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# Wound-healing and onboard care during long-duration human deep space exploration from a surgical perspective through the lens of a scoping review

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## ABSTRACT

**Objective:** The aim of this study was to develop a bridge between the fields of aerospace medicine and vascular surgery, and to emphasize the need for leading experts in vascular medicine, interventional radiology, and surgery to address the critical human spaceflight research gaps highlighted by the National Aeronautics and Space Administration (NASA).

**Methods:** A scoping review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted on literature published between 2000 and 2024. A well-defined search strategy was employed for keyword searches across multiple databases, including PubMed, Scopus, Cochrane, Embase, the NASA Life Science Data Archive, NASA technical reports, and Google Scholar.

**Results:** Our review identified 125 relevant studies. These included 30 studies on general health conditions in space and wound healing, 38 addressing risk factors associated with the space environment, and 57 studies examining prevention and treatment options. These findings address NASA's identified gaps in wound care capabilities (ExMC 4.07), contribute to defining the potential list of medical conditions that could arise during deep-space missions (ExMC 4.24, Med07, Med12, Medical-101), and serve as a milestone for developing integrated exploration medical system models for missions to the Moon and Mars (Medical-501).

**Conclusions:** Many of the identified NASA knowledge gaps—some of which have even been marked as closed due to a lack of research in the field—cannot be effectively addressed without bridging aerospace medicine with related disciplines, such as vascular surgery and chronic wound care. (J Vasc Surg Venous Lymphat Disord 2025;13:102249.)

**Keywords:** Fluid shifts; Radiation; Spaceflight; Venous system; Wound care

Government-based and commercial spaceflight activities have greatly expanded in the past decade. As humans prepare to return to the Moon, medical, interventional, and surgical and perioperative treatment protocols must be developed. Radiation, altered gravity environments, limited resources, and distance to terrestrial medical care are factors that must be accounted for. "Spinoffs" from space research are also applicable for developing countries and austere Earthly environments. The United States National Aeronautics and Space Administration (NASA) has identified several knowledge gaps through its Human Research Program (HRP), recognizing the importance of these factors for future human spaceflight missions, and particularly relevant to mission planning for the Moon and Mars, where evacuation to Earth for definitive treatment is not immediately feasible. Accordingly, there is a need for advanced theoretical and clinical expertise in wound healing, coupled with a comprehensive understanding of lymphatic and venous system function in weightlessness and other altered gravity environments. Given the physiological complexity of this issue, benchtop to clinical expertise in vascular medicine and interventions, as well as surgical protocols, will be needed to bring translative theory and process from terrestrial analogs to operationalization in spaceflight.

This paper aims to bridge the fields of aerospace medicine, vascular medicine, interventional radiology, and surgery, and to present the need for leading vascular specialists to address specific gaps outlined in the NASA HRP.

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### Primary endpoint

The primary endpoint of this study was to evaluate effectiveness of current wound-healing treatments in long-duration spaceflight, including potential adaptations of Earth-based medications and therapies.

### Secondary endpoint

The secondary endpoint of this study was to 3xamine the influence of microgravity, radiation, and other space-specific factors on wound-healing processes, identifying the most effective mitigatory approaches.

## METHODS

A scoping review was conducted utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[1]

### Inclusion and exclusion criteria

The review scope encompassed a diverse study population, including professional, commercial, and analog astronauts, military personnel, healthy civilians, and people with pre-existing health conditions. The interventional and exposure areas include the International Space Station (ISS), terrestrial high- and low-volume vascular settings, and low-resource austere environments (eg, Antarctica, combat zones). Non-English literature, inaccessible full-text articles, and studies involving pediatric populations (under 18 years) were excluded. Additionally, gray literature (eg, theses and dissertations) and non-peer-reviewed papers were excluded.

### Search strategy and data extraction

A scoping review of relevant literature was conducted using keyword searches across PubMed, Scopus, Cochrane, Embase, NASA Life Science Data Archive, NASA technical reports, and Google Scholar search engines, encompassing publications from 2000 to 2024. The full search algorithm is detailed in the Supplementary Appendix (online only).

Search results were imported into the Covidence platform, and the initial phase involved screening the article titles and abstracts. Publications meeting the inclusion criteria progressed to detailed evaluation in the full-text phase and then underwent extraction. This search strategy aims to establish a standard methodology useful for addressing other research gaps.

**Quality assessment.** Two independent reviewers (C.L., K.K.) screened the included articles, conflicts were resolved by a third reviewer (D.B.) reaching consensus, and the Covidence quality assessment tool was used to eliminate biases and remain objective.

### NASA HRP gaps that requires vascular surgery/medicine expertise include

- **ExMC 4.07:** Limited wound care capability to improve healing following wound closure.
- **ExMC 4.24:** Lack of knowledge regarding treatment of conditions on the Exploration Medical Condition List in remote, resource-poor environments.
- **Med07:** Lack of capability to comprehensively process medically relevant information to support medical operations during exploration missions.
- **Med12:** Lack of capability to mitigate select medical conditions.
- **Medical-101:** Need to characterize medical conditions that can occur during exploration missions and their relevant associated end states, management options, and the capabilities necessary to manage them (what can happen, how bad could it be, what can we do to improve it?).
- **Medical-501:** Need to develop integrated exploration medical system models for the Moon and Mars.

## RESULTS

Keyword searches identified 4118 articles, with 46 articles added externally to provide background information for an explanation of terrestrial physiology. After excluding 984 duplicates, first-line review proceeded for 3180 studies, with 2561 articles excluded. The remaining 619 articles were full-text reviewed, and 125 underwent data extraction (Fig 1.).

A summary of study characteristics of the extracted papers is available in Table I.

## DISCUSSION

Wound healing is a complex process adapted to Earth's one-gravity environment. In altered gravity settings, both minor injuries and major trauma can pose significant challenges. Limited spaceflight resources and expertise heighten the critical importance of wound care for astronaut health, mission success, and sustainability of space exploration. Although prevention remains a countermeasure cornerstone, addressing potential injuries and efficient wound healing is vital to ensure astronaut well-being and mission success.

## PHYSIOLOGICAL WOUND HEALING IN THE TERRESTRIAL ENVIRONMENT

A wound is defined as any tissue injury, including cuts, scrapes, burns, punctures, or sores that may or may not interrupt skin integrity. The mechanisms underlying wound healing are complex, and involve a dynamic sequence of overlapping phases: hemostasis, inflammation, proliferation, and maturation. This multi-step cascade is essential for restoring tissue integrity and function.[21]

Hemostasis prevents excessive bleeding through vasoconstriction and platelet activation, triggered by extravascular collagen detected via integrin receptors. Activated platelets release growth factors and glycoproteins, forming a platelet plug. Liver-derived clotting factors create a stabilizing fibrin clot. Platelet granules release growth factors (eg, platelet-derived growth factor [PDGF], transforming growth factor-β [TGF-β], vascular endothelial growth

