infection), two-drug intravenous coverage is suggested, using an aminoglycoside (gentamicin, tobramycin, or amikacin) with an ureidopenicillin such as piperacillin/tazobactam. The advantages of two-drug combinations include a decrease in antibiotic resistance and synergy against some resistant Gram-negative bacilli (51,86). However, the use of aminoglycosides during an exploration-class mission has potential complications. For example, aminoglycosides may be nephrotoxic, and patients presenting with ARS may also have concomitant renal failure (pre-renal secondary to hypovolemia or renal damage from direct irradiation) (56). Additionally, for optimal dosage to prevent renal toxicity, serum levels are usually determined—a capability that may not be present in a space vehicle.

Infections with GI syndrome: The risk of perforation from GI damage is an expected complication of this syndrome. Antibiotic coverage for Gram-negative bacilli,

Gram-negative aerobes, gram-positive cocci, and anaerobes (especially *E. coli* and *Bacteroides fragilis*) are particularly important aspects of medical therapy. The Surgical Infectious Society has published guidelines on the use of antibiotics for intra-abdominal infections (62). Based on their recommendations, antibiotics should be maintained until the symptoms have clinically resolved. If there is not resolution, a source of the infection should be sought out; if possible, the source drained or endoscopically corrected (62). A longer course of antibiotics is indicated in patients where a focus cannot be identified, or if identified, cannot be definitively managed, which may be likely in space, as short-course antibiotics are associated with higher morbidity (62). Given the high-risk nature (high APACHE-II score, low albumin, other concomitant illnesses) of potential radiation-induced perforation, the guidelines suggest the use of single agents (piperacillin/tazobactam, imipenem/cilastatin, or meropenem) or combination therapy (ciprofloxacin plus metronidazole, cefepime plus ciprofloxacin or metronidazole) (62). Based on the guidelines, the use of aminoglycosides is not recommended.

Unresponsive infections: The differential diagnosis of a fever that continues despite antibacterial therapy includes viral infection, a slow responding or drug-resistant bacterial infection, fungal infection, or drug fever. Initial antibiotic therapy for neutropenic fever of unknown origin usually requires a minimum 3-d trial to determine effectiveness in neutropenic patients, which can be extended up to 7 d for high-risk patients (45). In a febrile neutropenic patient who is on fungal prophylaxis and potent multiple broad-spectrum antibiotics, it is unlikely that a fungal infection is occurring and other possibilities must be examined. If a patient becomes febrile while off antifungal prophylaxis, and the febrile episode is unresponsive to antibacterial treatment, treatment with voriconazole is again recommended. Invasive *Aspergillus* sinusitis is usually treated by surgical drainage and debridement on Earth (90). However, this may not be possible and, therefore, aggressive antibiotic management may be required. If sinus infection is suspected, ultrasound may be used to diagnose sinusitis accurately (98). The addition of a second-line antifungal agent such as liposomal amphotericin B may be necessary, especially if staining techniques reveal fungus (90).

Conclusions and Recommendations

There is considerable work being performed on the effects of chronic radiation exposure from GCR and transient high rate solar events during a potential mission to Mars, taking into account shielding modalities and career exposure limits. However, there is relatively little published work addressing the management, prognosis, and mission impact of a dangerous acute radiation exposure. This work is intended to stimulate debate on the type of medications, medical equipment, and mitigation strategies required on exploration-class space missions to deal with an acute radiation exposure. The following issues should be addressed to mitigate the hazards associated with acute radiation exposures in space:

1. A system using radiation monitors, dosimeters, and/or biological markers of radiation exposure to accurately determine the absorbed dose.
2. A consensus as to crew disposition and mission duties after receiving an acute symptomatic or asymptomatic radiation dose.
3. Continued research to further develop classes of drugs that can minimize the effects of acute radiation exposure, such as amifostine.
4. The capability to diagnose bone marrow suppression such as the ability to evaluate a CBC and differential.
5. The capability to treat bone marrow suppression such as the ability to safely store stem cells for future engraftment.
6. The capability to identify and correct severe electrolyte imbalances. This includes an ability to measure electrolytes and pH and also produce sterile water for injection with different concentrations of electrolytes (Na^+ , Cl^- , Mg^{2+} , K^+ , PO_4^{2-} , Ca^{2+}).
7. The capability to provide appropriate anti-infectious therapy. While much of the treatment will be empiric, basic microbiological techniques (ability to differentiate between gram positive, negative, and fungal specimens) may be of great benefit. At a minimum, first- and second-line treatment for the types of infections discussed is indicated.
8. The capability for laproscopic and endoscopic procedures.
9. The capability to deal with biological waste. A patient with GI syndrome, who has ongoing intractable emesis, diarrhea, melena, and hematochezia becomes a potential source of hazardous biological contamination.
10. The capability to assess patient volume status. The need to manage the fluid status of a patient with GI syndrome is critical for survival and current techniques may be inadequate for an accurate assessment.
11. The capability to ensure the effectiveness of medications over time. Some studies have shown an altered effectiveness of drugs on the ISS (75). Since much of the treatment regimens are medical, it is necessary to determine what effect travel on exploration class missions will have on selected medications.
12. A system to effectively triage an acute radiation exposure. Unfortunately, a spacecraft may have only limited resources to deal with multiple major medical problems, and those resources must be used effectively. The ability to make triage decisions depends on what resources are available. For example, without the ability to correct electrolyte abnormalities, a patient with GI syndrome becomes an expectant patient. Treatment would then shift from aggressive therapy to palliation.
13. The capability to deal with the mission impact of an ARS. In a six-person crew, if two patients have received an acute radiation dose sufficient to pro-

duce GI syndrome, the results of that exposure would significantly affect the ability of the crew to execute an exploration-class mission. These two crewmembers would likely be convalescent for many months and require the physician to be both a caretaker and manage their complex medical problems. This effectively reduces the crew capability by 50%. Even if these crewmembers recover sufficiently to ambulate in Mars' 1/3 gravity, they would be restricted from performing any act that exposes them to increased radiation, as they would have significantly exceeded their career radiation exposure limits. Flexible mission responsibilities should be incorporated into mission planning and training as a contingency plan for crew loss.

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REFERENCES

1. Aird W, Labopin M, Gorin NC, et al. Long-term cryopreservation of human stem cells. *Bone Marrow Transplant* 1992; 9:487-90.
2. Athanassiou H, Antonadou D, Coliarakis N, et al. Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2003; 56:1154-60.
3. Attarian H, Feng Z, Buckner CD, et al. Long-term cryopreservation of bone marrow for autologous transplantation. *Bone Marrow Transplant* 1996; 17:425-30.
4. Bardet E, Martin L, Calais G, et al. Preliminary data of the GORTEC 2000-02 phase III trial comparing intravenous and subcutaneous administration of amifostine for head and neck tumors treated by external radiotherapy. *Semin Oncol* 2002; 29(6, Suppl. 19):57-60.
5. Barth JL, Dyer CS, Stassinopoulos EG. Space, atmosphere, and terrestrial radiation environments. *IEEE Transactions on Nuclear Science* 2003; 50:446-82.
6. Benoff LJ, Schweitzer P. Radiation therapy-induced cardiac injury. *Am Heart J* 1995; 129:1193-6.
7. Boccia R. Improved tolerability of amifostine with rapid infusion and optimal patient preparation. *Semin Oncol* 2002; 29(6, Suppl. 19):9-13.
8. Bohme A, Shah PM, Stille W, et al. Piperacillin/tazobactam versus cefepime as initial empirical antimicrobial therapy in febrile neutropenic patients: a prospective randomized pilot study. *Eur J Med Res* 1998; 3:324-30.
9. Bolwell B, Goormastic M, Dannley R, et al. G-CSF post-autologous progenitor cell transplantation: a randomized study of 5, 10, and 16 micrograms/kg/day. *Bone Marrow Transplant* 1997; 19:215-9.
10. Buckley JC Jr, Gaffney FA, Lane LD, et al. Central venous pressure in space. *J Appl Physiol* 1996; 81:19-25.
11. Campbell MR, Kirkpatrick AW, Billica RD, et al. Endoscopic surgery in weightlessness: the investigation of basic principles for surgery in space. *Surg Endosc* 2001; 15:1413-8.
12. Cascinu S, Fedeli A, Fedeli SL, et al. Octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea: a randomized trial. *J Clin Oncol* 1993; 11:148-51.
13. Caster WO, Armstrong WD. Electrolyte metabolism after total-body x-irradiation. *Radiat Res* 1956; 5:189-204.
14. Centers for Disease Control. Acute radiation syndrome, fact sheet for physicians. Atlanta, GA: CDC; 2003.
15. Chao NJ, Schriber JR, Long GD, et al. A randomized study of erythropoietin and granulocyte colony-stimulating factor (G-CSF) versus placebo and G-CSF for patients with Hodgkin's and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. *Blood* 1994; 83:2823-8.
16. Chuang YY, Hung IJ, Yang CP, et al. Cefepime versus ceftazi-

