Spaceflight Effects on Human Physiology

- Muscle and bone weakening
- Elevated kidney stone risk
- Fluid Redistribution to upper body
- Plasma volume decreases, anemia
- Elevated radiation may increase cancer risk
- Dysregulation of the immune system
- Vision Issues
  - Otoliths in inner ear respond differently, eyes become main way to sense motion
The Immune System

• One of largest tissues in the human body, although largely in fluid state.

• Consists primarily of white blood cells (WBCs) located in lymph nodes and the peripheral blood.

• Responsible for protection against viral and bacterial infection, latent viral reactivation, tumor surveillance, wound healing, etc.

• Dysregulation can result in increased infection rate, malignancy, autoimmunity, allergy, etc.
Humoral immunity - Antibody mediated, effector cell B cells/plasmacytes. Antibodies bind specific antigens, signals other cells to engulf, kill and remove that substance from the body

Cell mediated immunity - Cell mediated. Effector cell cytotoxic T lymphocytes which destroy viral infected cells, transplant cells, some tumor cells

Innate Immunity - primary defense, immediate (constitutively present), non-specific, does not result in memory

Adaptive Immunity - Acquired; secondary defense, delayed (components not constitutively present), antigen-specific, results in memory
The Cytokine Network

- Innate/Inflammatory
- Growth Factors
- Humoral
- Th1/Th2
- Adaptive/regulatory
- Chemokines

Diagram showing the interactions between different cells and cytokines, including B-Cell, T-Cell, Neutrophil, Eosinophil, Basophil, Mast Cell, and Macrophage, with various cytokines such as IL-1, IL-6, IL-10, IL-12, TNFα, and IFNα.
RADIATION
Immune cells generally susceptible to radiation damage. Peripheral T and B cells via apoptosis induction; and via lethal damage to marrow stem cells

BONE
Within the bone marrow cavity, cytokines produced by immune cells also have important effects on regulating bone homeostasis. RANKL, M-CSF, TNF, ILs, and IFNs, affect the differentiation and activity of osteoclasts and bone resorption. During chronic inflammation, the balance of bone modeling and remodeling can be greatly affected.

NEUROLOGY
A reciprocal flow of information and functional connection exists between the nervous and immune systems. Communication occurs via soluble mediators and cell-cell contacts.

MICROBIOLOGY
Host-pathogen interactions determine susceptibility to disease. Microbial virulence in conjunction with immune status determines the magnitude and outcome of infection

NUTRITION
Proper nutrition is a requirement for a normal immune response. Deficiencies in any of several dietary requirements have been linked to diminished immune function and/or clinical illness

EXERCISE
Research is uncovering a link between moderate, regular exercise and a strong immune system. However, there is also evidence that too much intense exercise can reduce immunity and may even make you sick.
Figure 28-1a.—RNA synthesis rates in lymphocytes, cultured with and without PHA, obtained from the Skylab crews and control groups. The cells were pulsed with \(^{3}H\)-uridine at 23 h and harvested at 24 h after initiation of the cultures.
ISS Sample Types:

- Blood
- Saliva (Liquid)
- Saliva (Dry)
- Urine
- Health Survey

ISS Sample Schedule:

- Preflight
- Early (~2 weeks)
- Mid (2-4 mos)
- Late (R-1-2 days)
- In-flight
- R+0
- R+30
- Postflight
JSC Immunology Laboratory
- Leukocyte subsets
- Intracellular cytokine profiles (4hr culture)
- T cell function (24h culture)
- Mitogen-stimulated cytokine profiles (48h culture)

Mercer University
- Plasma cytokine balance
- Leukocyte cytokine RNA

JSC Microbiology Laboratory
- Latent herpesvirus reactivation (saliva/urine)

PHYSIOLOGICAL STRESS
- Stress hormone levels
- Circadian rhythm alignment

Immune System Changes (Status and Function)

Adverse clinical outcomes (Latent Viral Reactivation)
- Virus specific T cell number
- Virus specific T cell function
“Diseases are often accompanied by changes in the numbers or function of ‘fine’ lymphocyte subsets, even if changes in the bulk lymphocyte populations are not evident.”