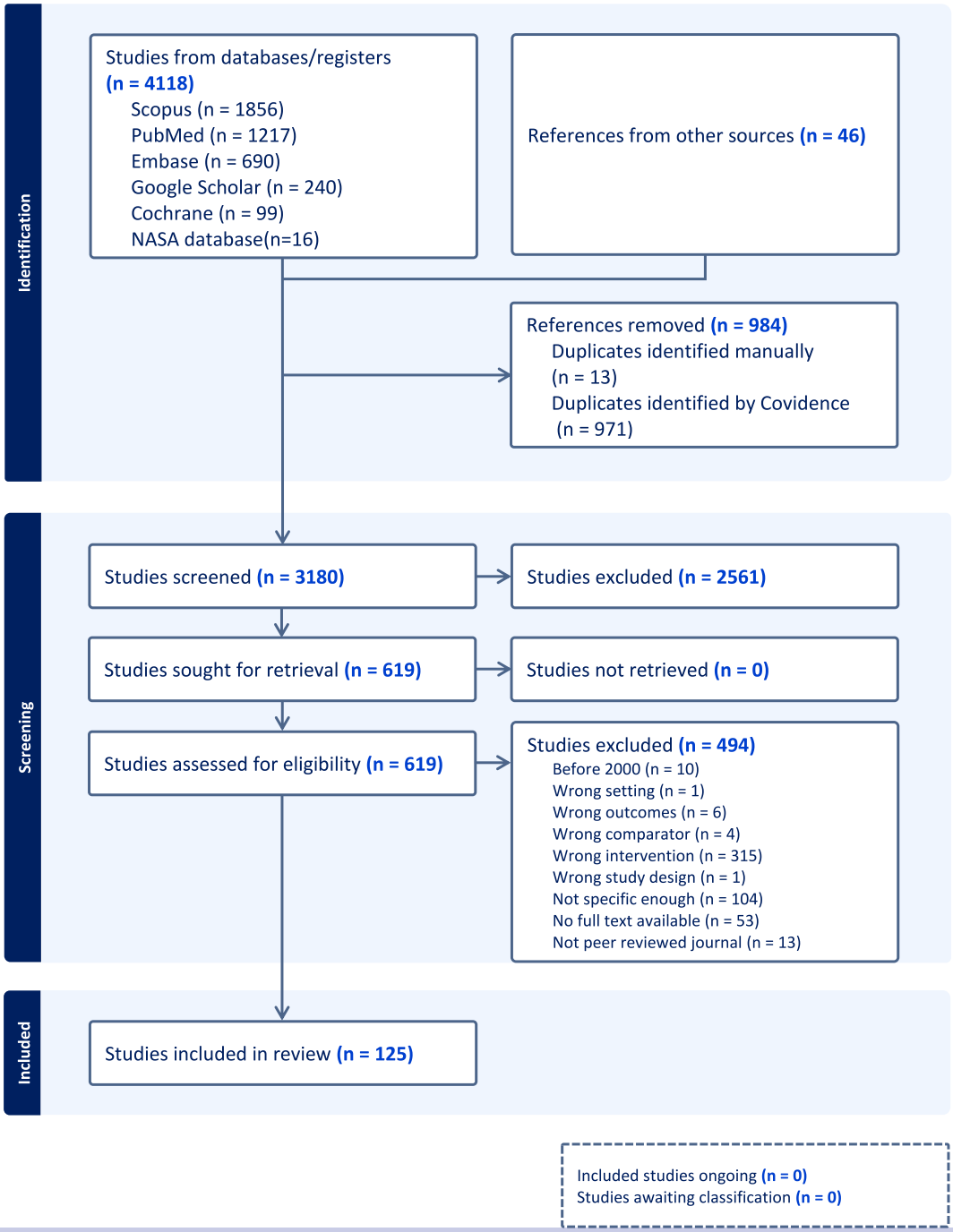



**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the systematic review process undertaken for this study.

factor [VEGF]), recruiting fibroblasts, neutrophils, and monocytes to initiate extracellular matrix formation and inflammation, essential for wound healing.

Inflammation, starting within 24 hours and lasting up to 2 weeks (or longer in chronic wounds), involves histamine and amines release from mast cells, causing redness, swelling, and pain. Neutrophils and macrophages bind to the endothelium via selectins to clear bacteria and debris. Cytokines (eg, interleukin [IL]-1, IL-6, tumor necrosis factor-α [TNF-α]) amplify inflammation, whereas growth factors (eg, PDGF, TGF-β, insulin-like growth factor 1 [IGF-1], fibroblast growth factor [FGF]) and chemokines recruit and regulate immune cells to maintain cleanliness and support healing. Macrophages transition the wound to the proliferative phase by activating fibroblasts. Lymphocytes like T-cells release IGF-1, recruiting keratinocytes to initiate epithelialization. B-cells also arrive, playing a crucial but unclear role in wound healing.[1,21,22]

**Table I.** Summary of extracted references categorized by their main findings and relevance for addressing National Aeronautics and Space Administration (*NASA*) Human Research Program (HRP) gaps

| Category | Number of extractions | Main finding | Gap | Citation number(s) |
|---|---|---|---|---|
| General (health in space) | 6 | Health in space is altered due to factors such as radiation, microgravity, and isolation. Novel ways of approaching medicine and a better understanding of human space physiology will help anticipate and treat complications. | Med07, Med12 Medical-501 | 2-7 |
| Wound healing in space | 16 | Isolation, stress, radiation, microgravity, and nutritional deficits all play a role in negatively impacting wound healing. The space environment can cause chronic inflammation and a delayed proliferation phase. | ExMC 4.07, Med12 Medical-501 | 2,5,7-20 |
| Wound healing on Earth | 14 | Wound healing follows an overlapping process of hemostasis, inflammation, proliferation, and maturation. | ExMC 4.07, Med12 Medical-501 | 1,21-33 |
| Pharmacology | 11 | Space conditions can reduce shelf life, bioavailability, and potency of medications. Storage is a complex issue. However, many drugs can and are still used with effective results. | Med07 ExMC 4.07 Medical-101 Medical-501 | 34-44 |
| Genetics | 7 | It will be important to increase screening for individual genetic variations that will predispose individuals to health problems in space, or provide opportunities for resilience during more selective missions. | Med07 Med12 Medical-501 | 16,18,28,29,45-47 |
| Immune response | 19 | Conditions during spaceflight such as radiation, stress, and microgravity disrupt fibroblast function, cytokine production, macrophage transition from M1-M2 states, and decrease activity of leukocytes. | Med07, Medical-101 Medical-501 | 1,22,24,46-61 |
| Microbiome | 3 | Although the exact mechanism is still unknown, the space environment creates microbiome changes. Altered skin pH, increased sebum due to lack of effective bathing, or contamination from surroundings, and epidermal thinning, are potential causes. These changes put astronauts at a higher risk of atopic or sebaceous dermatitis, and skin infections from opportunistic pathogens. | Med07, Medical-101 Medical-501 | 4,62,63 |
| Infections | 3 | Due to alterations in the immune response, astronauts are more at risk for reactivation of latent viruses such as herpes simplex, varicella zoster and Epstein Barr virus, as well as increased viral shedding. | Med07, Medical-101 Medical-501 | 5,48,49 |

**Table I.** Continued.

| Category | Number of extractions | Main finding | Gap | Citation number(s) |
|---|---|---|---|---|
| Radiation | 9 | Astronauts are exposed to space radiation, which can impair wound healing by causing DNA damage, increasing ROS, and promoting inflammation. | Med07, Medical-101 Medical-501 | 18,36,46,64-69 |
| Microgravity | 10 | Microgravity alters fibroblast migration and keratinocytes resulting in weakened scar formation and wound-healing. Microgravity also decreases total blood volume and circulating plasma, and redistributes body fluids towards the head. The lymphatic system is also affected. Microgravity promotes insulin resistance and dysregulates cellular apoptosis. | Med07, Medical-101 Medical-501 | 11-14,25,50,67,70-72 |
| VAC | 3 | VAC therapy effectively improves wound-healing in combat wounds, open fractures, and open surgical wounds. Its ability to maintain a sealed environment and promote healing makes it a promising technology. However, more analog research is needed as it has not been used in spaceflight to date. Limitations will include lack of expertise, maintaining a seal (yet to be proven in microgravity), transfer of fluid from dressing to container, and achieving adequate strength of negative pressure. | Med07 ExMC 4.07 Medical-101 Medical-501 | 73-75 |
| Nutrition | 9 | Optimal nutrition is difficult to maintain during space missions. Factors such as radiation and microgravity can impact vitamin stability, as well as disrupt the microbiome. The resultant nutritional deficiencies negatively impact essential pathways of wound healing. | Med07 ExMC 4.07 Medical-101 Medical-501 | 44,76-83 |
| Dressings | 10 | Traditional wound dressings may not be optimal for a weightless environment. Emerging technologies such as hydrogels, or electroceutical wound dressings may provide potential solutions. | Med07 ExMC 4.07 Medical-101 Medical-501 | 32,84-92 |
| AI | 2 | The possibility of AI trained in medical diagnostics and treatment plans provides a potential tool to be used to decrease reliance on Earth-based health care during long-duration missions. | Med07 ExMC 4.07 Medical-101 Medical-501 | 93,94 |

*(Continued on next page)*

**Table I.** Continued.

| Category | Number of extractions | Main finding | Gap | Citation number(s) |
|---|---|---|---|---|
| Bioprinting | 6 | Bioprinting is a promising technology that enables tissues to be manufactured in space. It can be used to treat astronaut wounds with hydrogels or personalized grafts and allows for medical self-sufficiency on long-duration missions. | Med07<br>ExMC 4.07<br>Medical-101<br>Medical-501 | 95-100 |
| Innovative therapies: plants, MPFF, nutraceutical, MSCs, PRP | 14 | MPFFs have antioxidant and anti-inflammatory properties, long shelf-life, and low storage requirements, which makes them a potential modality for treating wounds in space. Plants that have antioxidant properties also have promise for radioprotection. Similar benefits arise from food-based countermeasures. MSCs and PRP are seen as another possible solution to the wound-healing delays seen in space, because of their tissue repair abilities. | Med07<br>ExMC 4.07<br>Medical-101<br>Medical-501 | 5,45,101-112 |
| Surgery | 6 | Various surgical procedures can be adapted to a space environment with assistance from AI and telehealth protocols. Fluid dynamics are different, but blood can be controlled with hemostatic dressings, tourniquets, and tranexamic acid. Anesthesia and critical care are areas of active research. | Med07<br>ExMC 4.07<br>Medical-501 | 93,94,113-116 |
| Light- or sound-based therapies | 5 | Low-intensity ultrasound and photodiode therapies have been tested and shown by NASA to stimulate wound-healing mechanisms. | Med07<br>ExMC 4.07<br>Medical-101<br>Medical-501 | 43,117-120 |

*AI,* Artificial intelligence; *MPFFs,* micronized purified flavonoid fractions; *MSCs,* mesenchymal stem cells; *PRP,* platelet-rich plasma; *VAC,* vacuum-assisted wound closure.