- dime as empiric monotherapy for fever and neutropenia in children with cancer. *Pediatr Infect Dis J* 2002; 21:203–9.
17. Chung SC. Current management of acute gastrointestinal bleeding. *Scand J Gastroenterol Suppl* 2003; (237):9–12.
 18. Cometta A, Kern WV, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis* 2003; 37:382–9.
 19. Committee on Human Exploration, Space Studies Board, Commission on Physical Sciences maA. Scientific prerequisites for the human exploration of space. Washington, DC: National Research Council; 1993.
 20. Cordonnier C, Herbrecht R, Pico JL, et al. Cefepime/amikacin versus ceftazidime/amikacin as empirical therapy for febrile episodes in neutropenic patients: a comparative study. The French Cefepime Study Group. *Clin Infect Dis* 1997; 24:41–51.
 21. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991; 325:164–70.
 22. Cucinotta FA, Schimmerling W, Wilson JW, et al. Space radiation cancer risks and uncertainties for Mars missions. *Radiat Res* 2001; 156(5, Pt. 2):682–8.
 23. Cucinotta FA, Wu H, Shavers MR, et al. Radiation dosimetry and biophysical models of space radiation effects. *Gravit Space Biol Bull* 2003; 16:11–8.
 24. Dainiak N, Sorba S. Early identification of radiation accident victims for therapy of bone marrow failure. *Stem Cells* 1997; 15(Suppl. 2):275–85.
 25. Department of Homeland Security. Working Group on Radiological Dispersal Device (RDD) Preparedness: Medical Preparedness and Response Sub-Group. Washington, DC: Department of Homeland Security; 2003 May 1.
 26. Dubois A, Walker RI. Prospects for management of gastrointestinal injury associated with the acute radiation syndrome. *Gastroenterology* 1988; 95:500–7.
 27. Erman M, Akova M, Akan H, et al. Comparison of cefepime and ceftazidime in combination with amikacin in the empirical treatment of high-risk patients with febrile neutropenia: a prospective, randomized, multicenter study. *Scand J Infect Dis* 2001; 33:827–31.
 28. European Space Agency. CLUSTER. Paris, France: European Space Agency; 2004.
 29. Facorro G, Sarrasague MM, Torti H, et al. Oxidative study of patients with total body irradiation: effects of amifostine treatment. *Bone Marrow Transplant* 2004; 33:793–8.
 30. Fedorenko B, Druzhinin S, Yudaeva L, et al. Cytogenetic studies of blood lymphocytes from cosmonauts after long-term space flights on Mir station. *Adv Space Res* 2001; 27:355–9.
 31. Franzen L, Nyman J, Hagberg H, et al. A randomised placebo controlled study with ondansetron in patients undergoing fractionated radiotherapy. *Ann Oncol* 1996; 7:587–92.
 32. Gale RP. Immediate medical consequences of nuclear accidents. Lessons from Chernobyl. *JAMA* 1987; 258:625–8.
 33. Galmes A, Besalduch J, Bargay J, et al. A simplified method for cryopreservation of hematopoietic stem cells with –80 degrees C mechanical freezer with dimethyl sulfoxide as the sole cryoprotectant. *Leuk Lymphoma* 1995; 17:181–4.
 34. Garcia CD, Ramos JJ, Guzman dIG, et al. Octreotide therapy of large-volume refractory AIDS-associated diarrhea: a randomized controlled trial. *AIDS* 1994; 8:1563–7.
 35. George K, Durante M, Willingham V, et al. Biological effectiveness of accelerated particles for the induction of chromosome damage measured in metaphase and interphase human lymphocytes. *Radiat Res* 2003; 160:425–35.
 36. George K, Durante M, Wu H, et al. In vivo and in vitro measurements of complex-type chromosomal exchanges induced by heavy ions. *Adv Space Res* 2003; 31:1525–35.
 37. George K, Willingham V, Wu H, et al. Chromosome aberrations in human lymphocytes induced by 250 MeV protons: effects of dose, dose rate and shielding. *Adv Space Res* 2002; 30:891–9.
 38. Geraci JP, Jackson KL, Mariano MS. Fluid and sodium loss in whole-body-irradiated rats. *Radiat Res* 1987; 111:518–32.
 39. Goans RE, Holloway EC, Berger ME, et al. Early dose assessment following severe radiation accidents. *Health Phys* 1997; 72: 513–8.
