Infectious Disease Risk Associated With Space Flight

Human Exploration

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NASA Johnson Space Center
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SORRY, JUST BECAUSE YOU HAVE 20 MILLION MILES ON YOUR ODOMETER AND A FEW LOOSE TILES ON YOUR '74 VEHICLE, IT DOESN'T MAKE YOU ELIGIBLE FOR THE CASH FOR CLUNKERS PROGRAM.
Shuttle Has Been Moved To VAB And Will Be Attached To External Tank
# MICROBIOLOGICAL RISKS

<table>
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<th>Sources</th>
<th>Controls</th>
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<td>Crewmembers</td>
<td>Preflight screening, quarantine, vaccination, antimicrobials, antivirals</td>
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<td>Preflight/inflight monitoring, biocides</td>
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<td>Food</td>
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<td>Payloads</td>
<td>Preflight cleaning, biosafety assessment, disinfection</td>
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FACTORS INCREASING DISEASE RISK

- Crowded living conditions
- Closed-loop environment (water/air)
- Reduced capability for personal hygiene
- Limited clean-up and disinfection capability
- Inability to isolate contagious crew member
- Limited treatment capability and crew return
- Altered immune response
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<th>Positive Factors</th>
<th>Negative Factors</th>
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<tr>
<td>• Healthy well-conditioned crew</td>
<td>• Isolated/enclosed environment</td>
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<td>• Preflight exams &amp; restricted access</td>
<td>• Recycled air/water (urine, humidity condensate)</td>
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<td>• No exposure to many public health pathogens</td>
<td>• Limited diagnostics/treatment on board</td>
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<td>• Remote location/limited return pathogens (e.g. TB, HIV, Hep A/B/C)</td>
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<td>• Earth to orbit medical consult</td>
<td>• Uniquely stressful environment</td>
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<td>• Diminished Immunity</td>
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<td>• Increased virulence in bacteria</td>
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ADAPTATION TO SPACEFLIGHT

Psychological/Behavioral
- Performance issues

Taste and odor sensitivity

Gastrointestinal alterations

Fluid shifts, hematological changes

Muscle loss

Pro-sensory adaptations

Cardiovascular adaptations

Sleep and circadian rhythm disturbances

Bone loss

Immune changes
ENVIRONMENTAL FACTORS AFFECTING IMMUNITY

- Anxiety
- Confinement
- Isolation
- Physical
- Psychosocial
- Sleep deprivation
- Microgravity
- Acceleration
- Radiation

STRESS

CONTAMINANTS

- Microorganisms
- Mold spores
- Chemicals
- Dust mites
- Allergens
- Insects
HUMAN SPACE FLIGHT IMMUNOLOGY

- White blood cell count: Increased (neutrophils)
- Lymphocyte proliferative responses: Decreased
- Cell mediated immunity: Decreased
- Cytokine production: Increased/Decreased
- Humoral factors: No Change
- Specific antibody response: No Change
- Neutrophil/Monocyte functions: Decreased
- NK cell cytotoxicity: Decreased
- Latent virus reactivation: Increased
INFECTIONOUS DISEASES IN ASTRONAUTS
STS-1 Through STS-108

- Fungal infections
- Flu-like syndrome
- Urinary tract infections
- Aphthous stomatitis
- Viral gastrointestinal disease
- Subcutaneous skin infections
- Viral reactivation
- URI (common cold, sore throat)
- Sty

IMMUNE SYMPTOMS

- Allergic rhinitis
- Hypersensitivity
- Coughing/Sneezing
- Rashes/Skin disorders
- Infectious of cuts
- Delayed wound healing

Source: Medical Informatics & Health Care Systems Branch Epidemiology Section; July 2002
Stress Immune Response

SAM
Sympathetic Adrenal Medullary System

SYSTEM STRESSORS

HPA Axis
Hypothalamus Pituitary Adrenal Axis

When the system is stressed, the Hypothalamus releases CRH to the Pituitary Gland

The Pituitary Gland releases ACTH into the bloodstream, where it travels to the Adrenal Cortex

The Adrenal Cortex releases Corticosteroids (stress hormones) into the bloodstream

Stress hormones contribute to immune dysregulation

- Increased reactivation of herpes virus
- Allergies
- Others

When the system is stressed, electrical impulses travel along the nervous system to the Adrenal Medulla

The Adrenal Medulla releases Catecholamines (stress hormones) into the bloodstream
Why Herpes viruses?

