UPDATE ON SPACEFLIGHT IMMUNE SYSTEM DYSREGULATION, CLINICAL RISKS FOR DEEP SPACE MISSIONS, POTENTIAL COUNTERMEASURES

Brian Crucian, PhD, MT(ASCP)
The Immune System

**Pluripotent Stem Cell**
- Lymphoid Stem Cell
- Myeloid Stem Cell

**Adaptive Immunity**
- Secondary defense
- Delayed
- Antigen-specific
- Results in memory

**Cell Mediated Immunity**
- Mediated by cytotoxic T lymphocytes which destroy viral infected cells, transplant cells, some tumor cells

**Humoral Immunity**
- Mediated by B cells/Plasmacytes. Antibodies bind specific antigens, signals other cells to engulf and remove that target from the body.

**Innate Immunity**
- Primary defense
- Immediate
- Non-specific
- Does not result in memory

**Key Cells**
- T Lymphocyte
- NK Lymphocyte
- B Lymphocyte
- Plasma Cell
- Erythrocyte
- Megakaryocyte
- Monocyte
- Macrophage
- Granulocytes

**Diagram**
- Lymphoid Gland
- Lymph Nodes
- Thymus Gland
- Liver
- Spleen
Eat microbes

Cause Allergy

Direct ‘Right’ Kind of Response

Fight Parasites

Kill Infected Cells

Fight Cancer

Make Antibodies

Inflammation

Pathogen-specific Response

Keep ‘Control’

Protect you for life!
ALTERED MICROBIAL VIRULENCE
RADIATION
PHYSIOLOGICAL STRESS
PSYCHOLOGICAL STRESS
ALTERED IMMUNOCYTE DISTRIBUTION & FUNCTION
ALTERED CYTOKINE, REDOX, INFLAMMATORY BALANCE
LATENT VIRUS REACTIVATION
CANCER
AUTOIMMUNITY
CONSEQUENCES OF PERSISTENT VIRAL REACTIVATION
CHRONIC ALLERGY/HYPERSENSITIVITY
INFECTIOUS DISEASE
ALTERED NUTRITION
MICROGRAVITY
ALTERED MICROBIOME
CIRCADIAN MISALIGNMENT
CLINICAL INCIDENCE
Immunity and Disease

VIRAL INFECTION
- meningitis
  - JC virus
  - Measles
  - LCM virus
  - Adenovirus
  - Rabies
- Parotitis
  - Adenovirus
  - Epstein-Barr virus
  - Cytomegalovirus
- Ye infections
  - Herpes simplex virus
  - Adenovirus
  - Cytomegalovirus
- Gingivostomatitis
  - Herpes simplex type 1

BACTERIAL INFECTION
- Common cold
  - Rhinoviruses
  - Parainfluenza virus
  - Respiratory syncytial virus
- Pneumonia
  - Influenza virus, Types A and B
  - Parainfluenza virus
  - Respiratory syncytial virus
  - Adenovirus
  - SARS coronavirus
- Plague
  - Yersinia pestis
- Leprosy
  - Mycobacterium leprae
- Typhoid
  - Salmonella typhi
- Cholera
  - Vibrio cholerae
- Diarrhoeal diseases
  - Enterotoxigenic E. coli
  - Shigella
  - Campylobacter
  - Clostridium difficile

CANCER
- Lung
  - Non-small cell lung cancer
  - Small cell lung cancer
- Breast
  - Invasive ductal carcinoma
  - Invasive lobular carcinoma
- Prostate
  - Prostate adenocarcinoma
- Skin
  - Melanoma
  - Basal cell carcinoma
  - Squamous cell carcinoma

AUTOIMMUNE DISEASE
- Over 100 Different Types of Autoimmune Disorders
- Autoimmune disorders include:
  - Rheumatoid arthritis
  - Lupus
  - Sjögren’s syndrome
  - Inflammatory bowel disease
  - Thyroid disorders
  - Type 1 diabetes
  - Multiple sclerosis
  - Ankylosing spondylitis
  - Systemic lupus erythematosus

SHINGLES
- Blister formation
- Nerve fiber inflammation
- Postherpetic neuralgia

ALLERGY
- Skin reactions
- Respiratory symptoms
- Gastrointestinal symptoms
- Blood coagulation disorders
- Nerve damage
- Respiratory syncytial virus
Blood and Saliva Collection - ISS
Plasma Collection - ISS

