Challenges in Clinical Management of Radiation-Induced Illnesses During Exploration Spaceflight

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INTRODUCTION: Analysis of historical solar particle events (SPEs) provides context for some understanding of acute radiation exposure risk to astronauts who will travel outside of low-Earth orbit. Predicted levels of radiation exposures to exploration crewmembers could produce some health impacts, including nausea, emesis, and fatigue, though more severe clinical manifestations are unlikely. Using current models of anticipated physiological sequelae, we evaluated the clinical challenges of managing radiation-related clinical concerns during exploration spaceflight.

METHODS: A literature review was conducted to identify terrestrial management standards for radiation-induced illnesses, focusing on prodromal symptom treatment. Terrestrial management was compared to current spaceflight medical capabilities to identify gaps and highlight challenges involved in expanding capabilities for future exploration spaceflight.

RESULTS: Current spaceflight medical resources, such as those found on the International Space Station, may be sufficient to manage some aspects of radiation-induced illness, although effective treatment of all potential manifestations would require substantial expansion of capabilities. Terrestrial adjunctive therapies or more experimental treatments are unavailable in current spaceflight medical capabilities but may have a role in future management of acute radiation exposure.

DISCUSSION: Expanded medical capabilities for managing radiation-induced illnesses could be included onboard future exploration vehicles. However, this would require substantial research, time, and funding to reach flight readiness, and vehicle limitations may restrict such capabilities for exploration missions. The benefits of including expanded capabilities should be weighed against the likelihood of significant radiation exposure and extensive mission design constraints.

KEYWORDS: acute radiation sickness, exploration spaceflight, long-duration spaceflight, astronaut health, space radiation, solar particle event.

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In future exploration spaceflight outside the protection of the Earth's geomagnetic field, astronauts will be exposed to charged particle radiation from interplanetary galactic cosmic ray (GCR) radiation and solar particle events (SPEs). Although background GCR radiation is a concern, SPEs represent a potential for acute radiation exposures at levels that are orders of magnitude higher than ambient GCR.[37] The ability to predict the occurrence or magnitude of future SPEs, and the likely doses or dose-rates received by exposed crew, are limited.[61,62] The acute radiobiological effects of whole-body exposures to SPEs are not well understood and are confounded by the inhomogeneous distribution of radiation doses to sensitive organs and difficulties in extrapolating animal model data to humans.[19,21] Additionally, it remains unclear how the human health response to SPEs will be affected by concurrent GCR exposure, multiple SPE exposures over a short time period, or the added stressors of the microgravity environment.[21]

Despite these numerous unknowns, a response plan for radiation-induced illness is necessary to protect exploration crews. Exploration vehicles will have limited habitat volume,

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mass, power, communication and telemetry with the Earth, and delayed or no evacuation capability after departing low-Earth orbit (LEO).[44] Inclusion of dedicated medical resources to manage radiation illness will come at the expense of other crucial resources.[9,109] A balance is needed to ensure that likely medical conditions can be managed without putting the crew at risk of mission failure due to traded exclusions of other mission-critical resources.[12,44]

During SPEs, the sun ejects large quantities of charged nuclei consisting of mostly protons (96%) and other constituents including helium (4%) and heavier ions (< 1%).[31,63,122] Between 1973–2001, 479 SPEs were measured in LEO.[60] While only a very small number of these had operational impact, more extreme historical SPEs have been used to predict potential occurrence and associated radiation exposure of future SPEs.[37,50,95] Predictive modeling of radiation exposure based upon these historical SPEs has been previously published, providing a basis for understanding potential radiation-induced sequelae during exploration spaceflight.[5,18,50] Although individual variation in symptoms manifest after radiation exposure, acute deterministic effects of irradiation are generally directly related to dose and dose-rate.[32,49]

The "areal density" of a spacecraft describes the mass per unit area ($g \cdot cm^{-2}$, typically given in aluminum-equivalent values) that a charged particle would encounter during traversal of the vehicle structure. SPE doses to crewmembers have been modeled using data from a 1972 SPE and an empty reference vehicle with areal density of 5 $g \cdot cm^{-2}$ of aluminum-equivalent shielding (for reference, Apollo-era spacecraft had an average crew module unpacked hull density of 6.15 $g \cdot cm^{-2}$ aluminum-equivalent[25,123]). A second scenario has been modeled for astronaut exposure during a 3-h extravehicular activity (EVA, 0.3 $g \cdot cm^{-2}$ aluminum-equivalent) at the peak of radiation flux.[50] Further modeling of an event twice as intense as the 1972 SPE and of sequential large SPE exposures have provided additional estimates of potential crew radiation exposure during extreme theoretical events.[50] These modeled values have been referenced in numerous articles and NASA technical reports to provide context for potential crew radiation concerns.[18,61,62]

These models predict that, in a minimally shielded vehicle (5 $g \cdot cm^{-2}$), large SPEs could deliver intravehicular doses of $\leq$ 0.5 Gy-Eq to internal organs and $\leq$ 2.5 Gy to skin, with a peak dose-rate of approximately 0.12 Gy-Eq $\cdot h^{-1}$ to blood-forming organs (BFO).[18,50,61] These values approach NASA's 1-yr spaceflight radiation permissible exposure limits (3.0 Gy-Eq to skin and 0.5 Gy-Eq to BFO, see **Table I**).[29,90,91] Models of acute exposure suggest that radiation-related prodromal symptoms (nausea, vomiting, anorexia, fatigue[4]) could occur, but significant clinical manifestations of the hematopoietic,[75] cutaneous,[46,118] gastrointestinal,[18,76] or cerebrovascular[18] subsyndromes are unlikely.[18,50]

Models of radiation exposure provide a probabilistic dose calculation that can be used for further discussion of medical implications.[18] A summary of likely biological effects related to modeled dose exposures and associated prodromal symptoms, infection and bleeding secondary to hematopoietic sequelae, and overall risk of death is shown in **Table II**.

