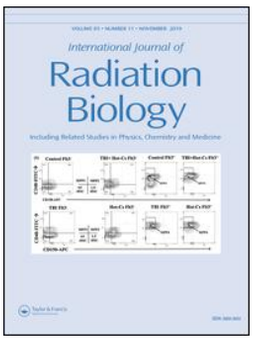

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Lisa S. Carnell

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Spaceflight medical countermeasures: a strategic approach for mitigating effects from solar particle events

Lisa S. Carnell

Biological and Physical Sciences Division, NASA Langley Research Center, Hampton, VA, USA

ABSTRACT

NASA was recently charged with returning humans to the lunar surface within the next five years. This will require preparation for spaceflight missions of longer distance and duration than ever performed in the past. Protecting the crew and mission from the hazards associated with spaceflight will be a priority. One of the primary hazards to address is the challenging radiation environment. Space is unforgiving when it comes to radiation. There is galactic cosmic radiation (GCR) that is pervasive in space and the possibility of solar particle events (SPE) that release high energy particles from the sun that can result in high doses of radiation to the crew if unprotected. NASA has been preparing and evaluating several means of ensuring that crew health is not compromised during these missions. Physical shielding, space weather monitoring, and more recently storm shelters are all possible means of protecting crew during a SPE. Medical countermeasures have not been necessary for operations in low Earth orbit; however, future human exploration missions should consider including therapies onboard to address radiation-induced health effects. While the likelihood of experiencing a significant SPE is very low, serious adverse health effects or even death could occur if no medical countermeasures were available. Having a Food and Drug Administration (FDA) approved medical countermeasure on board that could mitigate acute radiation-induced hematopoietic syndrome due to a SPE could provide life saving measures for the crew. This paper discusses the mitigation strategies that can be implemented for Artemis missions and identifies numerous areas of research for future improvements.

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Space; radiation; medical countermeasures; solar particle event; SPE; prodromal; acute radiation syndrome

Introduction

NASA is embarking on an ambitious mission to return humans to deep space exploration within the next five years. As spaceflights extend deeper into space and lengthen in duration, crew will be exposed to more galactic cosmic radiation (GCR) and solar particle events (SPE). This increased radiation exposure could result in adverse health effects. This paper looks at the risks specifically associated with exposure to SPE and suggests a strategic approach on how to mitigate radiation-induced health effects from SPE using medical countermeasures.

Crewed Artemis exploration missions will be the longest duration deep space missions ever performed. Although the first Artemis missions will be short in duration, their distance from Earth poses greater risk of being exposed to a SPE than any spaceflight since the Apollo missions. The first crewed mission, Artemis 2 (Figure 1), will send four astronauts to deep space for approximately 10 days to perform a lunar flyby. Follow-on Artemis missions will require crew to spend 30 days or more in lunar orbit while crew assemble the planned space Gateway and begin conducting human lunar landing missions. During these missions, crew could potentially reach medically significant radiation exposure levels due to a SPE.

Effects of SPE

Solar particle events occur when the sun experiences a solar flare or a coronal mass ejection (CME) releasing high energy protons 87% (hydrogen nuclei), 12% helium nuclei, and 1% the nuclei of heavier elements, called high (H) atomic number (Z) and energy (E) ions or HZE ions, into space (Simpson 1983). During a solar flare, the acceleration and energy of these particles can last for a short time or for days as is the case with CMEs. The magnitude of energy and velocity of SPE produce intense periods of increased radiation that have the potential to be lethal to crew if they are not protected in a timely manner.

The varying levels of SPE radiation can produce a broad spectrum of adverse radiation-induced health effects, which are nominally captured under the diagnosis of acute radiation syndrome (ARS). ARS can start with a prodromal

CONTACT Lisa S. Carnell lisa.a.scottcarnell@nasa.gov Biological and Physical Sciences Division, NASA Langley Research Center, MS 226, Hampton, VA 23681, USA