Proliferation (3-21 days post-injury) is driven by fibroblasts migrating to the wound site using proteases like zinc-dependent matrix metalloproteinases (MMPs). They attach to matrix proteins (fibronectin, vitronectin, fibrin) and move toward chemotactic growth factors, producing granulation tissue, collagen (primarily type III), and proteoglycans essential for healing. Collagen synthesis relies on vitamin C for stability. The low oxygen, pH, and high lactate levels stimulate angiogenesis[23] via factors like VEGF and TGF-β, which further activate fibroblasts and keratinocytes.[8] Granulation tissue, rich in vessels, macrophages, and collagen, forms a scaffold for contraction (via myofibroblasts) and epithelialization (via keratinocytes).[70] Surface cells migrate, proliferate, and reform the skin barrier, completing this stage.

The final stage (remodeling) transforms granulation tissue into scar tissue, involving capillary regression, apoptosis, reactive oxygen species (ROS) modulation, reduced metabolic activity, and gradual restoration of tensile strength. Initially, tensile strength reaches about 25% of normal, potentially increasing to 80% as collagen fibers reorganize and mature. Apoptosis equilibrates cell growth and death throughout all stages.[9]

## IMPACT OF THE SPACE ENVIRONMENT ON WOUND HEALING

The space environment can disrupt wound healing through altered skin flora, variable inflammatory factor production, and prolonged exposure to ionizing radiation, which may cause DNA damage, oxidative stress, cell dysfunction, abnormal collagen arrangement, and microvascular injury. Stress and hormonal changes also affect skin cell regeneration. Microgravity impairs macrophage functions, shifting from dermal homeostasis (M2)

to chronic inflammation (M1),[24] impacting immune responses, inflammation, tissue regeneration, and platelet activity[10]—all vital for hemostasis.

Scar tissue structure is altered in weightlessness, as gravity influences collagen fiber remodeling. The wound-healing cascade may be hindered by excessive inflammation, leading to fibrosis and delayed re-epithelialization, or insufficient inflammation, leaving the wound open, arrested in the hemostatic phase.[2] This balance is regulated by immunologic and physiologic processes. Additionally, the skin microbiome interacts with the spacecraft microbiome in closed environments, influencing wound healing. Although surgical wounds often heal easily on Earth, delayed healing and postoperative complications could impact recovery during long-duration spaceflight.

**Effects of microgravity on wound healing.** Skin, a mechano-sensitive tissue, undergoes significant changes under conditions of weightlessness (also known as 'microgravity'). Numerous studies have explored the altered cellular characteristics of skin in microgravity, with several studies focusing on the implications for wound healing during spaceflight. Researchers have utilized simulated microgravity environments, with various analog models providing critical insights into the impact of microgravity on skin and wound healing, advancing space medicine knowledge.[3]

One cell type affected by microgravity is fibroblasts, which actively remodel connective tissue. They have a pivotal role in the process of wound-healing by synthesizing collagen, maintaining cytoskeleton architecture, and producing extracellular matrix (ECM) components like laminin and fibronectin.[70] Fibroblast proliferation is modulated by key signaling molecules, including IL-1, IL-6, TNF-α, TGF-β, CXCL12, and PDGF. TGF-β1 is particularly important, spearheading the differentiation of fibroblasts into myofibroblasts.[11] These are contractile cells with special stress fibers called smooth muscle actin. This is the process of wound contraction: as the tissue heals, the edges of the wound gradually move closer, reducing the size of the wound.[12] This sensitive cascade might be interrupted by immune alterations and microgravity during spaceflight.[13,14,71] Studies simulating alterated gravity reported changes in fibroblast migration and scar tissue and keloid formation, leading to a delayed wound-healing process. The space environment is likely to delay fibroblast migration and result in weakened scar tissue formation.[14,15]

A research study has identified at least 32 mechanosensitive genes in keratinocytes, cells in the outer skin layer that proliferate and close wounds. Notably, 11 genes involved in stress response pathways were downregulated in response to the effects of weightlessness.[3] Under simulated microgravity conditions, skin models have shown a significant reduction in keratinocyte layers.[4] Furthermore, keratinocytes exhibited an accelerated transition to migratory and invasive behavior, a process termed epithelial-mesenchymal transition. This transition is closely linked to re-epithelialization, a critical component of wound healing. However, microgravity impairs fibroblast orientation and adhesion, thus disrupting cell alignment. This disrupts the keratinocyte-fibroblast interaction critical for proper tissue repair, homeostasis, inflammation, proliferation, and remodeling.[70] These findings highlight the cellular adaptations of skin cells to microgravity and the implications for wound healing in space environments.[3]

Microgravity can decrease total circulating plasma and blood volume within the first 24 hours, reducing overall tissue perfusion and oxygenation. Lack of oxygen is especially detrimental for wound healing. Oxygen is necessary for generation of free oxygen radicals that contribute towards cell proliferation, collagen synthesis, and bacterial defense.[25] Another notable physiologic impact of microgravity on wound healing is insulin resistance, observed in dysmetabolic conditions like metabolic syndrome or type 2 diabetes mellitus.[16] The pathophysiology is driven by a hypoactive state with reduced muscle activity, altered hormone signalling, inflammation, and fluid shifts. Ultimately, the apoptotic balance[17] is further dysregulated, leading to non-healing wounds as observed in diabetic ulcers, with implications for each wound-healing stage.[9]

Finally, true weightlessness causes a redistribution of bodily fluids. Fluid from the lower body shifts headward, leading to a 2-liter shift from the lower extremities.[26,45] This is a well-described phenomenon. Renewed efforts for countermeasure development, focused upon dermal and central lymphatic conducting system analog and weightlessness research, may offer enhanced therapeutics and restoration of nominal lymphatic function, potentially positively impacting the deleterious effects of spaceflight-associated neuro-ocular syndrome (SANS),[5] immune dysregulation, and chronic inflammation.[72]

**Effects of space radiation on wound-healing mechanisms.** Space radiation includes both ionizing and non-ionizing radiation. The key types of ionizing radiation include galactic cosmic radiation (GCR), solar particle events (SPEs), and particles trapped within the Van Allen radiation belts. Galactic and solar cosmic rays differ primarily in their particle energy levels. In interplanetary space, during minimal solar activity periods, the equivalent annual dose rate at a spacecraft's surface measures around 80 to 100 centiSieverts (cSv).