Table I. Dose Limits (30-d, 1-yr, and Career) for NASA Astronauts.

ORGAN	30-d LIMIT (mGy-Eq)	1-yr LIMIT (mGy-Eq)	CAREER LIMIT (mGy-Eq)
Lens	1000	2000	4000
Skin	1500	3000	6000
Blood-Forming Organ	250	500	—
Heart	250	500	1000
Central Nervous System	500	1000	1500

Table adapted from Cucinotta 2010.[29]

Numerous factors limit our ability to predict clinical responses resulting from these modeled exposures. By their very nature, SPEs are unpredictable—historical events may be representative of future extreme SPEs or may bear little similarity to future events.[21] SPEs are composed of protons with highly variable energies and may cause a range of biological sequelae as nonhomogeneous energy distributions can result in variable doses throughout the body and a spectrum of toxicity to different organ systems.[19] Given the limited understanding of the relationship between SPE exposure, dose deposition, radiobiological consequences, and synergistic interactions of radiation-induced organ system injuries, limitations occur when using historical events as a model for future SPEs that may occur during spaceflight.[19,50] Sequential SPEs could cause greater radiation doses and more deleterious biological sequelae than a single SPE; however, present models provide only limited interpretations of such sequential dose effects. Furthermore, future vehicles or EVA suits may offer different levels of protection than those considered by current models. Active monitoring and real-time analysis of radiation flux during missions already guide operational actions; future vehicles and missions are likely to continue the use of active dosimetry and analysis. In the event that active dosimetry indicated that radiation exposure had become a concern, EVAs would be terminated, returning astronauts to a more shielded vehicle environment in a matter of minutes. Exploration mission planners intend to include a vehicle shielding capability for crewmember protection during SPE exposure,[18,38,109] though final shielding design parameters have not been established. Enhanced shielding or advanced propulsion systems that minimize mission transit time may reduce the risk of SPEs during long-duration spaceflight.[82] NASA's Online Tool for Assessment of Radiation in Space (OLTARIS) provides further context for more heavily shielded vehicles.[103] Predicted skin and BFO doses for the EVA condition (0.3 $g \cdot cm^{-2}$) and the 5 $g \cdot cm^{-2}$ reference vehicle discussed above compared to skin and BFO doses modeled by OLTARIS for vehicles with 10–20 $g \cdot cm^{-2}$ shielding are provided in **Fig. 1**.

While increasing shielding would greatly reduce astronaut radiation exposure from SPEs, these design considerations are discussed in other venues and are not specifically addressed here.[18,30,37] Instead, because future shielding design is uncertain,[109] we sought to understand the operational and clinical implications of acute radiation events during spaceflight in

Table II. Medical Sequelae That Are Predicted to Result from an Event Similar to the 1972 SPE and SPE Roughly Double the Anticipated Dose of the 1972 Event.[18,50]

	RADIATION EXPOSURE SIMILAR TO 1972 SPE		DOUBLE-INTENSITY OF 1972 SPE EXPOSURE		TWO SEQUENTIAL 1972-LEVEL SPEs
SHIELDING	5 g · cm^{-2} ALUMINUM	0.3 g · cm^{-2} ALUMINUM	5 g · cm^{-2} ALUMINUM	0.3 g · cm^{-2} ALUMINUM	GENERALIZED PREDICTIONS
Nausea; Vomiting	2% incidence (CI: 0–35%) risk of nausea, no vomiting, lasting l–2 d	Moderate nausea, "near threshold" of vomiting*	37% incidence (CI: 12–69%), moderate nausea, a few episodes of vomiting	71% incidence (CI: 47–88%), severe nausea, a few episodes of vomiting	Higher incidence* and severity than risk for double-intensity SPE
Weakness; Fatigue	17% incidence (CI: 3–34%), mild symptoms by l0 d, persisting > 40 d	Moderate symptoms for l–4 d, some symptoms lasting > 40 d*	53% incidence (CI: 31–74%), moderate symptoms, lasting > 40 d	71% incidence (CI: 51–86%), severe symptoms, lasting > 40 d	Comparable incidence and severity risk to double-intensity SPE
Infection; Bleeding	Negligible	Low risk* of fever and headache at 25 d, lasts 12 d	Low risk* of fever and headache at 25 d, risk persists for 12 d	Moderate risk* of fever and headache at 25 d, risk persists for 12 d or more	Moderate risk* of fever and headache at 25 d, risk persists for 12 d or more
Lethality Risk	Negligible	< 0.1%	Negligible	3–5%	
Performance Decrements (RIPD)	Nadir 0.78 (16 h), > 1 mo at < 0.85		Nadir at 0.65 (16 h), 38 h < 0.75; > 1 mo at < 0.85		

Health effects were modeled for 41.6 d (1000 h) after exposure. Anticipated health effects are provided for crewmembers in minimal vehicle shielding (5 g · cm^{-2} aluminum) and for astronauts exposed during a 3-h extravehicular activity (0.3 g · cm^{-2} aluminum) at the peak of radiation flux. Predicted health effects are as described by Carnell et al.[18] and Hu et al.[50]
SPE: Solar particle event; RIPD: Radiation-Induced Performance Decrement.
* Percent likelihood and confidence intervals were not provided for certain scenarios.
Performance decrements are presented on the Radiation-Induced Performance Decrement ratio scale as defined by Anno et al.,[4] where a score of < 0.75 is considered operationally impactful.