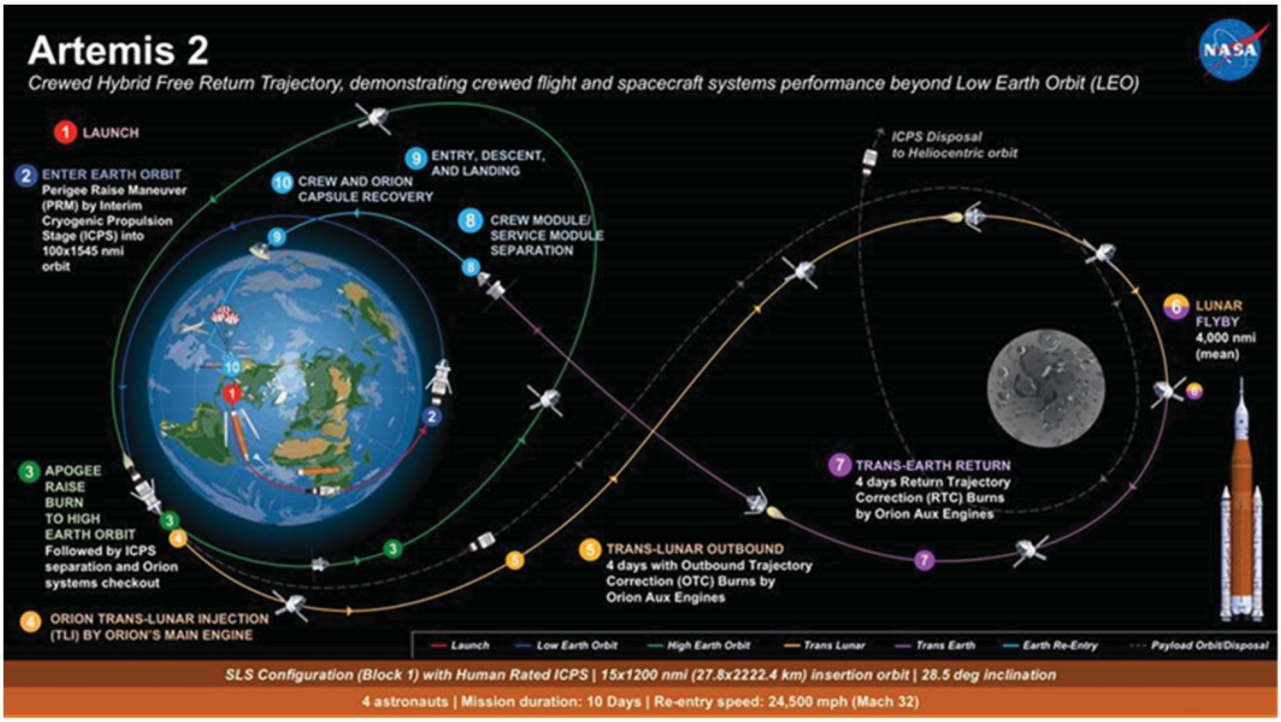

Figure 1. Trajectory for the crewed Artemis 2 lunar flyby mission (credit: NASA).

phase that includes nausea, vomiting, diarrhea and fatigue. Depending on the radiation dose, it can progress into hematopoietic ARS (H-ARS), cause skin dermatitis or in more severe cases develop into gastrointestinal or neurovascular ARS. The more severe acute radiation syndromes are not expected to occur at the anticipated exposure doses during current planned spaceflight missions and will not be addressed here. This paper focuses on a strategic approach to counter the ARS stages to include prodromal phase, H-ARS and skin dermatitis.

Current SPE mitigation strategies

Current NASA strategies to protect against SPE focus on physically shielding crew members from the radiation. Today, when a SPE occurs, crew are instructed about sheltering on the International Space Station (ISS). The ISS is protected by the Earth's magnetic field, significantly reducing the level of radiation exposure that coincides with a SPE. Crew also have the ability to return to Earth in a Soyuz vehicle if a severe situation occurs. On missions that will take crew further away from Earth, there will no longer be the protection of the Earth's magnetic field and atmosphere, and a return to Earth will take days rather than hours.

New habitats designed for deep space missions may be equipped with storm shelters to minimize health impacts to crew during SPEs. These measures should provide adequate protection to crew with maximum exposure estimates predicted to be 250 mGy-eq for the 30-day blood forming organ (BFO) permissible exposure limit (PEL) inside a storm shelter based on the 1989 solar flare data (Townsend et al. 2018).