T cell function

- Remove cells from body
- Stimulate cells with mitogens during culture, mimics an in-vivo immune response

Kinetics of T Cell Activation

T Cell Function vs. Disease
T cell function (early blastogenesis) data, expression of either CD69, or CD69/CD25 dual following 24hr culture in the presence of (A) staphylococcal enterotoxin A and B; or (B) antibodies to CD3 and CD28. Data are presented as mean ± standard error. Significance was evaluated by comparing all other data points to L-180 baseline data. Significant differences (p≤ 0.05) are indicated (*). Sample size for all data is 19 ISS astronaut subjects.
Secreted Cytokine Profiles: Detection by Cytometric Bead Array

- Stimulate cells in the presence of any mitogen (anti-3/28, PMA-I, LPS)
- Incubate for 48 hours
- Isolate and purify supernatants
- Freeze for batch analysis
- Analyze for cytokine concentrations by CBA
Secreted Cytokine Profiles: Mean ISS Data (n=17)

48hr Culture – anti CD3/CD28 Stimulation

Mean secreted cytokine levels following mitogenic stimulation. Data are expressed mean concentration in pg/ml ± SEM. * indicates statistically significant difference p≤0.05. Significance was evaluated by comparing all other data points to L-180 baseline data. Significant differences (p≤ 0.05) are indicated (*). Sample size for all data is 19 ISS astronaut subjects.
Secreted Cytokine Profiles: Mean ISS Data (n=23)

48hr Culture – PMA/I Stimulation
**Latent Viral Reactivation**

- **Herpes Simplex**
  - Gingivostomatitis
  - Mild pharyngitis
  - Fever

- **Varicella**
  - Chickenpox

- **Latent Virus**
  - Virus transit up peripheral nerve
  - Sensory neuron in dorsal root ganglion

- **Cold Sore**

- **Zoster (Shingles)**
  - Virus transit down peripheral nerve

- **Stress**
  - Activation of virus in neuron

- **Primary Infection**

- **Recurrence**

**Spinal Cord**
Latent Herpesvirus Reactivation in ISS Crewmembers

- Reactivation in 76% of crewmembers
- Reactivation in 65% of the crewmembers
Circadian Misalignment in ISS Crewmembers

Circadian rhythm of Salivary Cortisol in 27 healthy adults

International Space Station

PRE-FLIGHT

- 180

FLIGHT

Early

Mid

Late

POST-FLIGHT

Early

Late

Pierson and Mehta 2013
Mean Baseline Cytokine Concentrations

Plasma Cytokine - Normal Values
(L-180 mean data; n=17)

- INFLAMMATORY PRO-
- INFLAMMATORY ANTI-
- ADAPTIVE IMMUNITY
  - Th1
  - Th17
  - Th2
- GROWTH FACTORS
- CHEMOKINES

Cytokines and Growth Factors:
- IL-1a
- IL-1b
- TNFα
- IL-6
- IL-1ra
- IFNγ
- IL-2
- IL-17
- IL-4
- IL-5
- IL-10
- G-CSF
- GM-CSF
- FGFβ
- Tpo
- VEGF
- IL-8
- CCL2/MCP-1
- CCL3/MIP-1-alpha
- CCL4/MIP-1-beta
- CCL5/RANTES
- CXCL5/ENA-78
Plasma Cytokine Analysis

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.

<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>
</tr>
<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>TNFa</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>1.1*± 0.2</td>
</tr>
<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>IFNg</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>0.7± 0.3</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>
</tr>
<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>
</tr>
<tr>
<td>FGFb</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>
</tr>
<tr>
<td>VEGF</td>
<td>5.8± 0.9</td>
<td>6.2± 1.3</td>
<td>10.9*± 18</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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
Clinical Incidence onboard ISS?

- A definitive tabulation in the literature is lacking, although various NASA activities have created incidence numbers (Clinical Finding Forms, etc.)

- Inability to confirm diagnoses

- Restricted to electronic/remote examination

- Treatment options limited

- Data privacy restricted

- Missions vary in workload, stress

- Surgeons may record data differently

- Crew may be reluctant to report medical events
Spacecraft a perfect ‘petri dish’ for germs (confined space, recycled air, touching common surfaces with less opportunity to wash)

Aerosolized germs (microdroplets) do not settle out due to gravity

Immune system inhibited, microbes more virulent
### ISS Incidence Tabulation

Data tabulated from 37 long-duration ISS crewmembers (Exp. 1-28/29; totals 16.63 person flight years)

<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 
**4.18**
Case Study ISS Astronaut

- Unusually proficient medical record
- Typical busy pre-mission training schedule
- Launch on Soyuz; docking to ISS + 2 days
- 191 day mission onboard ISS
- 3 Shuttle dockings, 2 Progress dockings, 1 ATV docking
- 5 EVA activities (12 Shuttle EVA)
- Typically busy mission schedule
- Landing on Soyuz, GCTC 1 week
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
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.
T Cell Function
SEA+SEB (24hr)