 40. Goans RE, Holloway EC, Berger ME, et al. Early dose assessment in criticality accidents. *Health Phys* 2001; 81:446–9.
 41. Hamilton DR. Cardiovascular issues for space travel. In: Barratt ML, Pool SL. Principles of clinical medicine for spaceflight. New York: Springer-Verlag; (In press).
 42. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347:408–15.
 43. Hess U, Bohme C, Rey K, et al. Monotherapy with piperacillin/tazobactam versus combination therapy with ceftazidime plus amikacin as an empiric therapy for fever in neutropenic cancer patients. *Support Care Cancer* 1998; 6:402–9.
 44. Hiramata T, Tanosaki S, Kandatsu S, et al. Initial medical management of patients severely irradiated in the Tokai-mura criticality accident. *Br J Radiol* 2003; 76:246–53.
 45. Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34:730–51.
 46. Infectious Disease Society of America at ASoBaMT. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep* 2000; 49(RR-10):1–7.
 47. International Commission on Radiological Protection. Relative biological effectiveness (RBE), quality factor (Q), and radiation weighting factor (w(R)). A report of the International Commission on Radiological Protection. *Ann ICRP* 2003; 33:1–117.
 48. Jansen J, Thompson EM, Hanks S, et al. Hematopoietic growth factor after autologous peripheral blood transplantation: comparison of G-CSF and GM-CSF. *Bone Marrow Transplant* 1999; 23:1251–6.
 49. Jarrett DG. Medical aspects of ionizing radiation weapons. *Mil Med* 2001; 166(12, Suppl.):6–8.
 50. Kirkpatrick AW, Nicolaou S, Campbell MR, et al. Percutaneous aspiration of fluid for management of peritonitis in space. *Aviat Space Environ Med* 2002; 73:925–30.
 51. Klastersky J, Vamecq G, Cappel R, et al. Effects of the combination of gentamicin and carbenicillin on the bactericidal activity of serum. *J Infect Dis* 1972; 125:183–6.
 52. Komaki R, Lee JS, Milas L, et al. Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small-cell lung cancer: report of a randomized comparative trial. *Int J Radiat Oncol Biol Phys* 2004; 58:1369–77.
 53. Koukourakis MI, Kyrias G, Kakolyris S, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. *J Clin Oncol* 2000; 18:2226–33.
 54. Kouvaris J, Kouloulis V, Kokakis J, et al. Cytoprotective effect of amifostine in radiation-induced acute mucositis - a retrospective analysis. *Onkologie* 2002; 25:364–9.
 55. Kruse JJ, Strootman EG, Wondergem J. Effects of amifostine on radiation-induced cardiac damage. *Acta Oncol* 2003; 42:4–9.
 56. Levin ML. Aminoglycoside nephrotoxicity: keys to prevention. *J Crit Illn* 1994; 9:911–2, 915.
 57. Licitra L, Spinazze S, Roila F. Antiemetic therapy. *Crit Rev Oncol Hematol* 2002; 43:93–101.
 58. Linnemann RE. Soviet medical response to the Chernobyl nuclear accident. *JAMA* 1987; 258:637–43.
 59. Malangoni MA. Current concepts in peritonitis. *Curr Gastroenterol Rep* 2003; 5:295–301.
 60. Manatsathit S, Dupont HL, Farthing M, et al. Guideline for the management of acute diarrhea in adults. *J Gastroenterol Hepatol* 2002; 17(Suppl.):S54–71.
 61. Martin DS, South DA, Garcia KM, et al. Ultrasound in space. *Ultrasound Med Biol* 2003; 29:1–12.
 62. Mazuski JE. The Surgical Infection Society Guidelines on antimicrobial therapy for intra-abdominal infections: evidence for the recommendations. *Surg Infect (Larchmt)* 2002; 3:175–233.
 63. McDonald RE, Jensen RE, Urry HC, et al. A study of the irradiation syndrome. I. Water, electrolyte and nitrogen balances. *Am J Roentgenol Radium Ther Nucl Med* 1955; 74:701–10.
 64. NASA. ACE - real time solar winds [Web Page]. Houston, TX: NASA; 2004. Retrieved 2005 August from sec.noaa.gov/ace/ACERTsw_home.html.
 65. NASA. The Solar & heliospheric observatory (SOHO) [Web Page]. Houston, TX: NASA; 2004. Retrieved 2005 August from sohowww.nascom.nasa.gov.

