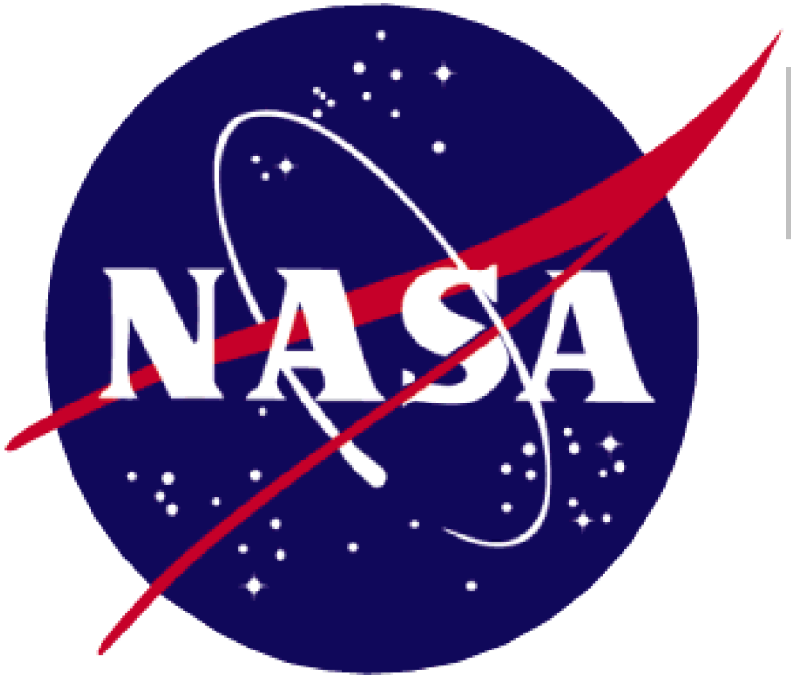


Infectious Considerations In Space Flight

Robert Haddon,MD,
Flight Surgeon
Medical Operations
Wyle/UTMB/NASA
September 15, 2009

Thanks to:

- The Cleveland Clinic Foundation and my colleagues here, for their counsel and instruction;
- Dr. Angelo Licata and the CCF Space Institute for a kind invitation and opportunity to speak;
- All who share the dream and practice of Space Exploration and who advance us thereby.

Mission to Mars; Touchstone Pictures 2000

Overview

This lecture is divided into three parts:

A review of the space environment.

Current and future research on immune and microbial aspects of space flight.

A practical guide to current operational practice.

Introduction

Slightly more than 500 people have flown in space, most of them for short periods of time. The total number of person-years in space is small. Given this fact, and given rigorous astronaut screening, it is not surprising that the accumulated infectious disease experience in space is also small, and mostly, theoretical. As the human space presence expands, we may expect mission length, total accumulated person-years and the environmental complexity to increase. Add to the mix both changes in human immunity and microbial virulence, and it becomes realistic to consider infectious scenarios and the means to mitigate them

Introduction

- This lecture will cover the inhabited space environment from the perspective of host-microbe interactions, current relevant research, and the current countermeasures used. Future challenges will be discussed and there will be opportunity to ask questions about Space Operations. The audience is encouraged to think about what medical tools you would choose to have in different types of mission, what you would be willing to leave behind, and how you would compensate for the necessary trade offs in mission design.

Thought Provocation I

Has anyone ever had pneumonia in space? No.

Could we treat pneumonia in space? Yes, with limitations.

Do the following items change in Space?

- Pulmonary blood flow? Yes
- Human immunity? Yes.
- Aerosol droplet trajectory? Yes
- Microbial virulence? Sometimes
- Antibiotic pharmacokinetics? Unknown
- So is pneumonia management in Space going to be routine? No.

Given a lunar base with1,000 people, will somebody sooner or later get pneumonia? Does lunar dust exposure increase the risk? What terrestrial industries have similar particulate exposures? Will you be treating on the moon or evacuating?

The take-away message:

Space infectious processes and their management will be for the most part familiar entities, but with the potential for variable presentations based on factors that manifest in the space environment.