Return Ambient – 45h Delay

- Early:
  - ~2 weeks
  - FD15

- Mid:
  - 2-4 mos
  - FD30
  - FD60

- Late:
  - R-1-2 days
  - FD120
  - FD180

Frozen on Orbit

6 Months Spaceflight
Innate immunocyte function dysregulated during spaceflight

- Plasma cytokine concentrations are altered in astronauts
- Astronauts experience persistent reactivation of latent herpesviruses, biomarker of reduced immunity
- Astronauts demonstrate elevated stress hormones and dysregulated circadian rhythms during spaceflight
- Astronauts have some degree of clinical incidence, primarily dermatitis, allergy and infections
- Dermatitis may be associated with viral etiology
- Some crew experience persistent symptoms requiring prolonged management

Peripheral leukocyte distribution in astronauts is relatively normal

T cell, NK cell function is inhibited by microgravity

T cell function is reduced in astronauts; appears to be a shift in the activation threshold

NK cells are disarmed, reduction in lytic molecule content

B cell function in astronauts appears unaltered (limited data)

Innate immunocyte function dysregulated during spaceflight

Plasma cytokine concentrations are altered in astronauts
Microgravity Cell Culture

1xG CONTROL
Red: Actin localization
Green: Microtubules/MTOC

MODELED MICROGRAVITY

Mayra Nelman-Gonzalez
T Cell Function

One method of the "co-stimulation" needed to activate T cells. If the T cell fails to receive "signal two", it dies by apoptosis. 

- CD4/69+ - CD8/69+
- CD4/69/25+ - CD8/69/25+

**SEA+SEB**

- n=23

**αCD3/αCD28**

- n=17

![Graphs showing T cell function](image)
NK Cell Function

Graphs showing NK cell function with different concentrations of PBMCs:
- Target cells only
- 1X PBMC (NK:target = 1:6)
- 10X PBMC (NK:target = 1:1)
- 20X PBMC (NK:target = 3:1)

Cells are analyzed for side scatter and forward scatter, CD66, CD71, P.I. (viability), and CD71 (target cells).
Data expressed as % change from baseline (L-180). NK-cell function did not differ between astronauts and controls at baseline.

**Spaceflight Reduces NK Cell Function**

- **K562 (Leukemia)**
  - Controls (n=6) vs. Astronauts (n=6)
  - NKCA per cell (relative to L-180)
  - L-180, L-60, FD-90, R-1, R+0, R+18, R+33, R+66

- **U266 (Multiple Myeloma)**
  - Controls (n=6) vs. Astronauts (n=6)
  - NKCA per cell (relative to L-180)
  - L-180, L-60, FD-90, R-1, R+0, R+18, R+33, R+66

- **221.AEH (HLA-E Transfected)**
  - Controls (n=6) vs. Astronauts (n=6)
  - NKCA per cell (relative to L-180)
  - L-180, L-60, FD-90, R-1, R+0, R+18, R+33, R+66

- **721.221 (Lymphoma)**
  - Controls (n=6) vs. Astronauts (n=6)
  - NKCA per cell (relative to L-180)
  - L-180, L-60, FD-90, R-1, R+0, R+18, R+33, R+66

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Dr. Richard Simpson
### Table 1: Twenty two cytokines for analysis by category

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Anti-Inflammatory</th>
<th>Adaptive/Regulatory</th>
<th>Growth Factors</th>
<th>Chemokines</th>
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</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td>IL-1ra</td>
<td>IFNγ</td>
<td>G-CSF</td>
<td>CCL2/MCP-1</td>
</tr>
<tr>
<td>IL-1β</td>
<td>IL-2</td>
<td>IL-17</td>
<td>GM-CSF</td>
<td>CCL3/MIP-1 alpha</td>
</tr>
<tr>
<td>TNFα</td>
<td>IL-4</td>
<td>IL-5</td>
<td>FGF basic</td>
<td>CCL4/MIP-1 beta</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-10</td>
<td>VEGF</td>
<td>Tpo</td>
<td>CCL5/RANTES</td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td></td>
<td></td>
<td>CXCL5/ENA-78</td>
</tr>
</tbody>
</table>
### Table 2: Mean plasma cytokine levels for ISS astronauts before, during, and following spaceflight.