the worst-case scenario of minimal shielding. Using modeled radiation exposures and anticipated clinical sequelae as context, we have evaluated potential adverse radiation events and medical sequelae. For the purposes of this assessment, we assumed 5 g · cm^{-2} of shielding to provide an understanding of the worst-case exposure scenario for medical system scoping. Any improvement in shielding may allow a decrease in onboard medical resources. We considered the benefits of various medical resources and current terrestrial capabilities and identified those with a solid evidence base for terrestrial treatment of radiation-induced clinical sequelae in the context of western medical gold standards. We also considered resources that, with additional research, design, and funding, could expand or improve the current LEO clinical medical capability to manage radiation illness during exploration spaceflight. We focused particularly on treatment modalities, including pharmaceuticals for prevention and management as well as more invasive therapeutic options used in terrestrial medicine. We examined published data from probabilistic modeling of large SPEs of the last century to evaluate the relative benefit of inclusion or exclusion of these capabilities within the context of expected medical sequelae of a radiation exposure in deep space.

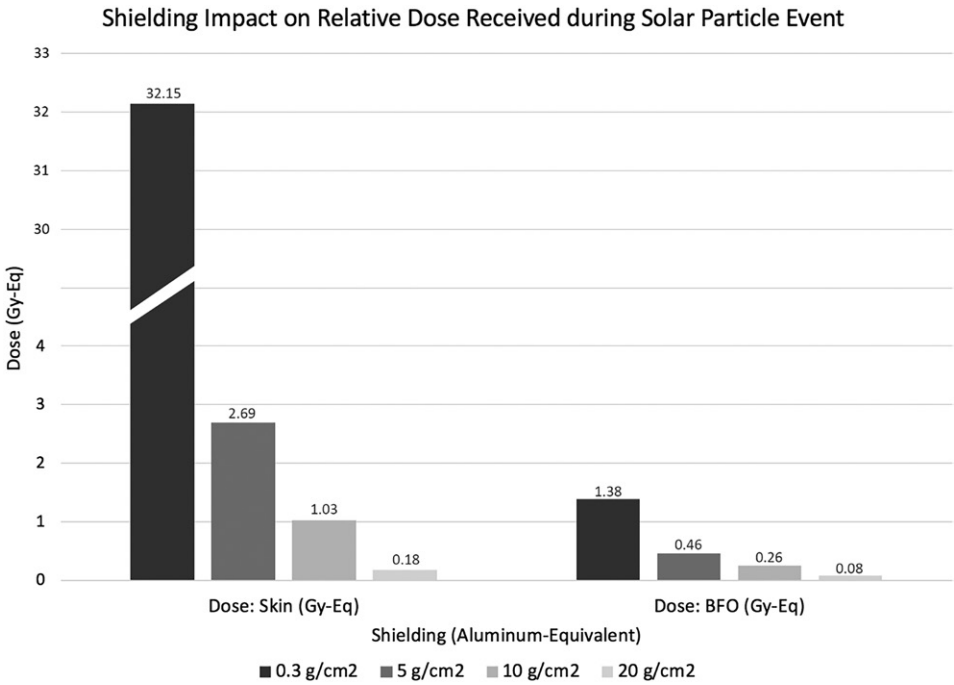

Fig. 1. Shielding impact on relative dose received during a solar particle event. Modeled doses predicted for skin and blood forming organs (BFO) exposed to a solar particle event similar to the 1972 event. Shielding parameters include minimal 0.3 g · cm^{-2} (similar to the minimal protection offered by a space suit during extravehicular activity) and 5 g · cm^{-2}, as published in Hu et al.,[18,50] and more heavily shielded conditions of 10 and 20 g · cm^{-2}, as calculated by NASA's Online Tool for Assessment of Radiation in Space (OLTARIS).[103]

METHODS

A systematic review was conducted of literature published in English regarding clinical interventions used after radiation exposure in human subjects for control of prodromal, infectious, bleeding, hematopoietic, fatigue, weakness, and quality-of-life sequelae of radiation exposure. Databases included PubMed, Web of Science, Scopus, Google Scholar, and NASA and military archives. Search terms used included radiation, prodromal, nausea, vomiting, emesis, diarrhea, fatigue, weakness, infection, bleeding, dehydration, hematopoietic, thrombocytopenia, anemia, neutropenia, and numerous terms related to all therapeutic modalities discussed below.

All titles and abstracts obtained from search criteria were reviewed. Studies published in a language other than English without available translation were discarded. Articles regarding radiation exposure that had no correlation with potential radiation exposure to humans during exploration spaceflight were discarded. Studies that addressed current, gold-standard, U.S. Food and Drug (FDA)-approved, off-label, experimental, or potential medical interventions or treatments for acute or chronic radiation exposure in humans were reviewed in entirety. The references of these manuscripts were also searched to identify additional applicable studies. Both human and animal studies were considered for inclusion, although only animal studies addressing treatment modalities currently used for clinical management of humans were ultimately included in the discussion below. Of note, given the relative paucity of data addressing symptoms specific to only radiation-related symptoms, articles addressing clinical sequelae of chemotherapy, or of combination treatments involving chemotherapy and radiation that have been used to predict or guide clinical management of similar radiation-related symptoms were also included. Studies that addressed radiation effects that were not applicable to the space environment were excluded. Studies that addressed experimental or bench research, or research in animal models alone without clinical correlates to human administration were also excluded. The remaining studies and reports were included in the analysis.