Historical example (public information) Apollo XIII 1969

- During the return of Apollo XIII to Earth approximately 4 days into the aborted mission, one crewmember developed a urinary tract infection during an interval of restricted water intake and dehydration. The mission was brief, but very stressful. We do not have insight into the crewmember's transient immune state. Effective treatment was not achieved in flight prior to landing.

Thought Provocation II

If extremity cellulitis is more aggressive and persistent in patients with a history of lymph node resection, how would extremity fluid shifts in Space affect the natural history of cellulitis on orbit? In the event of cellulitis in Space, which clinical experience and which patient categories should we draw upon in assessing risk and managing the illness?

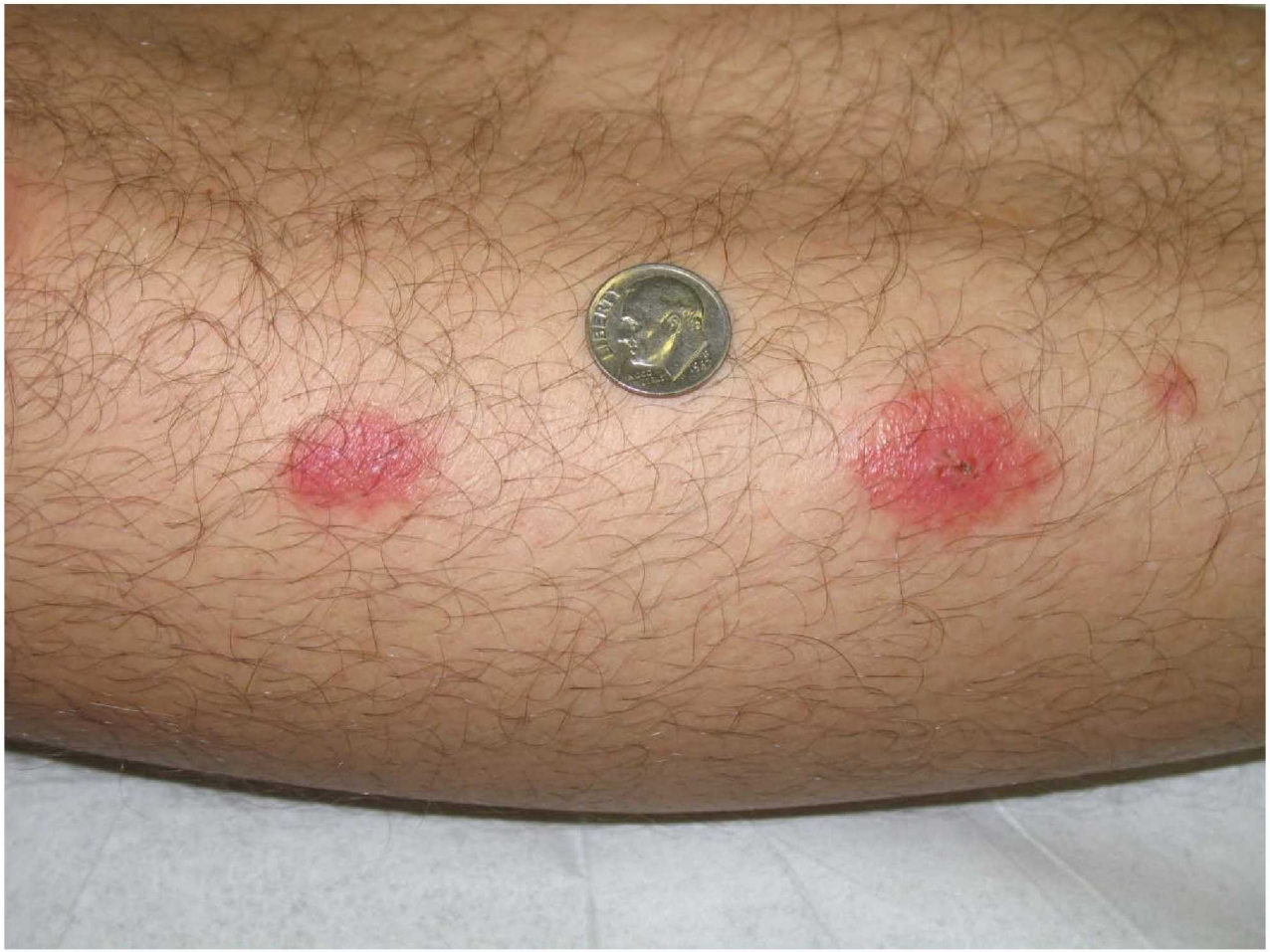
Short Case

- *At an unspecified time in the past few years, you are asked about a man in excellent health with abrupt-onset skin lesions on his leg.*
- *He noticed the lesions upon awakening from sleep in Florida, where he was staying in work-related temporary lodging in quarantine.*
- *The lesions were initially flat, firm, and mildly pruritic, with no streaking or induration. He otherwise felt well, and was looking forward to launching into space in 36 hours when he followed his customary practice and went swimming in the warm waters off of a Florida beach.*

Case 1 continued…

- *After a refreshing swim, during which he experienced no trauma and noticed no unusual marine organisms, he found that the pruritis has intensified. 24 hours before launch, his leg has the following appearance:*

Case 1 continued



Case I Differential

1. *Mosquito bite, sterile vs. super-infected*
2. *Bedbug, fire ant, brown recluse spider*
3. *Vibrio vulnificus, other gram-negatives*
4. *CA-MRSA (+/- PVL)*
5. *Marine organism envenomation*
6. *Contact allergy from neomycin*
7. *Contact allergy from nickel-containing electrode*

Case 1 considerations

- ***The health of the patient and the other crewmembers, and mission success are all critical. When risk hard to quantify, risk perception varies with the individual. NASA mostly a non-medical culture.***
- ***Limited hands-on follow-up anticipated***