Percent Positive

T Cell Function; SEA+SEB (24hr)

- CD4+/CD69+
- CD8+/CD69+
- CD4+/CD69+/CD25+
- CD8+/CD69+/CD25+

Graph showing the percent positive for different T cell functions over time.
Latent Herpesvirus Reactivation; EBV Specific T Cells

- SALIVARY EBV DNA
- SALIVARY VZV DNA
- EBV-SPECIFIC CD8+ T CELLS

Viral DNA - Copies/ml

1x10^3 Cells/ul

Time Points:
- L-180
- L-45
- FD25
- FD130
- FD191
- R+0
- R+90
Circadian Rhythm of Salivary Cortisol

Preflight
- L-180
- L-45

In-flight
- FD28
- FD130
- FD191

Landing
- R+0

Recovery
- R+30
Working Hypothesis: Spaceflight Summary Effects on Immunity

↓ Skin DTH during flight  
↓ T cell Function (general and virus specific) 
↓ Adaptive immunity cytokine profile  
↑ Persistent herpesvirus reactivation

INNATE
↓ NK cell function  
↑ Persistent hypersensitivity/pro-allergy  
↑ Persistent systemic low-grade inflammation  (Possible localized inflammation)

ADAPTIVE
Th1 → Th2 Cytokine Bias shift
No known effect on humoral immunity (MIR-18 vaccination study)
Conclusions

Immune System dysregulation persists during 6-month orbital spaceflight

Appears to be a pan-suppression of adaptive function, some sensitization of innate immunity

Latent herpesviruses, including VZV, persistently reactivate for the duration of a 6-month ISS mission.

Circadian misalignment occurs, difficult to regain a ‘normal’ circadian rhythm. (Sleep meds most commonly prescribed Rx)
Conclusions

• Case study: Mission events correlated well with observed symptomology

• Spaceflight is a granular experience consisting of chronic stress interspersed with periodic acute stressors

• Immune dysregulation during flight appears to be polar, with some adaptive processes depressed (T cell function, HV shedding); whereas some innate and other processes are elevated (inflammation, hypersensitivity reactions)

• Exploration immune countermeasures must be considered carefully
Immune Countermeasures for Exploration Missions?
Considerations

Have we completely characterized in-flight immune dysregulation?

Is there a clinical risk from the observed pattern of dysregulation?

Is the phenomenon likely to be exacerbated beyond Earth orbit?

What specific cellular dysregulation should be targeted for correction?

Countermeasures must be carefully targeted

Can immune countermeasures exacerbate elevated incidence hypersensitivity reactions?

What is the interdisciplinary/multi-system impact of an immune countermeasure?
Upcoming Immune Investigations onboard ISS

**Functional Immune (NASA)**

*Immuno-2/Neyroimmunitet (ESA/RSA)*

**Moroze (RSA)**

*Exploration Atmosphere (NASA)*
Tier 0
Already in place

Tier 1
Multidiscipline, benign

Tier 2
Nutritional supplementation

Tier 3
Pharmacological intervention
The primary purpose of the Flight Crew Health Stabilization Program (HSP) is to mitigate the risk of occurrence of infectious disease among astronaut flight crews in the immediate preflight period.

Infectious diseases are contracted through direct person-to-person contact, and through contact with infectious material in the environment.

The HSP establishes several controls to minimize crew exposure to infectious agents. The HSP provides a quarantine environment for the crew that minimizes contact with potentially infectious material.

The HSP also limits the number of individuals who come in close contact with the crew.

The infection-carrying potential of these primary contacts is minimized by educating them in ways to avoid infections and avoiding contact with the crew if they are or may be sick.

Primary contacts are also strongly encouraged to maintain updated vaccinations.
Tier 0
Already in place

- HEPA air filters
- In-line water filters
- Contamination resistant surfaces
- Water biocides
- Water pasteurization systems
- Minimize condensation
- Contain trash and human waste

C. Mark Ott, Ph.D., NASA Microbiologist
MedB 2.1 (L-90; L-30) “The examination will include collection of blood and urine from crewmembers for analyses to enhance the physician’s medical evaluation of crew health prior to flight”
  • CBC/Differential
  • CRP
  • Mouse IgE Allergen Panel

MedB 2.4 (L-90, L-30) “…to determine transfer or acquisition of Methicillin-Resistant Staphylococcus aureus (MRSA)”
  • Nasal Screen for Methicillin Resistant Staphylococcus aureus (MRSA)