Beyond Low Earth Orbit (LEO), astronauts face ionizing radiation primarily from protons, heavy nuclei, and smaller fractions of electrons and positrons. Radiation sources include SPEs, GCR, and secondary radiation within spacecraft. SPEs can deliver high-energy protons (>30 MeV) with fluences over $10^9$ protons/cm$^2$, causing

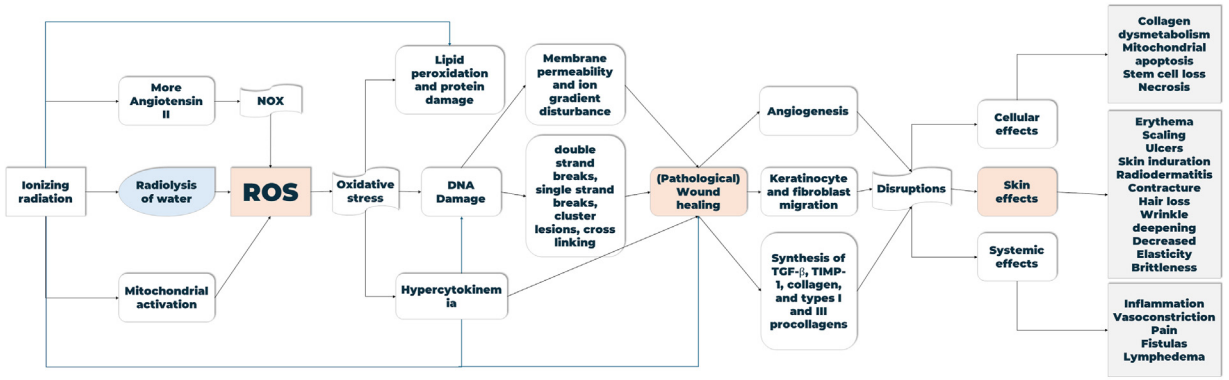



**Fig 2.** Schematic representation of how space radiation impacts skin regeneration and impairs wound-healing at the molecular level. *ROS*, Reactive oxygen species; *TGF-β*, transforming growth factor β; *TIMP*, tissue inhibitors of metalloproteinase.

spacecraft radiation doses of up to 100 mGy/hour, or 500 mGy/hour during extravehicular activities. SPE radiation, which mainly affects superficial tissues, can lead to skin lesions, and blood and immunological impairments.[3] GCR consists of high-speed nuclei from beyond the solar system, with hydrogen (87%) and helium (12%) as the primary components, and trace elements of lithium to nickel. The most concerning are HZE particles (H is "High", Z is "atomic number", and E is "energy"). Iron (Z = 26), can cause severe DNA damage difficult to repair. No current shielding blocks these particles effectively, presenting a significant carcinogenic risk for astronauts. Electrons and positrons are less concerning due to effective shielding. There is no prior data on how space radiation impacts wound-healing, although clinical observations from patients with cancer undergoing radiation therapy (RT) is useful for preventative strategies. RT patients often experience symptoms including skin atrophy, fibrosis, desquamation, epithelial ulceration, and fistula formation. Frequently wound healing is impaired, leading to delayed recovery and additional reconstructive procedures.

On a molecular level, ionizing radiation affects wound healing by directly creating double-strand breaks, single-strand breaks, cluster lesions, and DNA cross-linking. It also indirectly generates free oxygen radicals through radiolysis of water within the cellular nucleus and cytoplasm.[64] Mitochondria and/or cytosolic enzymes may be affected by radiation-induced ROS production, leading to lipid, protein, and genetic material damage.[101] This damage triggers stromal cell dysfunction, abnormal collagen deposition, and microvascular depletion, collectively hindering and delaying the wound-healing process.[65] Following irradiation, cells release damage-associated molecular pattern molecules, which activate the innate and adaptive immune systems, amplifying cytotoxic responses. For instance, radiation-induced inflammation triggers the release of cytokines by damaged endothelial cells and skin, attracting neutrophils to the injury site.[66] Neutrophils release TNFα, IL-6, and IL-1, amplifying inflammation and producing further harmful ROS. Monocytes, recruited to the wound, differentiate into macrophages and secrete PDGF, promoting angiogenesis and attracting fibroblasts. Alongside endothelial and epithelial cells, macrophages release TGF-β, a pro-fibrotic factor that binds to its receptor and activates Smads (small mothers against decapentaplegic), driving the transcription of pro-fibrotic genes. As detailed above, TGF-β stimulates the differentiation of fibroblasts into myofibroblasts, and thus the secretion of excessive extracellular matrix proteins like collagen, fibronectin, and proteoglycans. TGF-β can also inhibit MMPs, which normally break down these proteins, and can enhance expression of tissue inhibitors of metalloproteinases (TIMPs), which break down MMPs.[27]

The balance is therefore skewed in favor of abnormal tissue formation and increased stiffness. These fibrotic pathways may endure for years after the original insult.[34] This substantially increases the risk of chronic wounds and malignancy development over time. Radiation damage, combined with microgravity, may lead to dermal atrophy and metabolic alterations by similar mechanisms.[6] Termed 'radiodermatitis,' the final effect is pathologic skin thickening and scarring. Interestingly, modeled microgravity was found to not affect DNA repair genes for base and nucleotide excision repair; cellular alteration might be due rather to error-prone rejoining and damaged protein signaling.[46] An overview of radiation-induced cellular damage is provided below, adapted from Booth 2024[64] and Moulder 2022[34] in Fig 2.

**Impact of altered immune responses in the space environment on wound healing.** Recent studies[5,48] have shown that, during a 6-month orbital spaceflight, the human immune system experiences dysregulation and reactivation of latent herpes viruses. Some aspects of adaptive immunity are disrupted, whereas certain components of innate immunity are heightened. Although

**Table II.** Overview of significant changes in the immune system observed during spaceflight and spaceflight analogs, including head-down tilt bed rest, isolation, and parabolic flight

| Biologic | Increased | Decreased | Wound-healing implication |
|---|---|---|---|
| Cytokines | IL-1β, IL-18 (from B-cells)<br>IL12-p406, CXCL-8/IL-8, and CXCL-5<br>CCL-2, IL-10, CRP, IL-6 | IFN-γ, IL-17 (from T-cells)<br>TNF-α | Dysregulated inflammation in favor of hypo-inflammatory state |
| Macrophages<br>M1: Metabolize arginine at the wound into NO. Produce TNF-α, IL-1, and IL-6. Pro-nflammatory.<br>M2: Metabolize arginine at the wound to ornithine. Produce TGF-β and IL10. Produce collagen, anti-inflammatory, and angiogenic. | Anti-inflammatory activity (M2) | Number and function | Decrease in inflammation. Increase in the M2 pathway and increased activation of fibroblasts and the proliferative pathway. |
| Dendritic cells | Increased | | Increase in inflammatory cytokine response, expedited re-epithelialization. This was possibly due to autoreactivity with normal microflora. (See section on microbiome.) |
| Leukocytes | | Total leukocyte count | Less infection-fighting ability |
| Lymphocytes | Memory T- and B-cells, regulatory T-cells<br>CD4 | Total lymphocyte count<br>CD3, CD8, CD25 | Impaired keratinocyte stimulation via IGF1 |
| Protein kinase C | Altered | Altered | Dysregulated inflammation |
| Malondialdehyde (MDA) | Increased | | Marker for oxidative stress from decomposition of fatty acids. This indicates more ROS. |
| Natural killer cells | | Decreased | Less infection-fighting ability |
| Ratios:<br>• NLR<br>• GLR<br>• PLR | Elevated: NLR, GLR<br>Gradual elevation: PLR | | Predictive biomarkers for various diseases and more reliable than a single immune marker, which may be modulated by cortisol. Increased NLR induces inflammation. enzyme release, and ROS. Neutrophils also release MMP in secondary secretory granules; this would lead to delayed healing.<br>PLR increase suggests increased hematopoiesis and thrombopoiesis, approaching levels observed for autoimmune disorders. |
| Cortisol | Increased | | Anti-inflammatory effects |
| Hypersensitivity | | Delay, eosinophils, basophils, mast cells | Less endothelial response, less allergic response. |

*(Continued on next page)*

**Table II.** Continued.

| Biologic | Increased | Decreased | Wound-healing implication |
|---|---|---|---|
| Viral reactivation | Increased. Most common: HHV, EBV, CMV, VZV | | Susceptibility to chronic wounds. Over time, desensitization of cortisol receptors leads to a rebound immunogenic state. From hypo- to hyper-inflammation, this encourages a fibrotic wound phenotype. |

*CCL-2,* Chemokine (C-C motif) ligand 2; *CMV,* cytomegalovirus; *CRP,* C-reactive protein; *EBV,* Epstein-Barr virus; *GLR,* glucose to lymphocytes ratio; *HHV,* human herpes virus; *IFN,* interferon; *IGF-1,* insulin-like growth factor 1; *IL,* interleukin; *MMP,* matrix metalloproteinase; *NLR,* neutrophils to lymphocytes ratio; *PLR,* platelets to lymphocytes ratio; *ROS,* reactive oxygen species; *TGF-β,* transforming growth factor β; *TNF-α,* tumor necrosis factor α; *VZV,* varicella-zoster virus.