Artemis missions are expected to last more than 30 days with increasing duration in the out years. These later missions include lunar surface activities which add another circumstance to consider when planning for crew protection. For crew performing human lunar landing activities, there is no atmosphere or protection currently on the lunar surface; therefore, crew could be required to return to Gateway for physical protection from potentially harmful solar events. Much of the crew protection will rely on the ability to predict the magnitude and timing of the solar event and using that information to avoid exposure by sheltering in the storm shelter or other designated safe space on Gateway.

In the event a crew member is unable to reach the storm shelter in time, will exceed the 30 day BFO PEL, or is more sensitive to the radiation levels at the exposure dose, it is recommended that medical countermeasures to address radiation-induced health effects be included in the medical kit. In addition to adding MCMs to the medical kit, research should be conduct to examine if the threshold for acute radiation syndrome will change when the effects of a single SPE are confounded with the effects of prolonged exposure to galactic cosmic radiation (GCR). It is also unknown how changes in the human immune system from long duration flights may affect the response to these exposure events. Combined effects of a SPE simulated exposure with hindlimb unloading (a form of simulated microgravity) using a mouse model indicated alterations in immune system function (Kennedy 2014). How this translates to humans in microgravity is still unclear. These longer duration missions may also encounter multiple SPE exposures which could compromise both crew and mission. These are all open ended questions that should be addressed to support long duration spaceflight missions.

Medical countermeasures – treatments

Medical countermeasures to address SPEs have benefited largely from the research performed by federal agencies such as the National Institutes of Health/National Institutes of Allergy and Infectious Disease (NIH/NIAID), the Biomedical Advanced Research and Development Authority (BARDA), and the Armed Forces Radiobiology Research Institute (AFRRI). These agencies have primarily focused on addressing radiation-induced health effects due to an accidental exposure or a nuclear event (DiCarlo et al. 2011; Homer et al. 2016; Carnell 2019). SPEs have the potential of exposing crew to these higher doses of radiation; however, effects from SPE radiation can occur at relatively low doses (<1 Gy) with early symptoms including nausea, vomiting, anorexia and diarrhea (Mettler 2012). This is considered the prodromal stage of H-ARS.

Treatments for ARS prodromal phase symptoms

The prodromal stage is typically non-life threatening; however, without adequate treatment options, these seemingly innocuous symptoms could lead to more serious outcomes. To date, a limited number of medications have been tested in animal models under space-relevant doses and dose rates to establish efficacy for NASA relevant scenarios. A review by Kennedy (2014) describes several traditional and nontraditional medications that could be considered for inclusion in a spaceflight medical kit to treat the various symptoms anticipated with a low dose SPE exposure. Treatment options presented below are adapted from this review.

King et al. (1999) tested Ondansetron (Zofran®), a 5-HT3 serotonin antagonist, to treat nausea associated with prodromal effects. Ondansetron (Zofran®) is approved clinically for the treatment of nausea associated with radiotherapy, has demonstrated effectiveness in reducing emetic risk due to space-relevant ionizing radiation, and has been tested in crew on the ISS to alleviate motion sickness. Other potential anti-nausea medications that may be considered include granisetron (Kytril®), palonosetron (Aloxi®), and dolasetron (Anzemet®) – all 5-HT3 serotonin antagonists; prochlorperazine (Compro®), a dopamine receptor antagonist; and dexamethasone (Decadron®), a corticosteroid.

Depending on the level of exposure there is the possibility of crew developing diarrhea. This symptom could be treated with standard over-the-counter medications such as Imodium®, an oral anti-diarrheal agent. Imodium® is currently included in the ISS medical kit to ameliorate symptoms associated with diarrhea and will most likely be included for future Artemis or Mars missions.

Treating the dehydration that is commonly associated with diarrhea could become a challenge in the spaceflight environment. While intravenous (IV) normal saline is typically available, there is usually a very limited supply to treat crew, and for those that may suffer from extreme dehydration this could be problematic.

There is also the risk of infection that may arise from radiation skin burns or immune system impacts. NASA includes a range of antibiotics in the current medical kits, namely penicillins, cephalosporins, fluoroquinolones, and macrolides; and it is likely that a similar array of antibiotics will be available on future missions to support a weakened immune system (Taddeo and Armstrong 2008).