Herpesviruses are:

1. The most readily recognized latent viruses.
2. Ubiquitous and represent important infectious disease risks with monogenic potential.
4. Diminished immunity results in reactivation & shedding of latent viruses

Specific Application:
May be used as an early predictor of impending medically significant changes in the immune response.
Latent Viral Reactivation

Herpes Simplex
- Gingivostomatitis
- Mild pharyngitis
- Fever

Varicella
- Chickenpox

Primary Infection

Cold Sore

Zoster (shingles)

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

Spinal cord
- Virus transit down peripheral nerve

Stress
- Activation of virus in neuron

Recurrence
Herpes virus Infections

4 of 8 herpes viruses reactivate in response to spaceflight

- **Herpes Simplex Virus (HSV)**
  - Ocular herpes, encephalitis
- **Varicella-zoster virus (VZV)**
  - Chicken pox, shingles
- **Epstein-barr virus (EBV)**
  - Mononucleosis, tumors
- **Cytomegalovirus (CMV)**
  - Mononucleosis, hepatitis
Antarctica: EBV

Subject 1

EBV DNA O.D.

Pre
Isolation
Post

Days in Isolation

0
1
2
3
4

-100
-50
0
50
100
150
200
250

DTH response

Normal
Hypoergic
Anergic

Mehta et al., J. Medical Virology 2000
Space Shuttle EBV Copies

EBV Copies per ml Saliva

- n = 32
  Space Flights = 10

- Frequency: 16%
  EBV copies 417± 31

- EBV Frequency: 29%
  EBV copies 40± 2

- EBV Frequency: 16%
  EBV copies 44± 5

- Control
  n=18
  Frequency: 3%
  Copies: 40

Days Before Launch: 200-140, 139-60, 59-1
Days of Flight: 2-4, 5-7, 8-14
Days After Recovery: 1-30, 31-45

Pierson et al., Brain Behavior & Immunity, 2005
Fold Increase In EBV Copy Numbers

- NEEMO: n=12
- Antarctic: n=16
- Space Shuttle: n=32
- Mir: n=2
- ISS: ?
### Summary of Nested RT-PCR Analysis of EBV Gene Expression in Healthy Young Adults

<table>
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<tr>
<th>Subject</th>
<th>Actin</th>
<th>EBER1</th>
<th>Latency I-III</th>
<th>IE/E(^a) Replicative</th>
<th>Late Replicative</th>
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\(^a\)Legend (+++ = highly expressed; ++ = moderately expressed; + = low expression); \(^b\)Immediate early/early.
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<sup>a</sup> Legend (+++ = highly expressed; ++ = moderately expressed; + = low expression). <sup>b</sup> Collection time: Launch minus 10-days (L-10); Recovery/landing day (R+0). Average Shuttle flight = 11 days; average ISS mission = 180 days; <sup>c</sup> Immediate early/early.
Space Shuttle: CMV Frequency

% CMV Positive Urine Sample

Astronauts: n = 71
Control: n = 61
Incidence of Shingles and Post Herpetic Neuralgia (PHN)

Shingles: Reactivation of VZV producing blisters in dermatomal region
- Pain can be excruciating

PHN: Prolonged, sometimes incapacitating, lasting weeks, months, or years.

“In extreme cases, PHN can be worse than death.”

CDC

- One million cases of shingles per year
- Risk of shingles increases >10-fold with age
- Lifetime risk of developing zoster: 25-30%
- 100,000 to 200,000 cases of PHN per year
Childhood chicken pox becomes dormant in the nervous system.

Primary Disease (Chicken Pox)

Hair shaft
Initial stage consists of burning pain and sensitive skin

Weakened immune system reawakens virus

Skin surface
Blisters develop resembling chicken pox and fill with pus

Blisters eventually burst, crust over, and heal

Nerve damage can cause postherpetic neuralgia

Dormant Varicella virus

Nerve fiber

Stress on the immune system allows the latent virus to reactivate as shingles

Reactivation (Shingles)

Shingles outbreak
First Report Of
VZV DNA In Astronauts’ Saliva

Mehta et al., J Medical Virology, 2004

![Graph showing real-time PCR vs nested PCR results with n = 8 and # of Spaceflights = 3]
Clinical Significance?