reduced immune cell function can lead to increased susceptibility to infection, overactive immune responses can also result in conditions like allergies, asthma, eczema, and autoimmune disorders. Additionally, the interaction between adaptive and innate immunity seems to be altered.[49] A 2024 case of zoster reactivation in an astronaut on the International Space Station (ISS) for 6 months identified reduced T-cell function, cytokine imbalance, and increased stress hormones as a prodrome prior to onset of clinical symptoms. NASA's Twin Study, comparing genetically identical twin astronauts (ISS vs ground-based) showed that, over 340 days of spaceflight, significant immune-related pathway alterations were induced, affecting both the adaptive and innate immune systems. Notably, substantial changes in cytokine levels were observed before, during, and after spaceflight. Although data can differ between analog and spaceflight models, overall data identifies a decrease in various pro-inflammatory cytokines and chemokines, an impairment in the function of macrophages, and lowered activity of leukocytes and lymphocytes.[50] These changes can be due directly to spaceflight conditions, or secondarily due to increased cortisol secretion. Overall, immune blunting has evidence-based effects on the entire wound-healing cascade. Table II summarizes major immunological changes during spaceflight and spaceflight analogs (head-down tilt bed rest, isolation, and parabolic flight).[24,28,47-57,67]

**Influence of altered stress responses on wound healing.** The continuous isolation and interruption of daily sleep cycles and circadian rhythms (16 sunrises and sunsets each 24 hours for ISS crew) have significant associated psychological stressors. These factors play a pivotal role in shaping individual stress responses. Stress hormones, including cortisol and adrenaline, influence multiple wound-healing pathways. Earth-based space-simulation studies using *in vitro* models highlight the impact of chronic stress on astronauts: when fibroblasts were exposed to both cortisol and 1 Gy of iron ions, a significant reduced expression of IL-1RA, a regulator of pro-inflammatory cytokines, was observed compared with control groups exposed to 0 Gy. This finding underscores the vulnerability of fibroblast function, a critical component of wound-healing, under spaceflight conditions.[18,67] One possible reconciliation of the variable inflammatory observations of the immune response is that chronic stress can lead to cortisol receptor resistance. Over time, with less cortisol potency, a hypo-inflammatory state can rebound, becoming hyper-inflammatory and immunogenic.[58,59] Individuals in the 520-day Mars isolation experiment experienced atherosclerosis, endothelial dysfunction, oxidative stress, and increased homocysteine and plasminogen activator inhibitor-1. This creates a prothrombogenic state, contributing to aberrant mobilization of wound-healing factors during hemostasis.[7,60]

**Skin microbiome and wound healing in space.** The skin microbiome, influenced by both endogenous and exogenous factors, has been the subject of important ISS research. Astronauts face various stressors that could modify their microbiome composition, impacting their health and wound healing, and inducing skin changes. The skin hosts a diverse range of microorganisms essential for maintaining skin health, including bacteria, fungi, and viruses. In a confined spacecraft, the microbiome may change, with microgravity potentially enhancing the pathogenicity of certain microbial communities, further complicating wound healing. Table III summarizes spaceflight microbiome changes.[4,62,63]

**Nutrition and wound healing in space.** Optimal calorie and nutritional intake is still a critical challenge during long-duration space missions. Alterations in smell and taste due to fluid shifts, menu fatigue, changes in gut microbiome, and isolation exacerbate the issue. In space, zinc and copper are excessively excreted through feces, potentially impairing wound-healing. Zinc is critical for the functionality of TIMPs, being zinc-dependent proteins, whereas copper plays an essential role in angiogenesis, and supports the later wound repair stages.[76]

**Table III.** Composition of the normal skin microbiome and a comparison of common skin infections on Earth and in space environments

| Microbe | Changes in space/analog | Associated conditions |
|---|---|---|
| Fungal species | Increased | Malassezia spp. correlated with seborrheic dermatitis, pityriasis versicolor, folliculitis, and exacerbation of atopic dermatitis |
| Malassezia spp. (especially M. restricta) | | |
| Cyberlindnera jadinii | | |
| Candida boidnii | | |
| Firmicutes | Increased | Primary or opportunistic infection |
| Staphylococcus spp. | | |
| Streptococcal spp. | | |
| Actinobacteria | Increased | Propionibacterium correlated with antimicrobial peptides, and promotion of inflammation. |
| Propionibacterium spp. | | |
| Corynebacterium spp. | | |
| Gamma and beta proteobacteria | Reduced | Lack of acinetobacter correlates with increased inflammation |
| Pseudomonas | | |
| Moraxella | | |
| Acinetobacter | | |

Care is needed to ensure that space foods, typically bagged, processed, or dehydrated, are not overly high in sodium and iron. Excessive sodium intake increases calcium excretion, heightening kidney stone risk, whereas iron overload—exacerbated by space-induced red blood cell changes leading to adaptive anemia and bone loss—can cause multi-system damage.[5,77] Vitamins D, E, K, potassium, calcium, polyphenols, and polyunsaturated fatty acid concentrations have been noted as insufficient in meeting astronaut daily requirements.[78] Vitamins B1 and C were also found to be the most unstable. These deficiencies worsen with a general reduction in quality due to long-term storage, complex delivery systems, and extended exposure to space hazards.[76] Fibroblasts rely on Vitamin C during the proliferation phase for effective collagen synthesis, making adequate vitamin intake essential for optimal wound-healing.[70] Amino acids and fats are also indispensable for performance and skin health.[78] Antarctica has served as a space analog for nutrient development, especially the need for Vitamin D supplementation.[79]

Altered gravity has also been associated with immune suppression and changes in the gastrointestinal-skin axis. These changes affect Vitamin D metabolism, modify the gene expression of resident microbes (influencing biofilm formation), and enhance the virulence of potential pathogens. Resultant hypocalcemia can impair hemostasis, keratinocyte proliferation, and collagen remodeling.[30] Adequate Vitamin D and calcium are integral for bone homeostasis, whereas general hydration is important for skin elasticity and waste removal. Balanced and individualized nutrition offers potential for offsetting space hazards, like radiation, and glucose intolerance. Nutraceutical countermeasures merit their own discussion, but can include radio-protective foods like curcumin, intermittent fasting, flavonoids, mushrooms, and omega-3 fatty acids,[80] or microgravity-induced atrophy-countering strategies like plant proteins,[102] reduced sodium and probiotics.[78] 'Superfoods' like spirulina contain various macronutrients, vitamins, carbohydrates, lipids, amino acids, phenolic antioxidants, phytonutrients, and minerals for combined nutritional benefits and universal spaceflight hazard protection.[81,82] Spirulina, like other nutritional supplements, can have an unappealing taste and smell despite its high nutritional value and biogenerative properties. Food scientists, engineering botanists, and biochemistry laboratories continue to work on creating food-sourcing options that maintain systemic and cellular health while being palatable and regenerative of edible biomass in extreme environments.

## SURGICAL IMPLICATIONS AND PREVENTIVE STRATEGIES

### Pre-mission: astronaut candidate screening

Individuals with different genetic profiles will respond differently during wound healing, emphasizing the importance of thorough pre-flight examination. Genetic and epigenetic changes in wound-healing are listed in Table IV.[29,61] The purpose of screening is not to exclude spaceflight aspirants, but to anticipate and optimize personalized therapy and prescriptive health care. With

**Table IV.** Genetic and epigenetic factors that may influence wound-healing responses in astronauts during space missions