Treatment capabilities were examined within the context of published models and estimated radiation exposures that would have been experienced by crew under minimal vehicular (5 $g \cdot cm^{-2}$ aluminum) or EVA (0.3 $g \cdot cm^{-2}$ aluminum) shielding during the 1972 SPE.[50] Further consideration was given to an SPE with anticipated radiation exposure twice that of the 1972 event (a "double-intense" event) and, where possible, to cumulative effects of sequential SPE exposures, though extrapolation of sequelae was limited by model constraints.[50,61] We considered the relative benefits and risks of including or excluding various medical treatment modalities for a spaceflight mission outside of LEO and without the possibility of rapid evacuation to Earth.

RESULTS

Predicted Clinical Sequelae

Modeled predictions of clinical sequelae are presented in Table II and will be referenced throughout for clinical context; this table and the source references should be carefully reviewed for better understanding of the results as we have presented them.[18,50] In brief, crew exposure to an SPE similar to the 1972 event would likely induce prodromal symptoms, including short-term nausea, rare vomiting, and anorexia, with a limited potential for dehydration, electrolyte imbalance, and nutritional impacts; these symptoms would be self-limited, lasting a matter of days at most. Associated fatigue, weakness, and operational impact and poor performance would be more persistent, lasting for $>$ 1 mo after the SPE. The U.S. military developed a Radiation-Induced Performance Decrement (RIPD) model to identify relative detriment to performance after radiation exposure, expressed on a relative scale of 0–1, where 1 indicates normal operational performance and any value under 0.75 indicates significant functional impairment (tasks would take $1/0.75 = 1.33$ times as long as expected to complete).[5,50,117] Based on 1972 SPE modeling, SPE impact to minimally shielded crew would cause an anticipated performance impact with a nadir of 0.78 and an average value of 0.82 persisting for $>$ 1 mo.[5,50,61] Given the prolonged decrement to operational performance, even this level of functional impairment may lead to detrimental effects to mission timeline, critical goals and performance outputs, and overall mission success.[4,5,50] If astronauts performing EVA were exposed to an SPE similar in intensity to the 1972 event (and did not seek shelter or terminate the EVA), irradiation could lead to even greater operational impact, estimated at $<$ 0.75 for 1–2 d and just over 0.75 for $>$ 1 mo.[4,50,61] A double-intense SPE, or two sequential SPEs at levels equivalent to those of the 1972 event, would cause much greater fatigue and weakness, with resultant operational nadirs well below the RIPD threshold of 0.75.[4,50]

SPEs larger than the 1972 event and sequential SPE exposures would be associated with an increase in the incidence of vomiting, the severity and duration of fatigue and weakness, and the risk of fever (likely inflammatory, not infectious), but would only minimally increase the risk of hematopoietic suppression and infection, bleeding, or death compared to risks from SPE similar to the 1972 event.[50] Thus, control of prodromal symptoms of nausea and vomiting and operational impact from fatigue and weakness are likely the highest yield components of a radiation response capability.

Terrestrial Gold Standards

Terrestrial medical capabilities for the management of the potential radiation-induced clinical sequelae as described above are discussed in the subsequent sections. Pharmacotherapeutic options are further summarized in **Table III**.

Emesis control. Terrestrial research and clinical experience have demonstrated that 5-hydroxytryptamine (5HT3) antagonists are more effective than classic antiemetics, including metoclopramide and phenothiazines, and far more effective than placebo in controlling postradiation emesis.[40,41,89] Different 5HT3 antagonists have similar efficacy and side effects, including headache, constipation, diarrhea, and weakness,[41,99,100] which are generally well-tolerated.[92,97,101] Before or after radiation

Table III. Terrestrial Pharmacotherapy Options Considered for Acute Radiation-Induced Clinical Sequelae.

MEDICATION	CLASS	ROUTE	RADIATION EXPOSURE-RELATED INDICATION	PHARMACOGENETIC PATHWAY
Ondansetron	5HT3-antagonist	PO, ODT, IV	Antiemetic	CYP2D6
Granisetron	5HT3-antagonist	PO, IV, TD	Antiemetic	CYP3A
Dexamethasone	Steroid	PO,IV	Adjunct to 5HT3-antagonist	
Aprepitant	Neurokinin	PO, IV	Antiemetic, adjunct to 5HT3-antagonist	CYP3A4*
Ibuprofen	NSAID	PO	Anti-inflammatory	
Amifostine	Organothiophosphate	IV	Radioprotective	
PrC210	Aminothiol	PO**	Radioprotective	
Filgrastim	G-CSF	SQ	Colony stimulating	
Pegfilgrastim	G-CSF	SQ	Colony stimulating	
Sargramostim	GM-CSF	SQ IV	Colony stimulating	

The medications included are described in the context of therapeutic indications for treatment of terrestrial radiation-related illnesses only.
5HT3: 5-hydroxytryptamine; PO: oral; ODT: oral dissolving tablet; IV: intravenous; TD: transdermal; NSAID: non-steroidal anti-inflammatory drug; SQ: subcutaneous; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.
* While aprepitant does inhibit the CYP3A4 pathway, it does not appear to alter the specific metabolism of granisetron via the CYP3A pathway. **PrC210 is an experimental medication that has been given orally to rodents.

exposure, 5HT3-antagonists can be administered and rescue doses can be given after onset of emesis, demonstrating similar control despite wide variation in treatment timing.[43,79,129] The most commonly used 5HT3 antagonist, ondansetron, is available as a tablet, an oral-dissolving tablet, and in an injectable form; granisetron is available as a transdermal patch,[57,108] providing an alternative to oral administration without the need for intravenous access.