Is the Virus shed in Saliva Infectious?
Salivary VZV In Shingles Patients & Astronauts

VZV copies in saliva of a 21 yr old patients with symptoms of Shingles.

Mehta et al., 2008; Journal of Infectious Diseases
Change in Pain Index vs. Change VZV Copies After One Week of Treatment in Shingles Patients.

\[ \log_{10} \text{Change in VZV Copies in Shingles Patients} \]

Note in almost every case, data points fell in quadrant C (both decreased)
NFKB in Astronauts

% of NF-kB nuclear positive cells (Mean +/- SE)

- All (N=10)
- Shedders (N=7)
- Non-Shedders (N=3)
- Control (N=7)

Time Points:
- L-10
- R+0
- R+14
- Baseline
Cytokines

Graphs by ished
CONCLUSIONS

- Space flight is a unique stress model.
- Antarctic Science Stations model many aspects of space flight.
- Stress associated with space flight results in increased reactivation of EBV, CMV, and VZV.
- Viral reactivation in astronauts appears to be linked to duration in space (stress/microgravity?).
- Space flight-associated stress manifested through the HPA-axis result in increased stress hormones, reduced CMI, and increased viral reactivation.
- Viral reactivation may be used as an early predictor of impending medically significant changes in the immune response.

**VZV can reactivate subclinically in healthy individuals after acute stress.**
Changes in Microbial Pathogen Characteristics
Collaborative Studies
PI: Dr. Cheryl Nickerson, Arizona State University

*Salmonella typhimurium*

*Salmonella* grown in spaceflight analogues displayed increased virulence

*Salmonella* grown in spaceflight analogues altered their gene and protein expression
Classic virulence genes down-regulated
Ion response genes/pathways

*Salmonella* grown in spaceflight analogues altered their response to environmental stresses
Macrophage, acid, thermal, osmotic, oxidative

Rotating Wall Vessel bioreactor reproduces aspects of microgravity (Low fluid shear, low mass diffusion)

**MICROBE**

Shuttle Atlantis, STS-115, launch Sept 9, 2006

*Salmonella enterica* Typhimurium experimental design and results

---

*Salmonella* grown during spaceflight displayed increased virulence in rich media
Killed mice faster and killed mice at lower doses than identical bacterial cultures grown on the ground
Virulence change dependent on the growth media

*Salmonella* grown during spaceflight altered their gene expression
167 genes differentially regulated
Ion response genes/pathways
Identification of the global molecular regulator, *hfg*, ("master switch") of spaceflight induced cellular responses

*Salmonella* grown during spaceflight showed the presence of a material resembling a biofilm
Biofilms are important in disease causing potential and vehicle system failure

---

* Synchronous ground controls maintained under identical conditions as those on-board Shuttle - ground and in-flight hardware loaded with same sample.

Confirmed the effect of spaceflight on *Salmonella* virulence observed in MICROBE
Demonstrated a “spaceflight response” regardless of culture media

Established a link between the spaceflight response and media composition
Ion levels can be modulated to control spaceflight-associated virulence response of *Salmonella*
Phosphate ion sufficient to alter related pathogenesis responses in spaceflight analogue model.

In combination with MICROBE results, MDRV is showing a common conserved response in many microorganisms
MICROBE and MDRV also evaluating organisms, such as *Pseudomonas aeruginosa* and *Candida albicans*

* Synchronous ground controls maintained under identical conditions as those on-board Shuttle - ground and in-flight hardware loaded with same sample.

Wilson et al., 2008, PLOS One 3(12): e3923
Overview

Increased Stress
Increased Stress

Increased Stress Hormones

Norepinephrine Sympathetic Nervous System

CRH Corticotropin-releasing hormone

ACTH (adrenocorticotropic hormone)

Adrenal Cortex

Cortisol (glucocorticoid)

Immune system

Viral Reactivation
Increased Stress

Increased Stress Hormones

Decreased Immunity

Pre  Isolation  Post

Subject 1

EBV DNA O.D.