| Category | Biomarker | Implication for wound healing |
|---|---|---|
| Immune | Low eosinophils, low IgE<br>Higher periostin<br>Hemostatic and chemokine genes like CXCLs, which attract immune cells<br>TLRs<br>T-cell, B-cell, and neutrophil function, TNF-α, INF-γ, IL-1, IL-6, and IL-8<br>P-selectin, E-selectin and intracellular and vascular adhesion molecules ICAM-1 and VCAM-1 | Reduced likelihood of skin hypersensitivity and allergic reactions<br>Periostin is expressed in fibroblasts: improved ECM deposition, MSC proliferation, potential fibrosis<br>Appropriate localization of neutrophils and other immune cells in inflammatory response of wound healing<br>Appropriately identify DAMPs after injury<br>Appropriate inflammatory phase<br>Appropriate recruitment of leukocytes for inflammatory phase |
| Growth factors | VEGF, PDGF, FGF, IGF, KGF, and TGF-β (SMAD4 receptors)<br>iNOS regulated by HIF1α | Help with proliferation and remodeling<br>Too much can be associated with scar formation<br>Appropriate revascularization through VEGF |
| Skin | Type I and III collagen genes (COL1A1 and COL3A1)<br>TIMPs and MMPs | Protection against poorly healing and scarring wounds<br>Appropriate balance between proteinogenic and proteolytic processes. Could be adapted based on anticipated exposures eg more MMP expression if radiation-induced fibrosis is anticipated |
| Cardio-vascular | Normal levels of D-dimer, prothrombin time, partial thromboplastin time, platelet count, and fibrinogen. absence of Factor V Leiden mutation, absence of prothrombin G20210 A mutation<br>Cardiac adriamycin-responsive protein (CARP) | Lower risk of internal jugular vein thrombosis<br>Controlled hemostatic response<br>Less chance of hemorrhage<br>Less endothelial dysfunction<br>Involved in neovascularization and endothelial migration |
| Lymph | Less PIK3CA expression<br>VEGFR, FOXC2, GATA2, KRAS, MRAS, ARAF absence of mutations | Reduced change of lymphatic malformations and buffering of microgravity-induced fluid shifts 2<br>Normal expression protects against lymph pathologies. Alterations can also lead to lymphatic malformations and more severe microgravity-induced fluid drainage problems. |
| Skin | Type I and III collagen genes (COL1A1 and COL3A1)<br>TIMPs and MMPs<br>Good hydration, low transepidermal water loss, slightly acidic pH, good elasticity | Protection against poorly healing and scarring wounds<br>Appropriate balance between proteinogenic and proteolytic processes.<br>Less susceptibility to microgravity-induced skin damage |
| Cellular | ROS genes: SOD1, NOX, and catalase. | Protection, immune response, and balance between chronic wounds or fibrosis |
| Epigenetics | Applicable to any gene, including those listed above: methylation, histone modification, regulation of noncoding RNAs, long noncoding RNA, and circular RNA. | Screening for impaired wound-healing becomes increasingly complex when considering that the unpredictable milieu of spaceflight hazards can involve opposing incentives. For example, radiation will lead to lower MMP expression and fibrosis, which would suggest screening for high MMPs as a counterbalance. However, in the absence of radiation, high MMPs would lead to poor wound remodeling and healing. |

**Table IV.** Continued.

| Category | Biomarker | Implication for wound healing |
|---|---|---|
| Gender | Estrogen, testosterone, sex hormones | Women have more estrogen, which is beneficial for wound-healing. Women also demonstrate a stronger immune response via immunoglobulin production, cell mediated responses, and less hematological malignancies. However, women are more prone to autoimmune disorders.<br>Men have testosterone which may hinder healing through excess inflammation and ECM deposition.<br>However in space, hormone levels decrease for both sexes while T-cell induced IGF-1 may increase, potentially leading to uncontrolled epithelialization. |

*CARP,* Cardiac adriamycinresponsive protein; *CXCL,* chemokine C-X-C motif ligand; *DAMP,* damage associated molecular pattern; *ECM,* extracellular matrix; *FGF,* fibroblast growth factor; *FOXC2,* forkhead box C2; *GATA2,* GATA-binding protein 2; *HIF1α,* hypoxia inducible factor 1 α; *ICAM-1,* intercellular adhesion molecule 1; *IFN,* interferon; *IGF,* insulin-like growth factor; *IL,* interleukin; *iNOS,* inducible nitric oxide synthase; *KGF,* keratinocyte growth factor; *KRAS,* Kirsten rat sarcoma viral oncogene homolog; *MMP,* matrix metalloproteinase; *MRAS,* muscle RAS oncogene homolog; *MSC,* mesenchymal stem cell; *NOX,* NADPH oxidase; *PDGF,* platelet-derived growth factor; *ROS,* reactive oxygen species; *SOD1,* superoxide dismutase; *TGF-β,* transforming growth factor β; *TIMP,* tissue inhibitor of metalloproteinase; *TLR,* toll-like receptor; *TNF-α,* tumor necrosis factor α; *VCAM-1,* vascular cell adhesion molecule 1; *VEGF,* vascular endothelial growth factor; *VEGFR,* vascular endothelial growth factor receptor.
Screening will be performed to maximize precision personalized prescriptive pre/intra/post flight, not to exclude from crew assignments.

a recent case of significant retinal changes in an ISS crew member, the astronaut had two minor and two major alleles diagnosed as relevant for SANS development, and responded well to B vitamin supplements[5,121] (Table IV).

### In-flight

**Clinical evaluation.** Wounds are highly variable in nature, and can be classified based on Lazarus et al (1994), Robson et al (2001), and Chhabra et al (2017). Wounds can be classified based on the causative factors, skin integrity, wound depth, healing potential, and infection risk. Based on an evaluation of relevant literature, suggested classification and reporting standards for wound evaluation during long-duration human spaceflight are summarized in Table V.[84,95]

## WOUND-CARE STRATEGIES, SURGICAL SOLUTIONS, AND COUNTERMEASURES

Wound care in space closely mirrors Earth-based practices, including the removal of dead or infected tissue, foreign material, or debris; the application of biofilm-mitigating products; and the use of homeostatic regenerative supporting dressings.[19,85] Besides exercise, proper nutrition, and physical protective shields, advanced therapeutic wound care strategies may be employed to address unique spaceflight challenges.[19] Prevention strategy planning will remain key for injury avoidance; however, even a single poorly-managed event can potentially endanger the entire crew and mission.[113]

**Micronized purified flavonoid fractions.** Terrestrial data suggests prevention strategies would ideally encompass nutrition and micronutrients. In the field of venous and lymphatic medicine, several studies document using micronized purified flavonoid fractions (MPFFs) to support wound healing, and in one meta-analysis, general veno-lymphatic indications.[31,103]

MPFF is composed of 90% of diosmin and 10% hesperidin fraction (hesperidin, diosmetin, linarin, and isorhoifolin). Its antioxidant, anti-inflammatory, lympho-protective, and vasoprotective properties can mitigate endothelial cell activation, reduce leukocyte adhesion, and bolster capillary resistance and integrity. The American Venous Forum guidelines for the management of chronic venous disorders[26] note that MPFF has robust potential applications in wound healing related to chronic venous disorder mechanisms overlapping with chronic injury and soft tissue edema associated with dermal lymphatic dysfunction (inflammation, leukocyte adherence, TGF-β1 stimulating collagen to increase vascular thickening).[104] Due to the relatively long shelf-life, multiple therapeutic modalities, and low storage requirements of MPFF tablets, they could be a feasible solution for use in space and against space hazards, subject to radiation tolerance testing.[101,103-105]

**Dressing strategies.** Limited resources and anticipated autonomous medical care pose challenges for wound treatment. Weightlessness affects liquid behavior, affecting wound exudate management. Traditional wound dressings may not adhere effectively in space. Specific wound care technologies to tackle spaceflight challenges are under investigation, exploring materials like regenerative or disposable patterned electroceutical wound dressings,[86] hydrogels[87] and 3D-printed structures for spaceflight effectiveness.[106] The focus is on developing innovative tailored solutions tailored, aiming to optimize the healing process and prevent infections.[32,35,84,88,89,107]

**Table V.** Anticipated classification of wound types likely to occur during human deep-space missions

| Classification | Type | Description |
|---|---|---|
| Etiology | Incision | Clean, straight wound caused by a sharp object |
| | Abrasions | Superficial wound where skin is scraped off |
| | Punctures | Sharp object pierces the skin |
| | Burns | Thermal or chemical burns |
| | Avulsion | Tissue is forcibly torn away from its normal position |
| | Contusion | Subcutaneous tissue damage |
| | Hematoma | Localized subcutaneous blood collection |
| Skin integrity | Open wound | Direct exposure to the external environment |
| | Closed wound | Not exposed to the external environment |
| Wound complexity | Simple | Uncomplicated, and has a relatively straightforward healing process |
| | Combined | More significant damage, and may require specialized care and extended treatment |
| Infection risk | Clean | Low infection risk (eg surgical incision) |
| | Clean-contaminated | Higher infection risk |
| | Contaminated and infected | High infection risk/known to be infected |
| Wound onset | Recent | Injury happened <8 hours ago |
| | Old | Injury happened >8 hours ago |
| Healing potential | Acute | Healing within an expected timeframe |
| | Chronic | Prolonged healing that extends beyond the expected duration |
| Wound depth | Partial thickness | Affecting only superficial layers |
| | Full thickness | Involving all layers of the tissue |

**Vacuum-assisted closure.** Vacuum-assisted closure (VAC) therapy is often used to enhance wound healing for patients with complicated healing processes (like thrombosis-induced ulceration or infected, necrotic tissues). It has shown an ability to effectively treat wounds as combat wounds,[73] surgical wounds healing by second intention,[74] and open fractures. VAC can improve wound contraction, reduce wound size and depth, create a sealed environment which preserves moisture, prevent contamination, and remove exudate, which decreases the inflammatory cascade that can impair wound-healing.[75] Although such serious wounds are not anticipated in long-duration spaceflight, considering the impaired wound-healing in space, dysregulated immune response, challenges with sterilization, and difficulty managing exudate in microgravity, VAC is an effective strategy to prevent further complications and promote expedited tissue regeneration. Although not previously used in space, VAC's potential for ease of applicability, wound stabilization, improved wound-healing, coupled with its manageable mass and volume, promote inclusion in wound care strategies for long-duration missions where repatriation for treatment may not be feasible. Further VAC analog testing is required to determine effectiveness and sustainability in an extreme environment.