Recent research has demonstrated a pharmacogenetic component in the response to different 5HT3 antagonists. As these medications are metabolized by the cytochrome-P450 enzymes, genetic variation in enzyme metabolism can affect individual response to each medication.[1,13,48] For example, ondansetron is metabolized by the CYP2D6 enzyme; ultra-rapid metabolizers of the CYP2D6 pathway have a higher frequency of vomiting within 24 h of radiotherapy when treated by ondansetron compared to those who metabolize at a slower rate.[1,13,105] In contrast, granisetron is metabolized by CYP3A and is more effective than ondansetron for rapid metabolizers of the CYP2D6 pathway.[13,48,55] This suggests that therapies could be tailored based on genetic predispositions and that medications selected for an exploration mission could potentially be adjusted for individual crewmembers.[48,114]

Some studies show improved performance of ondansetron with adjunctive administration of oral dexamethasone.[41,64,89] However, while steroid administration may improve control of emesis, data has not shown significant improvement of fatigue, weakness, or other sequelae, including operational performance, after irradiation.[41,64,89] A recent study found that short courses of steroids may increase risks for subsequent infection and sepsis;[124] given that postradiation risk of infection could be a concern, liberal application of steroids to a treatment regimen may be contraindicated.

The neurokinin-receptor antagonist aprepitant has recently been shown to improve control of vomiting when used as an adjunct to 5HT3 antagonist therapy.[17,22,47] Case reports have also discussed improved outcomes when aprepitant was given prophylactically, before onset of emesis.[2] Side effects of aprepitant therapy are generally mild and well-tolerated and include fatigue/asthenia (9–26%) and constipation (8–22%).[17,47,80] Aprepitant inhibits CYP3A4 metabolism; however, it does not appear to alter the specific metabolism of granisetron via the CYP3A pathway.[15,48] This suggests that aprepitant may be a useful adjunct to 5HT3 antagonist therapy regardless of individual or genetic-mediated preference for specific 5HT3 antagonists.

If antiemetic therapy fails, parenteral repletion of fluids and electrolytes may be necessary.[43,105] Often this includes steady fluid administration by intravenous line as well as administration of oral or parenteral potassium, magnesium, and other electrolytes as needed.

Fever, infection, and hematopoietic sequelae. While unlikely, infectious sequelae of hematopoietic degradation after expected radiation dose exposures may pose a risk to more sensitive crewmembers,[52,110] even if radiation levels are low enough that BFO effects are self-limited. Even transient immunosuppression could lead to acute infection, with likely pathogens specific to the spaceflight environment.[26,37] Modeled data demonstrate a risk of fever and headache following large SPE, though symptoms may be secondary to inflammatory response rather than infection.[50] Models do not specifically indicate a risk of infection, though risk is likely to be very low in a 1972-level SPE and slightly higher for a double-exposure event, particularly for EVA exposures.[50]

Terrestrial management of acute infection following radiation exposure initially includes broad-spectrum coverage for bacterial and fungal infections, often with prophylactic use of fluoroquinolones and antifungal agents and subsequent narrowing of antimicrobial choice following identification and culture of organisms.[35,36,88] However, such therapies are generally initiated only after evidence of infection and neutropenia; in the absence of such, antimicrobial therapy is often withheld in favor of close monitoring and supportive care.

Recent terrestrial therapies have included the addition of radioprotective medications to minimize radiation-related DNA mutation and cell apoptosis, and for scavenging of free radicals. For example, nonsteroidal anti-inflammatory medications (NSAIDs), including ibuprofen and various cyclooxygenase-2 inhibitors, have been shown to enhance radiation sensitivity in cancerous cells while concurrently protecting

normal cells from radiation-induced damage.[24,70,72] NSAIDs are also useful as adjunctive therapies to manage other postradiation sequelae, including malaise and fever.

Another well-studied and FDA-approved radioprotective medication available for clinical therapy is amifostine, which is effective in prevention of xerostomia, mucositis, and other skin or soft tissue sequelae after radiation.[39,67] Use of amifostine in early radiation treatment regimens is associated with reduced incidence of esophagitis, pneumonitis, and lower gastrointestinal mucositis.[6,7,66] However, amifostine is associated with significant side effects and limited efficacy. Dose-related adverse events, seen with administration of amifostine in $>$ 30% of patients, can include hypotension, nausea and vomiting, somnolence, and severe hypersensitivity reactions, including anaphylaxis.[16,67] Amifostine does not cross the blood-brain barrier and, as a result, does not provide any radioprotection to the central nervous system.[67,83,126] Modified aminothiols such as PrC210 are similarly effective in conferring radioprotection without the extreme side effects;[96,113] however, these compounds are still in the very early experimental stages and it is not likely that there will be sufficient data on long-term safety and efficacy before exploration missions begin.

Finally, terrestrial management of hematopoietic insults after radiation exposure include therapies aimed at replacement, regeneration, or transplantation of affected hematopoietic cell lines or precursor stem cells. Administration of granulocyte colony-stimulating factors (G-CSFs) can enhance hematopoiesis and survival after large radiation doses.[33,77] The most commonly administered G-CSFs are filgrastim and pegfilgrastim, both FDA-approved for use in narrowly defined cases of severe neutropenia after chemotherapy or hematopoietic acute radiation syndrome.[85,111] Filgrastim is typically injected daily until neutrophil recovery; pegfilgrastim is usually a one-time injection following chemotherapy.[85,111] An automated subcutaneous delivery system has recently been approved for delivery of either filgrastim or pegfilgrastim as an alternative to repeated injection.[18] The granulocyte-macrophage CSF (GM-CSF) sargramostim is approved for use after chemotherapy-induced neutropenia and may prove similarly beneficial after radiation exposure.[18,112,128] Sargramostim is uniquely available in a lyophilized form, which reduces the mass required for storage and improves stability for long-duration flight.[18] However, CSFs are generally used after much higher whole-body radiation exposures than those expected from a 1972-like event, limiting the applicability of results to anticipated spaceflight exposures.[111] For example, CSFs were administered after a radiological accident in Turkey in 1998, but only victims exposed to $>$ 2 Gy to internal organs were treated with CSFs.[53,111]