- ***While there is limited medical capacity aboard Shuttle, serious complications could interrupt EVA schedule, or even require de-orbit. Iatrogenic complications, including allergic reaction or C. difficile colitis could themselves jeopardize Crew, EVA timeline and Mission.***
- ***In theory, you could delay the launch. Shuttle Crews do not normally have back-ups to replace individuals close to launch.***
- ***A definitive course of action is desired, you have 24 hours, what's next?***

Case 1 options: Pick One

1. *Do nothing, except cover lesions during launch and EVA*
2. *Topical steroids alone*
3. *Topical steroids/antibiotic mixture (no time to spare!)*
4. *Topical antibiotics alone*
5. *Oral antibiotics during mission (and launch with a supply of oral vancomycin as precaution against C. difficile)*
6. *Remove the offending agent and observe*
7. *Debridement and hospitalization*
8. *Diagnostic testing, treat in Space after launch based on results*
9. *Delay the mission and observe*

Case 1 continued

- *After some debate, the decision is reached to spend the next 12 hours using topical steroids, alone. This in fact was successful, with resolution of the pruritis and non-progression of the lesions in the day before launch.*
- *Use of antibiotics in parallel to steroids was specifically rejected.*
- *Why?*

Case 1 conclusion

In this case, the patient was not "sick," mosquito bite was considered most likely, with a good chance of demonstrable improvement before launch. Had antibiotics been used, it would have blurred the cause of the improvement, and would have prompted further use of antibiotics on orbit, at some risk. Had steroids alone failed, the antibiotic option remained before and after launch. The non-toxic appearance and failure to progress argued against the more dangerous items on the differential. The Crewmember did well and performed all scheduled tasks in a successful mission.

How is Case 1 typical of Space Medicine?

Basically healthy population.

Terrestrial organisms transferred into space, possibility of altered natural history due to some feature of space work environment.

Common problems have potential for high-stakes impact.

Risks are reduced, but cannot be taken to zero. Do no harm.

No problem is truly "common." The total Space corporate experience of any condition is either limited or theoretical, and the natural history cannot be assumed to be the same as that on Earth, for reasons to be further discussed.