66. NASA. Transition region and coronal explorer (TRACE) [Web Page]. Houston, TX: NASA; 2004. Retrieved 2005 August from sunland.gsfc.nasa.gov/smex/trace/mission/trace.htm.
67. Norrby SR. Carbapenems in serious infections: a risk-benefit assessment. *Drug Saf* 2000; 22:191–4.
68. Novikova ND. Review of the knowledge of microbial contamination of the Russian manned spacecraft. *Microb Ecol* 2004; 47:127–32.
69. Papas AS, Clark RE, Martuscelli G, et al. A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; 31:705–12.
70. Paris F, Fuks Z, Kang A, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. *Science* 2001; 293:293–7.
71. Parsons JL, Townsend LW. Interplanetary crew dose rates for the August 1972 solar particle event. *Radiat Res* 2000; 153:729–33.
72. Pissarenko NF. Radiation environment due to galactic and solar cosmic rays during manned mission to Mars in the periods between maximum and minimum solar activity cycles. *Adv Space Res* 1994; 14:771–8.
73. Priestman TJ, Roberts JT, Lucraft H, et al. Results of a randomized, double-blind comparative study of ondansetron and metoclopramide in the prevention of nausea and vomiting following high-dose upper abdominal irradiation. *Clin Oncol (R Coll Radiol)* 1990; 2:71–5.
74. Priestman TJ, Roberts JT, Upadhyaya BK. A prospective randomized double-blind trial comparing ondansetron versus prochlorperazine for the prevention of nausea and vomiting in patients undergoing fractionated radiotherapy. *Clin Oncol (R Coll Radiol)* 1993; 5:358–63.
75. Putchala L. Pharmacotherapeutics in space. *J Gravit Physiol* 1999; 6:165–8.
76. Raad II, Escalante C, Hachem RY, et al. Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. *Cancer* 2003; 98:1039–47.
77. Reames DV. Energetic particles from solar flares and coronal mass ejections [Web Page]. Greenbelt, MD: Goddard Space Flight Center; 2004. Retrieved 2005 Aug from <http://lhea-www.gsfc.nasa.gov/~reames/gsf3.html>.
78. Rowley SD, Bensingier WI, Gooley TA, et al. Effect of cell concentration on bone marrow and peripheral blood stem cell cryopreservation. *Blood* 1994; 83:2731–6.
79. Rowley SD, Feng Z, Chen L, et al. A randomized phase III clinical trial of autologous blood stem cell transplantation comparing cryopreservation using dimethylsulfoxide vs dimethylsulfoxide with hydroxyethylstarch. *Bone Marrow Transplant* 2003; 31:1043–51.
80. Saganti PB, Cucinotta FA, Wilson JW, et al. Visualization of particle flux in the human body on the surface of Mars. *J Radiat Res (Tokyo)* 2002; 43(Suppl.):S119–24.
81. Sanz MA, Lopez J, Lahuerta JJ, et al. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin for initial antibiotic therapy in haematology patients with febrile neutropenia: results of an open, randomized, multicentre trial. *J Antimicrob Chemother* 2002; 50:79–88.
82. Scheid C, Draube A, Reiser M, et al. Using at least 5x10⁶/kg CD34⁺ cells for autologous stem cell transplantation significantly reduces febrile complications and use of antibiotics after transplantation. *Bone Marrow Transplant* 1999; 23:1177–81.
83. Schmitz N, Dreger P, Zander AR, et al. Results of a randomised, controlled, multicentre study of recombinant human granulocyte colony-stimulating factor (filgrastim) in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. *Bone Marrow Transplant* 1995; 15:261–6.
84. Schuerger AC. Microbial contamination of advanced life support (ALS) systems poses a moderate threat to the long-term stability of space-based bioregenerative systems. *Life Support Biosph Sci* 1998; 5:325–37.