Data are expressed as mean concentration pg/ml ± SEM. Bold indicates statistically significant difference p≤0.05; n=28.

**Spaceflight**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>L-180</th>
<th>L-45</th>
<th>FD15</th>
<th>FD30</th>
<th>FD60</th>
<th>FD120</th>
<th>FD180</th>
<th>R+0</th>
<th>R+30</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1a</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.3</td>
<td>0.9 ± 0.5</td>
<td>0.3 ± 0.1</td>
<td>2.4 ± 1.9</td>
<td>0.6 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
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<tr>
<td>IL-1b</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.3</td>
<td>1.5 ± 1.0</td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.5</td>
<td>1.3 ± 0.9</td>
<td>1.1 ± 0.8</td>
<td>0.5 ± 0.2</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>TNFα</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>3.2 ± 1.0</td>
<td>2.0* ± 0.3</td>
<td>2.1* ± 0.4</td>
<td>2.2 ± 0.5</td>
<td>2.0 ± 0.4</td>
<td>1.3 ± 0.1</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
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<tr>
<td>IL-8</td>
<td>2.0 ± 0.3</td>
<td>2.1 ± 0.3</td>
<td>8.1* ± 2.1</td>
<td>7.9* ± 2.3</td>
<td>7.7* ± 1.7</td>
<td>7.3* ± 2.1</td>
<td>6.9* ± 2.3</td>
<td>2.1 ± 0.3</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>383 ± 40</td>
<td>370 ± 35</td>
<td>567* ± 65</td>
<td>563* ± 80</td>
<td>638* ± 101</td>
<td>728* ± 129</td>
<td>661* ± 85</td>
<td>682* ± 118</td>
<td>568 ± 146</td>
</tr>
<tr>
<td>IFNγ</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.5* ± 0.1</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>IL-2</td>
<td>2.2 ± 0.6</td>
<td>1.8* ± 0.5</td>
<td>1.7* ± 0.5</td>
<td>2.6 ± 0.8</td>
<td>2.4 ± 0.7</td>
<td>2.5 ± 0.7</td>
<td>2.4 ± 0.8</td>
<td>2.4 ± 0.7</td>
<td>2.7 ± 0.9</td>
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<tr>
<td>IL-17</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.3</td>
<td>0.9* ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.3</td>
<td>3.2 ± 1.7</td>
<td>0.3 ± 0.2</td>
<td>1.4 ± 0.7</td>
<td>2.1 ± 1.5</td>
<td>1.6 ± 1.2</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>IL-5</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.0</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>G-CSF</td>
<td>7.2 ± 1.9</td>
<td>7.0 ± 1.7</td>
<td>7.0 ± 1.8</td>
<td>4.5 ± 0.8</td>
<td>7.6 ± 2.0</td>
<td>14.7 ± 7.8</td>
<td>9.8 ± 3.2</td>
<td>10.3* ± 2.8</td>
<td>5.9 ± 1.4</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.6 ± 0.3</td>
<td>0.3 ± 0.1</td>
<td>3.4 ± 1.9</td>
<td>1.9* ± 0.8</td>
<td>2.7 ± 1.3</td>
<td>2.8 ± 1.9</td>
<td>2.7 ± 1.9</td>
<td>0.7 ± 0.4</td>
<td>0.7 ± 0.4</td>
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<tr>
<td>FGFβ</td>
<td>13.7 ± 5.4</td>
<td>15.4 ± 5.7</td>
<td>11.8 ± 3.3</td>
<td>21.9 ± 5.7</td>
<td>18.5 ± 4.9</td>
<td>12.1 ± 3.7</td>
<td>10.8 ± 2.7</td>
<td>11.7 ± 3.8</td>
<td>12.3 ± 4.3</td>
</tr>
<tr>
<td>Tpo</td>
<td>140 ± 16</td>
<td>146 ± 18</td>
<td>184* ± 18</td>
<td>189* ± 30</td>
<td>191* ± 22</td>
<td>196* ± 28</td>
<td>221* ± 24</td>
<td>141 ± 17</td>
<td>133 ± 16</td>
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<tr>
<td>VEGF</td>
<td>5.8 ± 0.9</td>
<td>6.2 ± 1.3</td>
<td>10.9* ± 19</td>
<td>15.8* ± 4.9</td>
<td>11.3* ± 1.7</td>
<td>12.5* ± 3.5</td>
<td>11.7* ± 1.9</td>
<td>5.1 ± 1.0</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>CCL2/MCP-1</td>
<td>72.4 ± 6.8</td>
<td>78.5 ± 7.7</td>
<td>71.7 ± 5.4</td>
<td>66.0 ± 5.8</td>
<td>77.0 ± 7.0</td>
<td>84.0 ± 7.0</td>
<td>87.0 ± 7.7</td>
<td>124* ± 18.1</td>
<td>90* ± 7.5</td>
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<tr>
<td>CCL3/MIP-1a</td>
<td>20.3 ± 5.0</td>
<td>16.6 ± 5.0</td>
<td>25.9 ± 8.1</td>
<td>15.0 ± 4.4</td>
<td>19.1 ± 6.6</td>
<td>22.7 ± 7.4</td>
<td>21.7 ± 8.6</td>
<td>19.4 ± 6.3</td>
<td>18.1 ± 5.5</td>
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<tr>
<td>CCL4/MIP-1b</td>
<td>16.2 ± 2.2</td>
<td>16.7 ± 2.7</td>
<td>22.3* ± 2.9</td>
<td>20.2* ± 2.5</td>
<td>22.2* ± 2.8</td>
<td>24.3 ± 5.1</td>
<td>21.6* ± 3.3</td>
<td>17.3 ± 2.3</td>
<td>19.3 ± 4.0</td>
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<tr>
<td>CCL5/RANTES</td>
<td>3613 ± 263</td>
<td>3292 ± 246</td>
<td>3618 ± 202</td>
<td>3746 ± 195</td>
<td>3575 ± 185</td>
<td>3818 ± 217</td>
<td>4030 ± 202</td>
<td>3410 ± 266</td>
<td>3623 ± 219</td>
</tr>
</tbody>
</table>
Plasma Cytokine Analysis