**Bioprinting, nanoparticles, and stem cells.** Advancements in bioprinting technology, using 3-D printing to produce viable tissues provide potential solutions to improve wound healing in space and regenerative medicine. Warth et al describe the German Space Agency's successful test of a prototype Bioprint First Aid. This handheld device allows the astronaut to apply a square of hydrogel directly to the injury site.[96] Hydrogels consist of crosslinking polymers that hold water mechanically or electrostatically, maintaining a moist environment. In combination with tissue cells, hyaluronic acid, chitosan, or other agents, this promotes wound healing by allowing for a personalized scaffold to use as a graft or deliver antimicrobial properties.[90-92,97] Bioprint First Aid was tested both on Earth and the ISS for its functionality and applicability. Even with minimal training, astronauts could apply the hydrogel to the desired site with relative ease.[96] As space agencies attempt longer-duration missions like Martian transits or establishing lunar bases, the need for self-sufficient treatment will grow. Tissue engineering from bioprinting has shown great potential to meet these new demands, improve wound care, and expand regenerative medicine capabilities.[95,98]

Mesenchymal stem cells (MSCs) are multipotent cells responsible for tissue turnover and longevity, and are

**Table VI.** Pharmacological treatment options for wound care in space

| Medication | Application in space missions | Caveats and considerations |
|---|---|---|
| Melatonin | Therapeutic against radiation. | Variable effects based on lipid solubility. Can also help with space-induced circadian disorders. Low toxicity. |
| Statins | Promotes apoptotic pathways through caspases 3 and 9, thus inhibiting neoplastic cells. Inhibit E-selectins in mesenchymal cells, which cancer cells depend on for metastasis and which neutrophils use for chemotaxis. Anti-inflammatory and anti-fibrotic effects. | Could be related to cardioprotective effects. Can cause myalgia and memory loss; may not be acceptable in space. |
| Amifostine | Gold standard for radio-protective agents, developed to counteract radiation from nuclear detonations. Antioxidant effects from thiol metabolites. Disulfide formation stabilizes DNA, giving more time for DNA repair mechanisms to work. | Hypotension, nausea, vomiting, chills are side effects. |
| 2-Mercaptopropionyl Glycine | Thiol-based antioxidant. Similar to amifostine. | Low toxicity. |
| NSAIDs | COX-2 inhibition decreases radiation effects and scarring through anti-inflammatory mechanisms. | Also analgesic. Can cause gastritis and nephropathy. Decreased renal function in space may increase renal calculi risk. |
| ACE-I and ARBs | Blocks the effects of angiotensin II that are increased by irradiation, and with downstream effects of ROS-mediated skin damage and apoptosis. Alleviate radiation nephropathy. Hematopoietic against radiation. | Anti-inflammatory effects may impact wound-healing. May exacerbate already low blood pressure in space. Worsens edema through bradykinin; fluid shift is already a lymphatic challenge. |
| Metformin | Mitigates ROS-induced damage, decreases insulin resistance, stimulates angiogenesis. Downregulates genes associated with fibrosis via autophagy with AMPK and mTOR. Anti-scarring. | Can exacerbate diabetic ulcers and non-healing wounds because it reduces keratinocyte proliferation. |
| N-acetylcysteine | Thiol-based antioxidant, improves wound-healing, and anastomoses. | Potential to counteract space-induced immunosuppression |
| Calcium channel blockers | Mitigate low density lipoprotein oxidation. Direct protective effect on cells (unknown mechanism) | Mitigates radiation-induced taste aversion as well. Edema risk because of vasodilatory side effects. |
| Beta-adrenergic blockers | Unknown mechanism | Hypotensive side effects can compound neurosensory changes of astronauts. |
| Fingolimod | Inhibits lymphocytic exit from lymph nodes thus reducing inflammation. Increases oligodendrocyte differentiation boosting neuron survival rates in radiation. | Can cause macular edema, which can be devastating with SANS. Can also be immunosuppressive. |
| Vitamins | Most promising are A, C, and E as rescue agents via free radical scavenging or direct involvement in matrix protein production. Vitamin D for calcium wasting and B complex for SANS. | May be less bioavailable through oral administration because of first-pass metabolism. Can be added to dressings. |

*(Continued on next page)*

**Table VI.** Continued.

| Medication | Application in space missions | Caveats and considerations |
|---|---|---|
| Trace Minerals | Selenium, iron, copper, manganese, and zinc have antioxidant and radioprotective effects. Selenium is needed for glutathione, an antioxidant. Iron produces ROS. Copper is anticlastogenic, inhibiting DNA replication of DNA-damaged cells. Zn inhibits decrease in hematocrit, thrombocytes, T-cell activation and reverses radiotoxicity. | Radiolytic iron loss is thought to underlie impairment of wound-healing. This must be reconciled with evidence of increased iron in astronauts in spaceflight environments. Low-doses of copper can have a sedative effect which can be helpful for disrupted sleep. Mn excess can cause schizophrenic side effects. |
| Hesperidin | A bioflavonoid found mainly in citrus which may have bone-protective abilities, provide cardiovascular and anti-radiation support through antioxidant and antiinflammatory properties, boost immune function, and be neuroprotective. It is a component of MPFF (Daflon). | Considerations should be made for mild gastrointestinal discomfort, poor stability in space, and potential interaction effects with antihypertensives and blood thinners. More research is needed. |
| Growth factors (PDGFs, FGFs, EGF, TGF-β, VEGF, GM-CSF) | Reduced levels observed in ulcers and chronic wounds. Injection can stimulate ECM and collagen synthesis, keratinocyte migration, myofibroblast differentiation, chemotaxis of healing cells, facilitate all stages of wound-healing | Injection, isolation of the factors, and administration is complexified in the space environment. They can be added to dressing to boost healing topically. |
| Glucans | Yeast polysaccharide that is radioprotective through immunomodulation. Antibacterial through increased macrophage activation. Lead to increased production of GM-CSF. | Can cause gastrointestinal side effects. Can also be added to gauzes and dressings. |
| Pentoxifylline | Anti-inflammation by inhibiting fibroblast growth factor 2. | Potentially useful for lymphedema. |
| Plant extracts | Triphala, mint, curcumin, aloe vera, eucalyptus. Many others, but these agents have more evidence. | Lack of standardized dosing, variable compositions, and unknown combination effects. Variability in administration and application. |
| Antibiotics (amoxicillin/clavulanate, azithromycin, sulfamethoxazole, trimethoprim, vancomycin, cephalosporin, fluoroquinolones) | Can have radio-protective effects and facilitate wound disinfection, especially when applied topically. | Can be used in conjunction with other therapies medications and therapies, like PBM, silver dressings. Can also be used for other indications besides wound healing. Variable stability when exposed to space hazards. |

*ACE-I*, Angiotensin converting enzyme inhibitors; *AMPK*, adenosine monophosphate-activated protein kinase; *AR-I*, angiotensin receptor blockers; *ECM*, extracellular matrix; *EGF*, epidermal growth factor; *FGF*, fibroblast growth factor; *GM-CSF*, granulocyte-macrophage colony stimulating factor; *mTOR*, mammalian target of rapamycin; *NSAID*, nonsteroidal anti-inflammatory drug; *PBM*, photobiomodulation; *PDGF*, platelet-derived growth factor; *ROS*, reactive oxygen species; *SANS*, spaceflight-1 associated neuro-ocular syndrome; *TGF-β*, transforming growth factor β; *VEGF*, vascular endothelial growth factor.
Some medications may be combined for enhanced efficacy. As these are experimental, they are not yet recommended for mitigating space-related hazards without further research.

involved in wound healing. After an injury, the inflammatory cascade creates a chemical gradient that attracts MSCs, which then proliferate, release signaling molecules, and initiate repair. With hazards like radiation, cell death occurs faster than MSCs can respond, leading to chronic or poorly healed wounds. Stem cells derived from adipose tissue or bone marrow can be applied topically, systemically, or in bioscaffolds to wounds to therapeutically counteract damage.[99,108] Similarly to MSC therapy, platelet-rich plasma,[109] an autologous blood product with a high platelet concentration, can deliver multiple growth factors for tissue repair. Its role in wound healing is well-established, and it is commonly injected for various surgical operations and treatments.[20,55] These technologies could potentially be implemented for spaceflight.