Timelines are tight, personnel not easily interchangeable.

Patients are remote. Access, examination, diagnostics and treatment all severely constrained. Orbit up-mass costs $5,000 - $10,000 per pound, also constrained by competing mass/volume/power requirements. Emergency de-orbit for medical care is complex and is best obviated by preventing emergency in first place.

Consultation is readily available, implementation, difficult.

Infection is an Ecological Phenomenon

Space ecology

As a practical matter, the term "Space environment" is used in this lecture to refer to the inhabitable space environment. So, under near-terrestrial conditions, terrestrial hosts and microbes, themselves subtly changed, interact.

Instead of being challenged by the exotic, we will be challenged by variations on the familiar.

So, from an infectious perspective, how does the space ecological "tripod" differ?

1. Physical environment

2. Host (human physiology)

3. Microbes

Physical environment

- "Shirtsleeve" environment. Temperature, gas mix, pressure typical of sea level office space.
- Dry. Humidity run 30-50%
  - Sweat forms layers when excessive
  - Water may absorb into hydrophilic surfaces
  - Water forms spheres and has the potential to form "ponds"
- Radiation slightly higher than earth, but not dramatic.
- Air convection and mixing *does not occur* unless driven. Fans and HEPA filters are used.
  - CO2 pockets
  - Droplets, flakes *do not fall down*