The treatments described above have been successfully delivered orally or via intramuscular injection on previous spaceflight missions. A summary of medical countermeasures that either exist in the current NASA medical kit or could be considered for inclusion on future exploration missions to address radiation-induced health effects from exposure to a solar particle event is outlined in Table 1 with proposed new MCMs in bold.

Table 1. Solar particle event indications and treatment recommendations.

Symptom	MCM Recommendation
Nausea/Vomiting	Ondansetron (Zofran®), **Granisetron (Kytril®)** Dexamethosone (Decadron®) **Palonosetron (Aloxi®), Dolasetron (Anzemet®) Prochlorperazine (Compro®)**
Diarrhea	Imodium®
Dehydration	Intravenous (IV) normal saline
Infections	Penicillins, cephalosporins, macrolides, ciprofloxacin
Hematopoietic	**G-CSF (Neupogen®) Peg-G-CSF (Neulasta®), GM-CSF (Leukine®)**
Burns	Silver sulfadiazine, sterile gauze, parenteral opioid analgesics, crystalloid solutions, corticosteroid cream

Treatments for hematopoietic acute radiation syndrome (H-ARS)

H-ARS can follow the prodromal phase and can manifest at relatively low radiation doses. The CDC identifies the possibility of death at 1.2 Gy total body exposure (CDC 2019), though given the ability to shield against the majority of the SPE radiation, the anticipated doses for crew on long duration missions should be much lower than 1 Gy. Even with shielding, H-ARS could still be a concern given the potential for the bone marrow to be compromised at doses as low as 0.5 Gy (Mettler 2012).

Several federal agencies have developed and tested numerous medical countermeasures to treat H-ARS in the event of a public exposure to radiation (Singh et al. 2015). Many of these MCMs are still in the research pipeline for validation. To date, only three of the medical countermeasures investigated by other agencies have received FDA approval. NIH/NIAID achieved success when recombinant granulocyte colony stimulating factor (G-CSF) filgrastim (Neupogen®, Amgen) received FDA approval in 2015 for the additional indication to 'increase survival in patients acutely exposed to myelosuppressive doses of radiation' (FDA 2015a). The recommended dosage for patients acutely exposed to myelosuppressive doses of radiation is 10 mcg/kg/day by subcutaneous injection (Amgen 2015).

The sustained release version, pegfilgastrim or Peg-G-CSF (Neulasta®, Amgen), reduced neutropenia in studies involving SPE-like protons (Romero-Weaver et al. 2013). Neutropenia occurs when neutrophil counts drop to an abnormally low level impacting the ability to fight off infections. Neulasta® received FDA approval (FDA 2015b) for the same indication as Neupogen® with a recommended dosage of 6 mg delivered subcutaneously once per week for

two weeks. An automated subcutaneous delivery system was released by Amgen to facilitate delivery of Neupogen® and Neulasta® (Amgen 2015). Both drugs have been used clinically for treatment of neutropenia following chemotherapy since the early 1990s.

Sargramostim (Leukine®, Partner Therapeutics) is a recombinant human granulocyte macrophage colony stimulating factor (GM-CSF) which stimulates proliferation and differentiation of hematopoietic progenitor cells to divide and differentiate into neutrophils, monocytes, macrophages and myeloid-derived dendritic cells, and it is also capable of activating mature granulocytes and macrophages. Leukine® is FDA approved to be used clinically for treatment of neutropenia following chemotherapy similar to Neupogen® and Neulasta®. As a result of substantial support from BARDA, it recently received FDA approval (FDA 2018) to increase survival in adult and pediatric patients acutely exposed to myelosuppressive doses of radiation. Prescribing information for Leukine® indicates it should be delivered daily and continued until an absolute neutrophil count (ANC) >1000 cells/mm^3 is maintained for 3 consecutive days. Leukine® (250 mcg) is available in a lyophilized (freeze-dried) form, that is reconstituted with 1.0 mL of bacteriostatic water for injection, USP (0.9% benzyl alcohol) making it attractive for storage and stability on long duration missions.