Chemokines

Anti-Inflammatory Cytokines
Stress Hormones/Circadian Rhythm

Circadian rhythm of Salivary Cortisol in 27 healthy adults

PRE-FLIGHT

FLIGHT

POST-FLIGHT

Collection Time
Latent Herpesvirus

Latent Viral Reactivation

Herpes Simplex
Gingivostomatitis
Mild pharyngitis
fever

Varicella
Chicken pox

Primary Infection

Cold Sore

Zoster (shingles)

Latent virus

Virus transit up peripheral nerve

Sensory neuron in dorsal root ganglion

Virus transit down peripheral nerve

Spinal cord

Stress → Activation of virus in neuron

Recurrence
Latent Herpesvirus

Reactivation in 76% of the crew members.

Reactivation in 65% of the crew members.
Latent Herpesvirus

- Zoster Patients (n=42) 100% positive
- Astronauts (n=23) 2-3 samples per crew = 59 total samples – 29/59 positive (49%)

No VZV DNA was detected pre-flight for any crew (L-180 or L-45)
## Clinical Incidence

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Total events</th>
<th>Events/person year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Reaction</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Upper Respiratory Infection (combination of rhinitis, nasal stuffiness and sneezing)</td>
<td>5</td>
<td>0.301</td>
</tr>
<tr>
<td>Eye Infection</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>5</td>
<td>0.301</td>
</tr>
<tr>
<td>Otitis Media/Externa (ear pain, or ear stuffiness+congestion)</td>
<td>17</td>
<td>1.022</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Sinus Infection</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Skin Infection (including scalp pruritis, pus forming wounds on wrist, finger)</td>
<td>5</td>
<td>0.301</td>
</tr>
<tr>
<td>Skin Rash/Hypersensitivity (including skin conditions such as tinea versicolor, dermatitis, rosacea)</td>
<td>23</td>
<td>1.383</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Malignancies*</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Autoimmunity*</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Infections, Other*</td>
<td>11</td>
<td>0.666</td>
</tr>
</tbody>
</table>

**Total:** 69  
**Events/person year:** 4.18
Clinical Incidence

Case Study ISS Astronaut

- Allergic symptoms in a non-allergic subject
- Subject developed an Atopic Dermatitis on mission day 17
- Rash was bothersome, at times severe
- A variety of treatments employed
- At times the medications of choice were exhausted
- Rash never resolved for the duration of the mission, although it was successfully managed to a tolerable level
- Rash spikes generally correlated well with operational stressors
- Research findings confirm immune dysregulation persisted for the duration of the mission
Clinical Incidence

- Rashes were observed to occur in the following locations: scalp, face, neck, chest, back, trunk, abdomen, arms and hands.