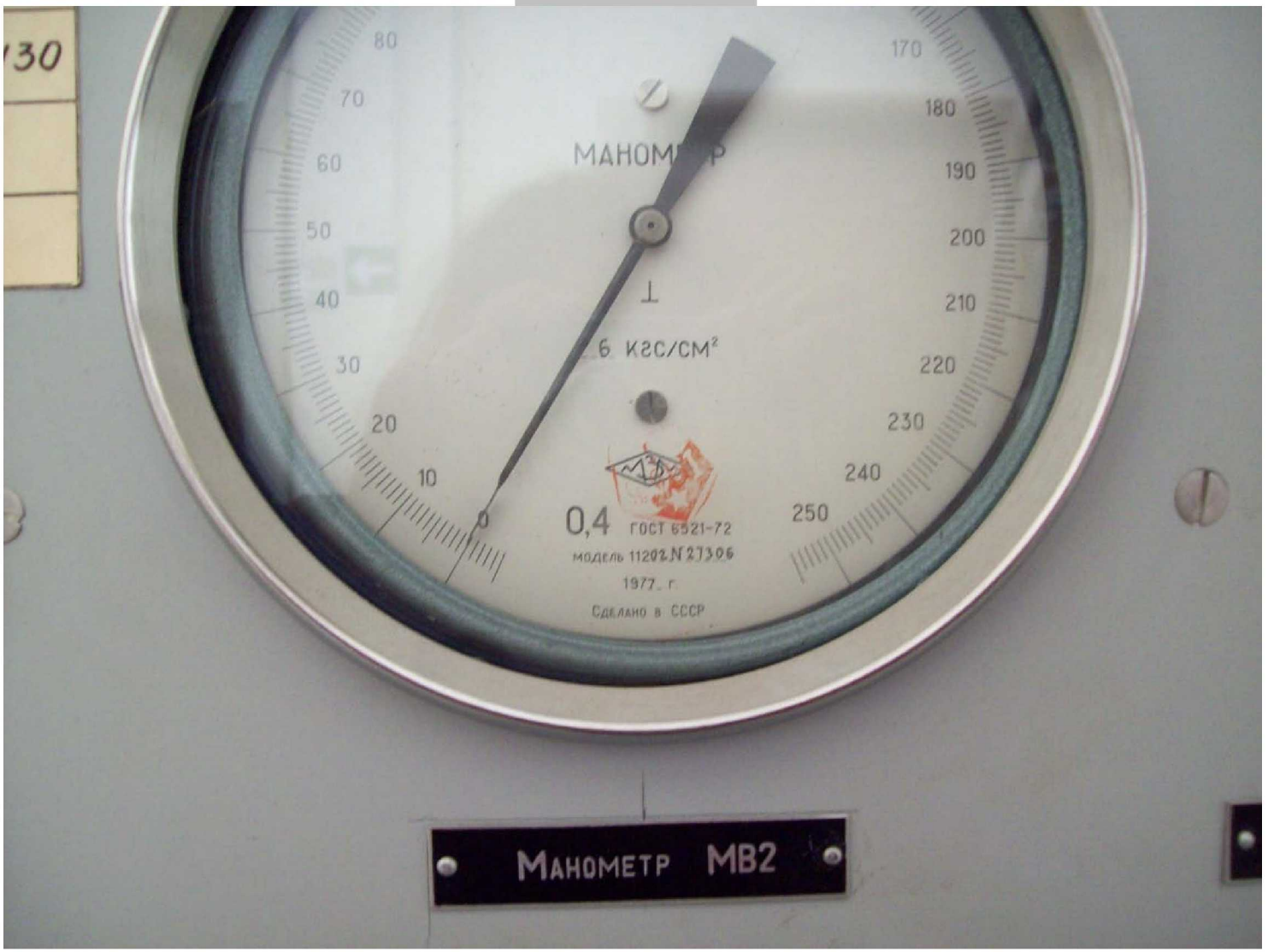
Space Environment II

- There is plenty of gravity at the orbital altitude of the ISS (after all, the Moon doesn't just float away). So, "microgravity" is a term of convenience.
- Objects in orbit are falling freely within a gravitational field.
- The distinction between true microgravity and free-fall is important when modeling the forces upon organisms

Space Environment III

- No crowds. Crewmembers arrive in small batches, generally pre-exposed to each other and quarantined.
- No reservoirs or vectors.
- No large-scale organics: no soil, vegetation, or large bodies of water

Air



ISS Air

ISS air is sampled using impeller samplers and is normally assessed for total colony counts. Samples for speciation have been obtained periodically and the results are shown on the following slide:

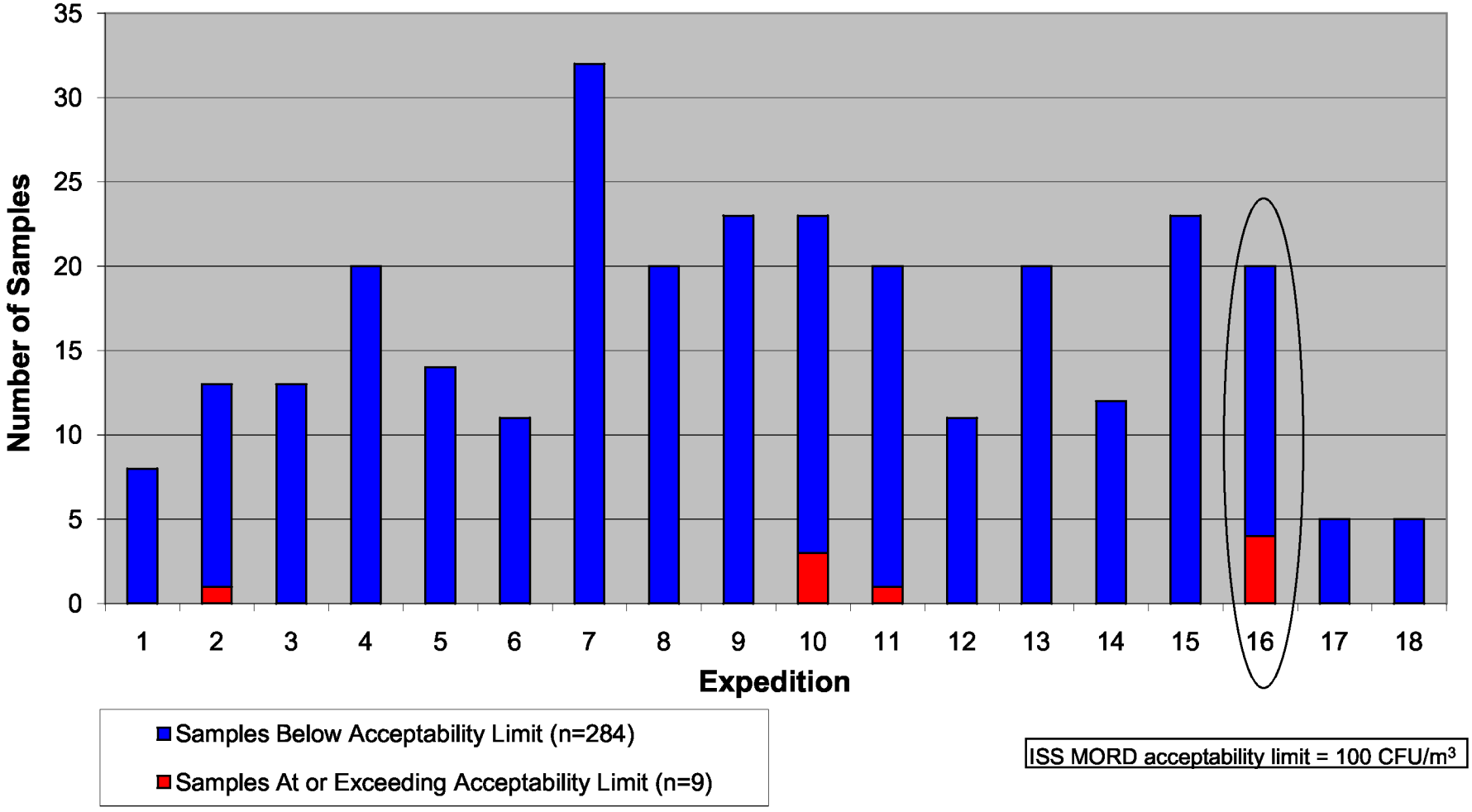
Bacteria in ISS air by species

Acinetobacter calcoaceticus
Acinetobacter lwoffii
Acinetobacter species
Alcaligenes xylosoxidans
Bacillus licheniformis
Bacillus thuringiensis
Bacillus species
Bacillus subtilis
Corynebacterium afermemtans
Corynebacterium riegelii
Corynebacterium species
Enterobacter aerogenes
Kocuria varians (formerly *Micrococcus*)
Micrococcus species
Non-viable organism
Paenibacillus amylolyticus
Paenibacillus glucanolyticus
Staphylococcus aureus
Staphylococcus auricularis
Staphylococcus capitis
Staphylococcus cohnii
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus lugdunensis
Staphylococcus pumilis
Staphylococcus saprophyticus
Staphylococcus simulans
Staphylococcus species
Staphylococcus vitulinus
Staphylococcus warneri
Staphylococcus xylosis
Streptococcus species
Stenotrophomonas maltophilia