Any of these three FDA-approved medications should be considered for inclusion in future spaceflight medical kits. The number of treatments that may be required for each crew member will depend on the radiation dose received and their biological response to treatments. Each design reference mission will require careful consideration and selection based on the probability of a SPE or multiple SPE. Shorter duration Artemis missions may only warrant a single dose per crew member since it should be possible to return to Earth within days while Mars missions may encounter multiple SPE, necessitating more than one dose per crew member.

Treatments for skin exposure/radiation dermatitis

SPEs generate an inhomogeneous dose distribution which can lead to higher radiation doses to the skin without compromising the BFO (Hu et al. 2009). Radiation-induced skin damage could occur if skin doses reach 4.5–5 Gy. At these higher doses, there is an increased likelihood of radiation dermatitis, which can result in irritation, pain, and skin infections that may ultimately compromise the immune system (Ryan 2012). In studies involving minipigs exposed to 5 or 10 Gy of SPE-like protons, a topical steroid cream (mometasone, Elocon®) mitigated radiation-induced skin damage (Kennedy 2014). As of today, radiation exposure to skin would be treated as a burn; however, crew members have reported increased skin sensitivity (Crucian et al. 2016) and immune system alterations during spaceflight (Crucian et al. 2018) which may present confounding effects. It is unknown what radiation damage to the skin and its consequence on the immune system during spaceflight will be, and since it may alter the threshold for skin damage or onset and recovery of H-ARS, it should be examined to ensure the best treatment options are selected for inclusion on future spaceflight missions. Currently, medical kits provided on the ISS include silver sulfadiazine, sterile gauze, parenteral opioid analgesics, corticosteroid cream and crystalloid solutions (Marshburn 2008), although more advanced treatment options may be required for longer duration missions, particularly if there are confounding effects that result from skin sensitivity or immune system alterations. Fortunately, partner agencies have been investigating new treatments to address skin damage due to radiation exposure (Singh et al. 2017; Carnell et al. 2016). NASA can leverage these studies when exploring advanced treatment options that may be necessary for long duration missions.

Medical countermeasures – diagnostics

Future spaceflight habitats will be equipped with dosimeters to monitor the radiation dose and dose-rate at all times. During a SPE, communication blackouts may occur limiting flight surgeon recommendations from the Earth. The crew may be required to make judgment calls based on symptoms observed and deliver therapeutics as necessary, which increases the need for onboard diagnostic capability.

Point-of-Care diagnostics devices

In the event of a SPE, it will be important to have a device capable of measuring white blood cell count (WBC) with differential in order to determine if a crew member needs to take a medical countermeasure for possible neutropenia. Currently, HemoCue® is the only point-of-care device commercially available that is capable of providing a WBC count with differential. It requires a finger stick and provides results in minutes. The proposed G-CSF, Peg-G-CSF and GM-CSF medical countermeasures are recommended to be delivered if the absolute neutrophil count (ANC) drops below 1000/mm^3 with regular monitoring of ANC recommended and additional doses of G-CSF or GM-CSF administered as prescribed (Amgen 2015; FDA 2018). Several new technologies are currently in development that may provide complete blood count (CBC) in miniaturized, rapid reporting devices. NASA is currently monitoring the development of these devices with the goal of including one on long duration missions.

Determining individual sensitivity from radiation exposure would help guide delivery of appropriate MCMs. BARDA has funded the development of a biodosimeter (REDI-Dx®, DxTerity) based on an 18 gene signature readout corresponding to radiation damage. The REDI-Dx® test system is designed for determining individualized levels of absorbed radiation using a blood sample taken from a finger prick and measures the relative expression of a panel of 18 genes, then uses a proprietary algorithm to estimate absorbed dose. Although there are devices available that can be used to measure levels of external radiation, there is no FDA approved test that can be used to determine the

amount of radiation that an individual person has absorbed. The REDI-Dx® system was tested over a range of 0–6.4 Gy with accuracy near 99% at doses below 0.5 Gy with 8-fold faster turnaround (six hours versus 2.4 days) for predicting radiation exposure compared to the industry standard dicentric chromosome assay (DCA or DIC) (2017 personal communication B. Terbrueggen; unreferenced, see 'Notes'). Though this type of system may be more relevant to GCR exposure, it could help detect and understand overall absorbed radiation doses, which would have two possible benefits:

1. Eliminating the need for a separate WBC device, and
2. Helping to determine treatments needed to mitigate combined effects of GCR and SPE.