In the case of severe postradiation bleeding, blood product transfusion is occasionally indicated,[68,73,134] though this treatment modality is unlikely to be indicated for 1972-level exposures or even exposures twice the magnitude of the 1972 event.[50] Other terrestrial treatment options include stem cell transplantation to minimize radiation-induced immunocompromise. However, doses in the ranges predicted (BFO exposures of $<$ 0.5 Gy-Eq) are unlikely to produce severe hematopoietic sequelae that meet criteria for stem cell transplantation, and most individuals who develop hematopoietic symptoms after modeled SPE exposures would recover without such extreme measures. More recent animal research has suggested that space radiation-induced coagulopathies may induce hemorrhagic sequelae within the range of anticipated doses from the largest predicted SPEs;[58,59,104] however, there are few terrestrial clinical correlates for this risk.

Current Spaceflight Medical Capabilities

Emesis control. The medical capabilities onboard the International Space Station (ISS) currently include 30 doses of ondansetron 4-mg tablets.[115] Dexamethasone is currently available onboard the ISS and could be used as an adjunct to 5HT3 antagonist therapy if desired. The ISS formulary does not include aprepitant. Continuous intravenous fluid administration is possible with ISS-level medical capabilities, though limited onboard fluids would be exhausted if all crewmembers required prolonged hydration. Technologies have been developed to generate sterile crystalloid fluids during spaceflight; for example, the Intravenous Fluid Generation experiment successfully generated sterile saline solution from potable ISS water stores.[81] However, the ISS formulary does not include electrolyte repletion capabilities, by oral or parenteral routes.[115]

Fever, infection, and hematopoietic sequelae. Infection remains a concern in the spaceflight environment, particularly as microgravity conditions are known to be associated with immunosuppression and increased risk of clinical sequelae.[27,56,121] Based on historical spaceflight microbiological evidence, the most likely infectious pathogens include *Staphylococcal* and *Streptococcal* species, *Pseudomonas aeruginosa, Escherichia coli,* and fungal infections, including *Aspergillus* and *Candida*.[37,93] *Pseudomonas aeruginosa* has previously caused crew health problems during spaceflight even in the absence of radiation-induced immunocompromise; for example, this bacteria was isolated from an astronaut who developed a urinary tract infection during the Apollo 13 mission.[119–121] In an article addressing radiation-induced infection during spaceflight, Epelman and Hamilton[37] recommended that an exploration mission pharmacy include fluoroquinolones (with gram positive activity), trimethoprim-sulfamethoxazole, piperacillin/tazobactam, fluconazole, voriconazole, and potentially amphotericin B to effectively cover the most common spaceflight-related pathogens after radiation-induced immunocompromise.[51,93,107]

Currently, antibiotics available in the ISS formulary include levofloxacin, trimethoprim-sulfamethoxazole, and fluconazole;[115] the remaining medications recommended above are not available. Although infectious risk is assumed to be low,[50] a crewmember experiencing true febrile neutropenia or other indications of infection would require broad-spectrum antimicrobial therapy, including coverage of *Pseudomonas,* for 2–4 wk. Treatment of just one crewmember would severely deplete current limited onboard doses. Treatment of all crewmembers would not be possible with current ISS supplies, which are

generally limited to < 100 doses per antibiotic and fewer doses of antifungal agents.

Radioprotective medications like amifostine are not included in current spaceflight medical capabilities, nor are any of the CSFs. There is currently no capability for blood product transfusion aboard the ISS.

DISCUSSION

Data extrapolated from SPEs in the last century suggest that radiation-induced illness from similar future exposures would likely be limited to prodromal and minimal hematopoietic insult, with the possibility of coagulopathic sequelae. If current LEO medical capabilities such as antiemetics are maintained for exploration spaceflight, this may be sufficient to address the needs of a limited radiation impact with some expansion of onboard pharmaceutical volume. Based on the literature reviewed, the most practical needs for an exploration medical capability and the needs most easily achieved include the expansion of onboard antiemetic options. Current ISS stock of antiemetics (30 doses of ondansetron) would be insufficient to manage prodromal symptoms following a significant radiation event involving multiple crewmembers, particularly as most clinical guidelines for control of postradiation emesis recommend administration of ≥ 8 mg/dose of ondansetron, often given every 6–8 h for days after radiation exposure.[40,41,129] Modeled outcomes suggest that antiemetics would be needed only for the first 1–2 d after an SPE.[50] However, crewmembers with CYP2D6 genetic polymorphisms may be undertreated with ondansetron therapy alone.[13,48,105] Increased supplies of 5HT3 antagonists and the addition of 5HT3 antagonists other than ondansetron, particularly if tailored to individual genetic predisposition, could improve management of prodromal symptoms.