CMI

Normal

Hypoergic

Anergic

Days in Isolation
Increased Stress  
Hormones  
Decreased Immunity  
Increased Viral Reactivation

**EBV Frequency**
- Frequency: 29%  
  EBV copies 40± 2
- Frequency: 29%  
  EBV copies 44± 5

**Space Flights**
- Space Flights = 10  
  Frequency: 16%  
  Copies: 417± 31
- Frequency: 16%  
  EBV copies 44± 5

**Control**
- n=18  
  Frequency: 3%  
  Copies: 40
Increased Stress

Hormones

Increased Stress

Decreased Immunity

EBV DNA O.D.

Increased Viral Reactivation

EBV Frequency: 3%

EBV Reactivation: 40 ± 5%

Disease Risks:
- Mononucleosis
- Skin Lesions
- Tumors
- Ocular Herpes
- Shingles
- Hepatitis A

Subject:
- Pre-Infection
- Post
- Normal
Increased Stress

Increased Stress Hormones

Decreased Immunity

EBV DNA O.D.

Subject 1

Isolation

Post

Normal

Hypoergic

Anergic

Increased Viral Reactivation

Increased Risk of Disease

Disease Risks
- Shingles
- Ocular Herpes
- Hepatitis
- Tumors
- Mononucleosis
- Skin Lesions

Cases of Shingles/1000/year
Source: New England Journal of Medicine

Age Group

0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80+

0
2
4
6
8
10
12
Collaborators

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• Janet S. Butel, Ph.D., NSBRI/Baylor College of Medicine, Houston, TX
• Indresh Kaur, Ph.D., M.D. Anderson, Houston, TX
• Alan Feiveson, JSC-NASA, Houston, TX
Questions?
IMPACT OF STRESS

STRESS LEVELS AND MISSION IMPACT

Low

High

Space Shuttle

ISS

Mir

Moon

Mars
Figure 1: NF-κB activation in the PBMC of astronauts at different time points. Cells from astronauts at different time points were collected were analyzed for nuclear p65 as described in Materials and Methods.

In the cytoplasm (that is; in normal conditions), NF-κB consists of a heterotrimer of p50, p65, and IκBα. When it gets activated, that is; under stressed or diseased conditions IκBα undergo phosphorylation and separated from the p65-p50 complex. Then the p65-p50 subunit translocated to the nucleus, attach to specific regions of DNA (that is; the promoters of some genes) and initiates gene transcription that are involved in inflammation and cancer. In this figure black arrow represents inactivated form of NF-κB (in the cytoplasm), white arrow represents nuclear translocation of NF-κB (p65-p50 complex) and red arrow represents hematoxyylene staining in the nucleus of the cells that have inactivated form of NF-κB.
# CMV In Space Shuttle And International Space Station Crewmembers

<table>
<thead>
<tr>
<th></th>
<th># of Space Shuttle crewmembers shed CMV</th>
<th># of International Space Station crewmembers shed CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before flight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 d before Launch</td>
<td>0/7</td>
<td>0/5</td>
</tr>
<tr>
<td>45 d before Launch</td>
<td>0/7</td>
<td>0/5</td>
</tr>
<tr>
<td>10 d before Launch</td>
<td>3/7</td>
<td>not done</td>
</tr>
<tr>
<td><strong>After flight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Landing</td>
<td>4/7</td>
<td>4/5</td>
</tr>
<tr>
<td>14 d after landing</td>
<td>4/7</td>
<td>not done</td>
</tr>
<tr>
<td>30 d after Landing</td>
<td>not done</td>
<td>4/5</td>
</tr>
<tr>
<td>Overall</td>
<td>4/7</td>
<td>4/5</td>
</tr>
</tbody>
</table>
Conclusions

1. Four of the eight herpes viruses reactivate in response to short term shuttle and long term ISS flights.

2. Reactivation and shedding of EBV, CMV, and VZV on ISS was more pronounced and shed for longer time post flight than short duration shuttle flights.

3. Effects of stressors associated with spaceflight are mediated through the HPA axis and the SAM axis resulting in diminished cellular immunity.