Further advances in technology and sample processing are expected in the future which could provide for a reasonable timescale for inflight absorbed radiation dose determination. In order to support space exploration missions, any tool or platform relying on gene signatures identified for terrestrial application would require validation for space radiation to ensure the tool or platform is applicable in the space radiation environment.

Computational modeling

NASA has developed an organ dose projection model to be used in future deep space exploration missions that is based on a probabilistic model of acute radiation risk, Acute Radiation Risk and BRYNTRN Organ Dose Projection (ARRBOD), designed to help predict the biological dose to the blood forming organs (Kim 2010) ARRBOD incorporates a temporal profile of the SPE and uses this information to create a temporal report of the BFO dose rate expected. This information would be provided to the NASA Radiation Health Officer (RHO) and shared with the Flight Surgeon to inform decisions on medical countermeasure needs and determine performance decrements in crew. The current model is based on the hematopoietic system including impacts to acute health response information of lymphocyte depression, granulocyte modulation, fatigue and weakness, and upper gastrointestinal distress. However, the current model does not take into account other spaceflight stressors such as the combination of microgravity and radiation, which can impact skin sensitivity and immune system response. Updates to the model to include these effects may provide better information to the RHO and Flight Surgeon, which would help guide discussions and decisions for specific individual crew medical countermeasure interventions.

Implementation

If a MCM shows promise for providing radioprotection or mitigation to NASA crew, it will be required to go through the NASA Transition to Operations (TtO) process to obtain approval for administration to crew for the demonstrated indication. This process is described in NASA NPR 8900.1A Appendix D: Transition to Operations Review Process (TORP 2016). It involves the Office of the Chief Health and Medical Operations (OCHMO), Flight Surgeons, Radiation Health Officer (RHO), Human Research Program (HRP) Management and other board representatives. Once a MCM is approved for use in spaceflight operations, the onboard medical kit will be outfitted to carry the MCM along with the required handling, storage, and delivery equipment and methods. Though not specifically called out in the TORP, a flight surgeon with specific radiation expertise may better facilitate the understanding and decision process for approving a MCM for radiation-induced health effects.

Filgrastim, peg-filgrastim and sargramostim are all viable candidates for treating H-ARS if necessary. It is recommended that NASA select one of these drugs and transition it to operations for inclusion in the medical kit in support of long duration missions. When selecting the drug, NASA should take into account storage, ease of administration, shelf-life and stability. A comparison of these properties for each H-ARS candidate is outlined in Table 2. Storage will be a critical factor since refrigeration may be a challenge particularly in early missions. While lyophilized drugs offer weight and storage savings, reconstitution may be a challenge in spaceflight predominantly due to bubble formation. This may warrant a pilot study on the ISS to test whether bubble formation would be an issue if lyophilized drugs are selected for the medical kit in support of a mission. Ease of administration is important in addition to shelf life and stability of the MCM. Given the length of the proposed missions and the environment, a shelf-life of more than three years may be required to ensure the MCM maintains efficacy and does not degrade into toxic byproducts over the duration of the mission.

In order to determine the appropriate dose for crew for any proposed MCM, the pharmacokinetics and pharmacodynamics need to be determined. Pharmacokinetics (PK) describes the rate at which a drug moves through the body. It considers absorption, distribution, metabolism, and excretion while the pharmacodynamics (PD) of a drug focuses on the mechanism of action and how the drug concentration and rate impact the physiological and biochemical response (Meibohm and Derendorf 1997). It will be important to evaluate any proposed MCM in a spaceflight environment to determine the PK/PD since there has been indication that medication efficacy can be altered in space (Kast et al. 2017). Testing in both female and male models will also be important since many studies have shown differences in efficacy between sexes (Whitley and Lindsey 2009) and it is unknown if those effects will be more pronounced in spaceflight.

Conclusion

NASA is embarking on the most ambitious exploration missions ever undertaken by humans over the next decade. The thrill of exploration also requires a balance of well measured plans to ensure that the crew remains healthy and the mission is a success. The probability of encountering a SPE on

Table 2. Comparison of Storage, Shelf-Life and Delivery for H-ARS Treatments.