Continuous intravenous fluid hydration has not been performed during spaceflight and would need to be demonstrated prior to reliance upon this technique. Expanding onboard intravenous rehydration capability or improving fluid generation technologies and including electrolyte repletion capabilities might improve management of emesis, dehydration, or electrolyte disturbances that might accompany prodromal symptoms. Given the utility of including fluid rehydration, antiemetics, and adjunctive therapies for treating other medical scenarios aside from radiation risk, expansion of such resources would provide a benefit for an exploration medical capability. Addition of aprepitant might offer further options for control of postradiation emesis and associated sequelae, although much work would be needed to prepare appropriate packaging, identify potential spaceflight-induced detriments to the medication, and ensure stability of the drug before it is approved for flight.[9,130,132]

Similarly, although risk of radiation-induced neutropenia and subsequent infection is low, current onboard antibiotic and antifungal capabilities are insufficient to manage radiation-induced infection in a neutropenic crewmember. Current radiobiological models do not address factors related to immunosuppression in the spaceflight environment or how such factors may alter risk prediction of infection;[71,78,121] it is possible that the estimates of infection discussed above are not conservative enough for the space environment. Broad-spectrum coverage of bacterial and fungal threats and increased volume of antimicrobials, with selection of medications based on known pathogens in the spaceflight environment, might be beneficial in the case of immunosuppression. Furthermore, expanded antibiotic capabilities could be helpful in a wide range of medical scenarios in addition to radiation events. However, expanding antimicrobial capabilities would require dedicated mass/volume as well as extensive pharmaceutical research regarding drug stability, appropriate packaging, and space environment effects on flown drugs.[9,130,131] Moreover, many of the medications used for broad-spectrum coverage are associated with multiple drug interactions and side effects; in some cases, adverse medication sequelae can be severe. For example, amphotericin B has been associated with severe electrolyte disturbances, hepatotoxicity, and multiorgan failure,[98,125,135] none of which would be easily managed during exploration spaceflight. Another example would be the concurrent administration of 5H3T antagonists and levofloxacin, known to prolong the cardiac QT interval and potentially increase the risk of developing Torsades de Pointes, ventricular fibrillation, and sudden cardiac death.[84]

Radioprotective medications like amifostine are not included in current spaceflight medical capabilities. However, given the extensive and severe side effect profile, administration of this medication poses a significant risk to crew. As significant ground research would be required for amifostine to reach flight readiness, and given known drug-related safety concerns, inclusion of amifostine or other, less developed radioprotective pharmacotherapy in early exploration capabilities is unlikely.

CSFs have been considered for inclusion in an onboard medical capability. In particular, the lyophilized GM-CSF sargramostim may prove ideal for inclusion in an exploration-class medical capability given the relatively low mass/volume requirements for lyophilized medications. Filgrastim and pegfilgrastim may similarly be useful additions to the onboard formulary if effective packaging can be developed in time to ensure shelf life and stability for the nonlyophilized forms of the CSFs. However, research into stability and utility of CSFs for long-duration spaceflight remains in early stages, and dedicated time and funding would be needed to prepare such medications for inclusion in onboard medical capabilities.[130] It is unlikely that G-CSFs would be indicated by classic terrestrial treatment standards (> 2 Gy) at the SPE doses identified by historical precedents.[50] Even so, CSFs may theoretically be beneficial in counteracting even mild sequelae in crewmembers experiencing hematopoietic depression after any dose of radiation, even if SPE doses are below the classic terrestrial treatment threshold.[18]

There is currently no capability for blood product transfusion aboard the ISS; research is ongoing regarding whether this capability should be included for exploration-class missions as a response to a variety of potential medical events.[18,65] Indications for transfusion secondary to hematopoietic suppression are unlikely according to predicted radiation doses,[50] though

bleeding secondary to coagulopathy may be a more significant risk.[58,59] Storage limitations and viability of blood products pose the greatest limitation to such capabilities at this time. Epelman and Hamilton[37] discussed the feasibility of stem cell cryopreservation for transplantation during spaceflight, as literature has reported successful transplantation years after cryopreservation of autologous donation.[3,11] However, cryopreservation and storage of autologous stem cells for postradiation transplantation would require significant technological development and mass/volume requirements. Crewmembers would need to be trained in transplantation techniques, including preparation of cryopreserved samples, invasive procedures, and careful monitoring of response after transplantation. There is also risk associated with autologous donation harvesting,[23] which would be necessary in the preflight time period, and there is high potential for adverse events following even successful transplantation.[10,74,94] The likelihood that an astronaut exposed to even an extreme radiation event under minimal shielding would experience severe hematopoietic suppression requiring stem cell transplantation is low.[50] Given the risks of stem cell transplantation and the immaturity of technology required for implementation during a spaceflight mission, it is unlikely that these capabilities will be realized for an exploration mission. Additionally, crewmembers who would require such extreme measures for severe hematopoietic depression would likely experience other critical sequelae of the radiation event, including more severe bleeding events or infection; heroic measures are impractical for many reasons and are unlikely to be successful in such circumstances.

Still, development of these modalities is worth following as clinical applications mature through terrestrial markets. For example, the ability to transfuse blood products may be useful in a variety of medical conditions during long-duration spaceflight; development of this capability may have utility for other reasons, but the likelihood that an astronaut would need a blood product transfusion after radiation-induced sequelae is low and such extreme events would most likely lead to poor clinical outcome regardless. The remaining therapeutic options, including radioprotective drugs like amifostine and the development of in-flight cryopreservation and stem cell transplantation capabilities, are extreme. Time, funding, research, training, and storage requirements are cost-prohibitive for inclusion on an exploration vehicle, particularly given near future design freezes for early exploration vehicles and the time required to approve a new drug for clinical use.[86] Risks of experimental treatments may be seen as unreasonable given the possibility of adverse reactions. Again, the likelihood that a crewmember will survive a radiation impact and require such therapies, but not otherwise exceed the medical capabilities of the mission medical architecture, is exceedingly low.