- The appearance of the rashes generally consists of bumps/nodules and/or small brown scaly patches, with or without petechiae, redness/hyperemia and itching.
Clinical Incidence

Herpes Simplex Virus type-1 reactivation associated with a case of persistent dermatitis during Spaceflight

43rd International Herpesvirus Workshop; Vancouver, Canada; July 21-25, 2018
Clinical Incidence

<table>
<thead>
<tr>
<th></th>
<th>In-Flight</th>
<th>R+0</th>
<th>R+14</th>
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</thead>
<tbody>
<tr>
<td><strong>Saliva</strong></td>
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<td></td>
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</tr>
<tr>
<td>VZV</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HSV1</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>(CT-22; 5.4x10^6 copies per ng total DNA)</td>
<td>(CT-15; 1.4x10^9 copies per ng total DNA)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin Lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Negative</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>HSV1</td>
<td>Positive</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>(CT-29; 2.4x10^4 copies per ng total DNA)</td>
<td></td>
<td></td>
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</tbody>
</table>

**Tertiary** infection using the cells and media from the secondary infection. Negative control (*left*), Serial dilution 10⁻¹ (*center*), and serial dilution 10⁻⁶ (*right*).
Peripheral leukocyte distribution in astronauts is relatively normal.

T cell function is inhibited by microgravity.

T cell function is reduced in astronauts; appears to be a shift in the activation threshold.

NK cell function is reduced in astronauts.

NK cells are disarmed, reduction in lytic molecule content.

B cell function in astronauts appears unaltered (limited data).

Plasma cytokine concentrations are altered in astronauts.

Astronauts experience persistent reactivation of latent herpesviruses, biomarker of reduced immunity.

Astronauts demonstrate elevated stress hormones and dysregulated circadian rhythms during spaceflight.

Astronauts have some degree of clinical incidence, primarily dermatitis, allergy and infections.

Some crew experience persistent symptoms requiring prolonged management.
Recent studies have established that dysregulation of the human immune system and the reactivation of latent herpesviruses persists for the duration of a 6-month orbital spaceflight. It appears certain aspects of adaptive immunity are dysregulated during flight, yet some aspects of innate immunity are heightened. Interaction between adaptive and innate immunity also seems to be altered. Some crews experience persistent hypersensitivity reactions during flight. This phenomenon may, in synergy with extended...
Potential Immunologic Countermeasures for Deep Space Missions

**Precision Countermeasures**

**Pre-Mission Immunological Screen**
- Personal history of allergy/hypersensitivity, etc.
- Medication history (antihistamines, etc.)
- Leukocyte distribution (NK cell subsets)
- Cytokine concentration: Th1/Th2, etc.
- Allergy screen, patch testing
- Latent herpesvirus sero-positivity

**Pathogen-Specific Mitigations**
- Antiviral (VZV) vaccination

**General Countermeasures**

**Already in Place/Will be Optimized**
- Pre-flight medical operations screening of crewmembers
- Pre-flight quarantine
- Microbial screening of vehicle/payloads/foods
- Environmental control
- Optimized exercise equipment
- Radiation shielding

**Multisystem Countermeasures**
- Optimized exercise regimen
- Adequate sleep schedules
- Psychological support - family communication
- Stress relieving techniques

**Specific Countermeasures**

**Nutritional Countermeasures**
- Diet optimized to reduce nutrient deficiency
- Functional foods/bioactive compounds
- Nutritional supplements:
  - Antioxidants
  - Probiotics
  - Omega 3 fatty acids
  - Supplemental nucleotides
  - AHCC
  - Pegylated-IL-2

**Pharmacological Intervention**
- Beta blockers
- Anti-cortisol
- Antibiotics
- Antiviral
- Anti-inflammatory
- Cytokine therapy

**In-flight Monitoring of Immune Parameters?**

**PRE-FLIGHT**
**LAUNCH**
**TRANSIT PHASE**
**CIS-LUNAR STATION/LUNAR SURFACE OPS**
**MARS FLYBY or ORBIT/MARS SURFACE OPS**
Spaceflight
Immunologists
NASA JSC
Immunology/Virology Laboratory