	Form	Storage	Delivery	Shelf-life	Dose	**Additional supplies
G-CSF	Liquid	2 °C–8 °C	Subcutaneous injection	Room temperature 24 h Refrigerated 30 months	Single-dose vials containing 300 mcg/mL or 480 mcg/1.6 mL **OR** Single-dose, prefilled syringe with a 27 gauge, 1/2 inch needle containing 300 mcg/0.5 mL or 480 mcg/0.8 mL	1 mL syringe with a 25 to 30 gauge 5/8-inch needle sterile alcohol swabs
Peg-GCSF	Liquid	2 °C–8 °C	Subcutaneous injection	Room temperature 48 h Refrigerated 3 years	* 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual administration	1 mL syringe with a 25 to 30 gauge 5/8-inch needle sterile alcohol swabs
GM-CSF	Liquid **OR** Lyophilized powder	2 °C–8 °C	Subcutaneous injection	Room temperature 1 week Refrigerated 3 years	250 mcg single-dose vials of lyophilized powder **OR** 500 mcg/mL multiple-dose vial of liquid	Sterile or Bacteriostatic water to reconstitute lyophilized powder 1 mL syringe with a 25 to 30 gauge 5/8-inch needle sterile alcohol swabs

*The on-body injector delivery method for peg-GCSF is not recommended for treating H-ARS.
**Mass and volume of supplies will depend on packaging and design reference mission requirements

one of these future missions increases with the distance and duration of the missions. In order to ensure the crew safety while achieving the goal of human exploration, it would be advantageous for NASA to take conservative actions to address adverse health effects that may arise from the threat of exposure to SPEs.

This paper presents a strategic approach for improving protections for crew after SPE radiation exposure. Though NASA does have some MCMs to ameliorate radiation-induced health effects, the following additional actions are recommended:

1. *Evaluate the four additional medications identified in Table 1 and determine the most efficacious MCM to address nausea and vomiting (prodromal ARS) for inclusion in the spaceflight medical kit*
2. *Select and transition to operations one of the three FDA-approved medications to counteract H-ARS*
3. *Conduct* additional research in each of the following areas:
   - *MCM storage, shelf-life and stability*
   - *MCM administration needs*
   - *For lyophilized formulations, determine reconstitution capabilities in spaceflight to mitigate bubble formation*
   - *Evaluate PK/PD in spaceflight for every MCM selected*
   - *Conduct research on the radiation threshold for H-ARS with immune system alterations*
   - *Conduct* research on the radiation threshold for skin damage with increased skin sensitivity
4. *Monitor MCMs being evaluated by partner agencies for H-ARS and skin treatments*
5. *Include a WBC or CBC diagnostic tool on spaceflight missions; monitor development of advanced tools that may be able to provide individual absorbed dose (e.g. REDI-Dx®)*
6. *Update the ARRBOD Model to include additional spaceflight stressors (e.g. microgravity) and their effects on the immune system and skin sensitivity*
7. *Include a flight surgeon with radiation expertise on the TORP panel*
8. *Develop formal operational guidance and training for crew that provides instruction on what to do in the event of a SPE*

NASA continues surveillance of new treatments to address H-ARS and radiation-induced burn therapies along with technology developments for advanced point-of-care diagnostics currently in the acute radiation research pipeline. Several federal agencies including NIH/NIAID, AFRRI, and BARDA have been studying, testing and developing MCMs to address radiation exposures that may result from nuclear accidents, weapons of mass destruction, or other unforeseen means. NASA continues to stay apprized of new MCM candidates that may be of benefit to future exploration missions by participating in multiple interagency groups, meetings and workshops. Leveraging the research performed by these partner agencies will provide NASA with solutions that can be tested and validated in a timely manner to support future spaceflight missions.

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The views expressed in this manuscript are those of the author; no endorsement by NASA or any other US Government agency has been given, implied, or inferred. The author declares that there is no financial conflict of interest.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Notes on contributor

Lisa Carnell is the senior Senior Scientist for Partnership Development in the NASA Space Life and Physical Sciences Research Applications Division at NASA Headquarters.

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