Regardless of medical capability, we should not minimize the potential impact of even a relatively low-level SPE on crew performance. The RIPD is a tool used to predict how highly trained military personnel will perform familiar tasks. As described above, large SPEs and poorly shielded conditions could impart performance decrements near the RIPD threshold for operational impact. Comparing operational performance during spaceflight to performance during military operations may be erroneous; while military operations can certainly be performance-critical, spaceflight-related operations are regularly mission-critical, single-fault tolerant events, and even small impacts to performance could result in significant mission impact. In addition, long-duration astronauts may experience some degree of cognitive impairment from the spaceflight itself.[106,116,127] Long-duration flight will be accompanied by stressors, including extreme isolation and communication delays, all of which are likely to increase stress and potentially degrade performance. Thus, the anticipated operational impact suggested by the RIPD model may underestimate the true effects on crewmembers. Unfortunately, there are no gold-standard therapies for managing operational detriments associated with radiation exposure. Management of nausea, vomiting, and dehydration may improve systemic symptoms, but the only means of mitigating performance decrements in spaceflight is through engineering methods, such as automation, that minimize human inputs.

We have chosen to accept a previously published modeled radiation context and all associated shortcomings in order to present the clinical interpretation of radiation exposure risks. Even so, SPEs, doses, and dose rates are highly unpredictable and interpretation of acute SPE exposure outcomes is difficult. Previously, spaceflight-specific literature has focused on risk-based assessments of radiation exposures without clear clinical interpretations. Large exposures to space radiation pose a potential risk for prodromal, degenerative, and carcinogenic outcomes.[19] We have focused only on the potential prodromal/acute effects of radiation exposure; however, large SPE doses may instigate degenerative effects associated with cancer, ocular cataracts, respiratory and digestive diseases, and microvasculature damage.[28] For simplicity, these chronic radiation sequelae have been omitted from the discussion here, but may be considered pertinent to long-term and postflight crew health concerns.

Many of the studies surveyed used animal models,[45,87] high dose rates, and varying types of radiation (for example, gamma vs. proton),[20] all of which limit the conclusions drawn here.[19] Most studies did not involve full-body human radiation exposures and did not challenge multiple organ systems to respond concurrently to multiple stressors as would be seen in spaceflight. Modeled outcomes do not include the low-flux cumulative effects of GCR, which may impact tissue degradation, immune function, and similar factors that may alter an astronaut's response to acute SPEs.[21] Finally, the synergistic effects of spaceflight-induced alterations to stress, performance, radiation susceptibility, and immune function are currently underrepresented in radiation-related research. Studies have identified decrements to these systems secondary to long-duration spaceflight.[27,116,127] Excluding these factors in space radiation research may underestimate the role of the spaceflight environment on radiation-induced effects. Overall, these disparities contribute to large uncertainties in the interpretation of space radiobiology studies and models referenced here and the conclusions we have drawn. In short, the lack of human exposures to doses and dose rates of heavy

charged particle radiation similar to those found in interplanetary space limits the ability to provide sound, evidence-based clinical interpretation.[21]

Similarly, there are limited data available to predict pharmaceutical stability during exploration missions.[14] While some studies have demonstrated alterations to pharmacokinetics and pharmacodynamics during spaceflight,[42,69,102] evaluation of space environment effects on pharmaceuticals has been limited to convenience samples of drugs flown in space and a single controlled study of alterations to active pharmaceutical ingredient content of formulary medications.[34,131,133] Even those medications flown on the ISS are regularly replaced by ground resupply, limiting our understanding of the long-term effects of drug exposure to radiation or other spaceflight factors. We have mentioned the challenges of approving new medications for spaceflight in the discussion above; however, even currently approved pharmaceuticals should be evaluated before they are considered stable for long-duration and deep-space missions.[8,54]

Finally, we have chosen to omit discussion of adjunctive resources for radiation mitigation, such as genetic or individualized risk profiling, diagnostic capabilities, or onboard monitoring techniques. Similarly, we have deliberately avoided topics such as heavy shielding or storm shelters, advanced warning systems, active dosimeters, and other engineered preventive measures to focus on medical capabilities in a worst-case shielding scenario. Indeed, our chosen shielding level of 5 $g \cdot cm^{-2}$ is particularly minimal. In a recent publication, Mertens et al. presented an advanced model for predicting radiobiological sequelae of SPEs.[82] This article presented modeled doses, based on historical SPEs, for vehicles inclusive of a radiation storm shelter that would provide shielding of $\geq$ 30 $g \cdot cm^{-2}$ aluminum-equivalent. Not surprisingly, anticipated dose exposures were substantially lower using this model compared to those presented here, with an associated elimination of most clinical sequelae after events even five times greater than the largest SPEs of the last century.[82] Mission architecture that provides preventive capabilities by limiting radiation exposure, either through effective shielding or real-time early warning systems that alert crew to take appropriate safety measures, will likely be far more beneficial than expanded onboard medical capabilities that treat detrimental radiation effects.[30,109] While we have attempted to identify those resources that might provide the best benefit in medical treatment scenarios, it must be stated that prevention will always be preferable to any treatment scenario, and that research efforts directed toward prevention, shielding, and crew protection should be the focus and goal of any exploration mission effort.

This discussion has sought to weigh the benefits of potential medical resources and associated limitations to evaluate their relative impact on outcomes of a medical response to extreme radiation events during an exploration-class mission. It is worth remembering that the health events and sequelae described herein are predictions derived from radiation models of the most extreme SPEs of the last century and minimal vehicular shielding; it is currently not possible to accurately predict the occurrence of future SPE or the radiation dose that crewmembers would incur from SPE exposures. While our discussion addresses only currently available medical treatment resources, and future expansion of terrestrial capabilities may enhance future spaceflight resources accordingly, we hope that this structured approach provides a framework for near-future medical system decision-making and risk assessment. Any improvement of understanding, prediction of the space radiation environment, or to vehicular shielding capabilities, may significantly alter the conclusions described here.

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