4. Changes on circadian rhythms of cortisol and DHEA occur both ISS and SS crewmembers.

5. Spaceflight developed PCR technology has been transferred to Physicians’ laboratories for diagnosis of Shingles and post herpetic neuralgia.
# Summary of Nested RT-PCR Analysis of EBV Gene Expression\(^a\) in Aging

<table>
<thead>
<tr>
<th>Subject</th>
<th>EBER-1</th>
<th>Qp</th>
<th>Cp/Wp</th>
<th>LMP-1</th>
<th>EBNA-2</th>
<th>BZLF-1</th>
<th>SM</th>
<th>Fp</th>
<th>gp220</th>
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<tbody>
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<td>6</td>
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<td>+</td>
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</tbody>
</table>

Note: accumulated data for multiple (2-3) timepoints for each elderly subject.

\(^a\)Legend (+++ = highly expressed; ++ = moderately expressed; + = low expression)

\(^b\) + = EBV DNA present
CURRENT FOCUS: ON VZV

Unlike other neurotropic alphaherpesviruses in which primary infection is often asymptomatic, VZV (chickenpox) is characterized by malaise, fever, and an extensive vesicular rash.

The occurrence of VZV 2 days before space flight in a 47 year-old healthy astronaut from a pool of 81 physically fit astronauts prompted our search for subclinical VZV reactivation during times of stress.
NFKB in 10 astronauts before and after space flight

Mean +/- SE

% of NF-kB nuclear positive cells (Mean +/- SE)

- Non Shedders (N = 3)
- Shadders (N = 7)
- Control (N = 7)
PATHOGENS

Public Health

- Mycobacterium tuberculosis
- Helicobacter pyogenes
- Staphylococcus aureus (MRSA)
- Meningitis
- STD’s
- Salmonella spp
- Childhood diseases (e.g., measles)
- Escherichia coli 0157: H7
- HIV
- HAV, HBV, HCV
- Herpes viruses
- Influenza (respiratory viruses)

Space Flight

- MRSA
- Streptococci
- Escherichia coli
- Pseudomonas aeruginosa
- Legionella pneumophila
- Salmonella
- Herpes viruses
- Norovirus
- Aspergillus
- Penicillium
- Candida
- Giardia
- Cryptosporidium
PREVENTIVE MEASURES

- Crew Physical Examinations
- Immunization
- Health Stabilization Program
- Quarantine
- Preflight Food Testing
- Payload Biosafety Evaluation
- Establishment of Acceptability Limits
- Systems Design
- Environmental Monitoring
- In-Flight Housekeeping
- In-Flight Diagnostic Capabilities
- Antimicrobials
Salivary cortisol

Circadian rhythm of Salivary Cortisol in 27 healthy adults

**Space Shuttle**

<table>
<thead>
<tr>
<th>PRE-FLIGHT</th>
<th>FLIGHT</th>
<th>POST-FLIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 180</td>
<td>Early</td>
<td>Early</td>
</tr>
<tr>
<td>- 45</td>
<td>Mid</td>
<td>Late</td>
</tr>
<tr>
<td>- 10</td>
<td>Late</td>
<td>Late</td>
</tr>
</tbody>
</table>

**International Space Station**

<table>
<thead>
<tr>
<th>PRE-FLIGHT</th>
<th>FLIGHT</th>
<th>POST-FLIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 180</td>
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<td>Late</td>
<td>Late</td>
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</tbody>
</table>
The decline in CMI to VZV associated with zoster led to the hypothesis that infectious VZV would also be present in the saliva of astronauts subjected to stress of spaceflight. Herein, not only was the detection of salivary VZV DNA associated with spaceflight validated, but also infectious virus was also detected in saliva. **This is the first demonstration of shed of infectious VZV in the absence of disease.**

Recovery of infectious VZV from astronaut saliva. Human lung fibroblast cells cultures were inoculated with saliva from astronauts obtained on day 2 after landing. Typical herpes virus plaques were seen in cultures inoculated with saliva from subjects 1 and 2, but not with saliva from subject 3. The plaques stained with anti-VZV antibody but not with anti-HSV-1 antibody (not shown). magnification bar = 0.2 mm.