MedB 2.2 (L-21/18 months) “To detect and eradicate H. Pylori from crewmembers preflight to mitigate risk”
  • Serological H. Pylori IgG and IgA antibody test results; Urea Breath Test results, if indicated
**Tier 0**

Already in place

- Crewmembers
- Food
- Potable water
- Vehicle surfaces
- Vehicle air
- Cargo
- Biosafety review of payloads

Preflight Microbiological Monitoring

C. Mark Ott, Ph.D., NASA Microbiologist
Tier 0
Already in place

Microbiological Monitoring Onboard ISS

Surfaces
Air
Water

Quantified in-flight and returned to JSC for identification

C. Mark Ott, Ph.D., NASA Microbiologist
Tier 1
Multidiscipline, benign

• Environmental control
• ISS ‘Seat Swapping’
• Stress relieving techniques
• Exercise
• Sleep schedules
• Family communication
• Radiation shielding
• Propulsion/faster transit
• Yoga
Tier 2
Nutritional supplementation

- Supplemental nucleotides: Uridine/uridine (immune function)
- AHCC: active hexose-correlated compound (Th2 shift; innate immunity)
- Pegylated-IL-2 (NK cell #/function)
- Antioxidants (radiation effects, oxidative stress)
  - N-acetyl cysteine, ascorbic acid
  - a-lipoic acid
  - L-selenomethionine
  - Coenzyme Q10
  - vitamin E succinate
  - D-selenomethionine
Tier 2

Nutritional supplementation

- Omega 3 fatty acids (anti-inflammatory properties)
- Probiotics
- Wellimmune™
- BAM-FX (Zero Grav Sol. Inc.)
- Plant Extracts
**Probiotics/Extracts of Probiotics**
- Probiotics modulate innate and adaptive immunity (Aureli 2011)
- Mechanisms and actions of probiotics not fully understood (Oelschlaeger 2010)
- Supplementation with probiotics has positive benefits on the response to vaccination for influenza (Olivares 2007), polio (De Vrese 2005) and cholera (Paineau 2008)
- Positive effects may be via the release of cytokines after ingestion (Maassen 2008)

**Plant Extracts**
- 47% of pharmaceuticals trace to natural origins (Newman 2007)
- Plant derived medicines also modulate immune responses.
- Saikosaponin from Bupleurum falcatum – increased IL-2 production (Yamaguchi 1985)
- Silybum marianum (milk thistle) immunostimulatory (Wilasrusmee 2002)

**Biochemistry**
- Transcriptomic data from probiotics and plant compounds
- Combinations of lead compounds with and without addition of dietary vitamins and minerals
Sinus congestion and allergy symptom treatments included OTC antihistamines, decongestants, and adrenergics as well as prescription antihistamines and mast cell stabilizers.

Sleep medications among the most prescribed on-orbit

Medication efficacy may be altered during Spaceflight (no data).

Fluid shifts may effect absorption and distribution of medications.

There are some animal studies that indicate drug metabolism, ie liver enzymes, may be altered.

**Tier 3**

*Pharmacological intervention*

- Anti-Cortisol (Ketoconazole)
- Non-Steroidal anti-Inflammatory
- Beta blockers (Propranolol)
- Cytokine Antagonists/Blockers (IL-1, TNF, IL-4, IL-9, IL-13)
- Recombinant Cytokine Therapy

---

Immune Countermeasures?

---

Treatment of Medical Events

- Antibiotics
- Antiviral
- Corticosteroids
**Tier 0**
Already in place
- Pre-flight quarantine
- Microbial screening of vehicle/payloads/foods
- Med ops screening

**Tier 2**
Nutritional supplementation
- Supplemental nucleotides: Uridine/uridine (immune function)
- AHCC: active hexose-correlated compound (Th2 shift; innate immunity)
- Pegylated-IL-2 (NK cell #/function)
- Antioxidants (radiation effects, oxidative stress)
  - N-acetyl cysteine, ascorbic acid
  - a-lipoic acid
  - L-selenomethionine
  - Coenzyme Q10
  - vitamin E succinate
  - D-selenomethionine
- Omega 3 fatty acids (anti-inflammatory properties)
- Probiotics
- Wellimmune™
- BAM-FX (Zero Grav Sol. Inc.)

**Tier 3**
Pharmacological intervention
- Ketoconazole
- Antibiotics
- Antiviral
- Anti-inflammatory
- Beta blockers
- Cytokine therapy

**Tier 1**
Multidiscipline, benign
- Environmental control
- Stress relieving techniques
  - Exercise
- Sleep schedules
- Family communication
- Radiation shielding
- Propulsion/faster transit

Other options
- Antiviral (VZV) vaccination