85. Sentongo TA. The use of oral rehydration solutions in children and adults. *Curr Gastroenterol Rep* 2004; 6:307–13.
86. Sepkowitz KA, Brown AE, Armstrong D. Empirical therapy for febrile, neutropenic patients: persistence of susceptibility of gram-negative bacilli to aminoglycoside antibiotics. *Clin Infect Dis* 1994; 19:810–1.
87. Shinn JL, Nealy JE, Townsend LW, et al. Galactic cosmic ray radiation levels in spacecraft on interplanetary missions. *Adv Space Res* 1994; 14:863–71.
88. Sinclair WK. Radiation protection issues in galactic cosmic ray risk assessment. *Adv Space Res* 1994; 14:879–84.
89. Spitzer TR, Bryson JC, Cirenza E, et al. Randomized double-blind, placebo-controlled evaluation of oral ondansetron in the prevention of nausea and vomiting associated with fractionated total-body irradiation. *J Clin Oncol* 1994; 12:2432–8.
90. Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by Aspergillus. Infectious Diseases Society of America. *Clin Infect Dis* 2000; 30:696–709.
91. Thornton WE, Moore TP, Pool SL. Fluid shifts in weightlessness. *Aviat Space Environ Med* 1987; 58(9, Suppl.):A86–90.
92. Torres GA, Jimenez MA, Alvarez MA, et al. Optimal timing of granulocyte colony-stimulating factor (G-CSF) administration after bone marrow transplantation. A prospective randomized study. *Ann Hematol* 1995; 71:65–70.
93. Townsend LW, Cucinotta FA, Wilson JW, et al. Solar modulation and nuclear fragmentation effects in galactic cosmic ray transport through shielding. *Adv Space Res* 1994; 14:853–61.
94. Trifilio S, Verma A, Mehta J. Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: heterogeneity of current clinical practice. *Bone Marrow Transplant* 2004; 33:735–9.
95. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993; 29A:319–24.
96. Tuan IZ, Dennison D, Weisdorf DJ. Pneumocystis carinii pneumonia following bone marrow transplantation. *Bone Marrow Transplant* 1992; 10:267–72.
97. vanSonnenberg E, Wittich GR, Goodacre BW, et al. Percutaneous abscess drainage: update. *World J Surg* 2001; 25:362–9.
98. Varonen H, Makela M, Savolainen S, et al. Comparison of ultrasound, radiography, and clinical examination in the diagnosis of acute maxillary sinusitis: a systematic review. *J Clin Epidemiol* 2000; 53:940–8.
99. Verma A, Pedicano J, Trifilio S, et al. How long after neutrophil recovery should myeloid growth factors be continued in autologous hematopoietic stem cell transplant recipients? *Bone Marrow Transplant* 2004; 33:715–9.
100. Vey N, Molnar S, Faucher C, et al. Delayed administration of granulocyte colony-stimulating factor after autologous bone marrow transplantation: effect on granulocyte recovery. *Bone Marrow Transplant* 1994; 14:779–82.
101. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; 346:225–34.
102. Watanabe M, Suzuki M, Suzuki K, et al. Radioprotective effects of dimethyl sulfoxide in golden hamster embryo cells exposed to gamma rays at 77 K. II. Protection from lethal, chromosomal, and DNA damage. *Radiat Res* 1990; 124:73–8.
103. Wilson JW, Shinn JL, Tripathi RK, et al. Issues in deep space radiation protection. *Acta Astronaut* 2001; 49:289–312.
104. Yavuz MN, Yavuz AA, Aydin F, et al. The efficacy of octreotide in the therapy of acute radiation-induced diarrhea: a randomized controlled study. *Int J Radiat Oncol Biol Phys* 2002; 54:195–202.