Nanoparticles offer hope for various targeted therapies, diagnostics, and delivery systems. They can act as vessels

**Table VII.** Comprehensive summary of wound care strategies, including their adaptability and suitability for long-duration space missions

| Treatment type | Integration to space surgical protocols | |
|---|---|---|
| | Advantages | Disadvantages |
| Cleaning and debridement | • Essential for removing necrotic tissue<br>• Improves healing outcomes in contaminated wounds | • Requires sterile tools and skilled personnel<br>• Risk of infection or incomplete debridement in resource-limited settings |
| Stitching techniques (sutures, staples, and adhesives) | • Quick and effective for clean wounds<br>• Minimal equipment needed<br>• Promotes rapid healing<br>• Relatively short training time | • Limited efficacy for contaminated or infected wounds<br>• Surgical performance may reduce in the space environment<br>• Requires sterile tools and skilled personnel |
| Topical antiseptics | • Essential to reduce infection risk<br>• Storable | • Need for proper storage conditions to maintain efficacy in space |
| Advanced dressings (eg, hydrocolloid, foam, silver, chitosan, bacterial cellulose, ankeferd) | • Lightweight and easy to apply<br>• Provides moisture balance for optimal healing<br>• Some have antimicrobial properties (silver and chitosan) | • Limited availability of dressings if resupply is restricted<br>• Need for proper storage conditions to maintain efficacy in space |
| Hydrogels and alginate dressings | • Ideal for managing exudative wounds<br>• Some are antimicrobial<br>• Lightweight and storable | • Regular changes required<br>• Limited resupply and storage constraints |
| VAC | • Promotes wound healing and reduces infection risk<br>• Effective for complex and deep wounds<br>• Compact devices available | • Requires power<br>• Device failure or contamination risks in microgravity<br>• Logistics of securing NPWT in low-gravity environments |
| Thermal, ultrasound, electrical-stimulation, or light-based therapies | • May stimulate healing and reduce bacterial load<br>• Emerging compact devices available for space | • Requires power and specialized equipment |
| Biological agents (eg, growth factors) | • Can accelerate healing and improve outcomes<br>• Compact storage of synthetic agents possible | • Limited availability onboard<br>• Complex application process requiring expertise<br>• Potential degradation in prolonged storage |
| Skin grafts and substitutes | • Effective for large or complex wounds<br>• Advanced substitutes may be stored onboard | • Limited availability of donor sites for autografts<br>• High resource and skill requirements<br>• Risk of rejection for bioengineered grafts |
| PRP | • Enhances wound healing by modulating inflammation, angio-genesis, and re-epithelialization | • Difficulty with storage and transportation in space environment<br>• Autologous blood product so must be drawn pre-mission |
| Topical oxygen therapy | • Enhances healing in hypoxic environments<br>• Lightweight and compact devices available | • Power-dependent<br>• Requires oxygen supply, which is a critical resource |
| Sterile dressings | • Simple, lightweight, and versatile<br>• Essential for wound coverage and infection prevention | • Limited by storage space and resupply constraints<br>• Regular replacement needed, increasing workload |

*(Continued on next page)*

**Table VII.** Continued.

| Treatment type | Integration to space surgical protocols | |
|---|---|---|
| | Advantages | Disadvantages |
| Antibiotics (systemic and topical) | • Crucial for preventing and treating infections<br>• Lightweight and long shelf-life antibiotics available | • Risk of antibiotic resistance (can be mitigated with photobiomodulation or combined therapies optimized for space environment)<br>• Quinazoline derivatives diluted can withstand months in low temperature and space conditions<br>• Difficulty in matching antibiotic to pathogen without lab facilities<br>• Limited shelf-life of some medications |
| Telemedicine guidance | • Enables expert consultation with Earth<br>• Reduces need for onboard specialists | • Communication delays (up to 24 minutes one-way for Mars)<br>• Limited utility for immediate emergencies |
| AI and chatbots | • Rapid assistance<br>• High variety of diagnostic tools | • Requires human supervision |
| Stem cell therapy | • Can be applied to scaffolds to facilitate specific therapy<br>• Versatile and promising | • Requires more research for best administration and feasibility in space environment |

*AI*, Artificial intelligence; *NPWT*, negative pressure wound therapy; *PRP*, platelet-rich plasma; *VAC*, vacuum-assisted closure.

or binders for tailored substances (eg, growth factors, frequency-emitting markers, radioprotective molecules, antimicrobial agents, or even MSCs and platelet-rich plasma in a biodegradable form).[68,100] They can be injected systemically, ingested, inhaled, or topically applied for theoretically any health condition terrestrially or in space.

**Pharmacotherapy in space.** McLaughlin et al,[36] and Booth et al[64] identified various radioprotective therapies. Although useful against radiation, they may be counterproductive for wound healing or against synergistic damage wrought by combined space hazards.[37-39,110] Table VI summarizes potentially useful pharmacological therapies.[35,40-42]

**Technological interventions and wound healing.** On Earth, telemedicine and remote monitoring technologies are employed to evaluate wounds, and these hold promise for spaceflight (in non-urgent scenarios).[114] In emergencies, artificial intelligence may play a role in wound assessment.[115] Ongoing efforts aim to enhance artificial intelligence for medical assisting and algorithms for analyzing wound images, assessing healing status, infection risks, and required interventions. With trauma where surgery is unavoidable, robot-assisted telesurgery might contribute. However, it is not feasible for deep-space missions as a 0.8- to 1-second signal delay causes technical problems (signal delay from Earth to Mars up to 24 minutes).[93,94]

Another promising technology is photobiomodulation, which applies certain light frequencies to stimulate natural cell features like wound healing. The mechanism stimulates mitochondria to produce more ATP, leading to an alteration in ROS concentration. This stimulates various transcription factors that, especially in damaged tissues, can restore homeostasis, decrease apoptosis, stimulate fibroblast proliferation, reverse insulin insensitivity, and mitigate oxidative stress downstream.[43] The mitochondria absorb the photons to form oxygen. This has been demonstrated as antibacterial, analgesic, and significantly restorative.[117,118] A 2002 NASA technical report by Wheelan suggested using light-emitting diodes at near-infrared frequency and lasers to mitigate high-dose radiation, tissue breakdown, and microgravity-induced muscle wasting.[119] Through similar, but mechanical stimulation, utilizing the integrin/mitogen-activated protein kinase pathway, low-intensity ultrasound can mitigate tissue damage by upregulating collagen-I expression in stem cells and fibroblasts.[120] The greatest benefit could arise from combining a therapeutic and diagnostic tool in one lightweight device. Combining these advanced technologies with individualized care, nutraceuticals, and astrobotany will pave the way for sustainable surgical care during long-duration space missions. Other novel strategies for future discussion include hypothermia induction, torpor, and caloric restriction.[69,83]

Wound care strategies are summarized in Table VII.[3,5,6,8,11,33,88,94,98,99,111,112,115,116,119,122-124]

## LIMITATIONS

This study has several limitations. As recent human deep space missions and in-space wound treatment are yet to occur, direct data is unavailable. However,

there has been one documented case of asymptomatic deep venous thrombosis on the ISS, initially managed with Lovenox and later transitioned to Apixaban on day 43 following a resupply mission. A hypercoagulability workup was negative, though the use of oral contraceptives for menstrual suppression in flight was considered a potential contributing factor. Currently, there is no recognized indication for prophylactic anticoagulation in space. However, data on vascular events in space remains limited, highlighting the need for further research.[44,125] The reviewed literature consists of existing *in vitro* and animal studies, professional, commercial and analog astronaut missions, and military resources.

## CONCLUSIONS

Several critical NASA knowledge gaps—some deemed closed due to insufficient research—remain unresolved, and highlight the urgent need for interdisciplinary integration. Bridging the field of aerospace medicine with complementary disciplines, like vascular surgery and chronic wound care, represents a transformative approach that is essential for advancing our understanding and capabilities in addressing the unique medical challenges of space exploration.

## AUTHOR CONTRIBUTIONS

Conception and design: DB, KK, CL, MG, GO, MM, RC
Analysis and interpretation: DB, KK, CL, RC
Data collection: DB, KK, CL, RC
Writing the article: DB, KK, CL, MG, GO, MM, RC
Critical revision of the article: DB, KK, CL, MG, GO, MM, RC
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## DISCLOSURES

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