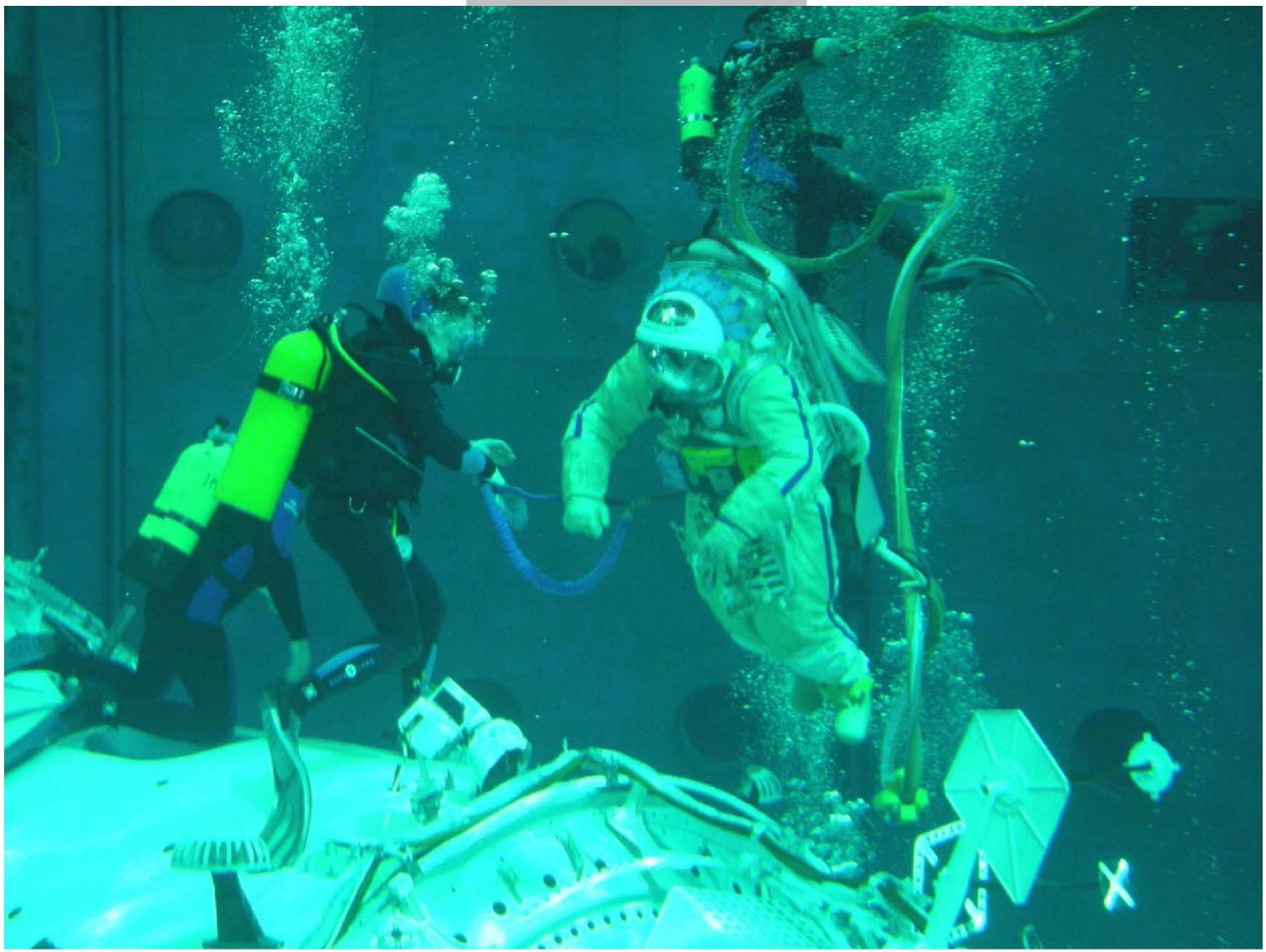
Fungi in ISS air by species

Fungi
Aspergillus flavus
Aspergillus nidulans
Aspergillus species
Aspergillus versicolor
Cladosporium species
Penicillium aurantiogriseum
Penicillium expansum
Penicillium species
Phoma species
Rhodotorula species
Scopulariopsis species

In-Flight Fungal Levels in ISS Cabin Air Using U.S. and Russian Hardware



Water



Water supplies in Space

- Water on Space Shuttle stored with dissolved Iodine, which is removed prior to use.
- Russian water on ISS is delivered municipal water treated on ISS with silver, potable water dispensed post a heating step. Filtering step in work.
- American water delivered and stored in 44 liter bags. Also recovered from condensate. Uses heat step for sterilization. Iodine not present in ISS water (could form precipitate with silver).
- Water in cooling loops contains *Ortho*-phthalaldehyde (OPA), to prevent bacterial matting and valve malfuntion. Cooling loops do not interact with consumable water supplies.
- Urine now recycled in US systems using acid pre-treat and heat step
- Human waste containerized and disposed on Progress module in atmosphere
- Potential exists for condensate collection. More of a problem on *Mir,* with small “ponds” forming behind panels. Shell heaters reduce likelihood.
- Water is split electrically by both US and Russian systems yielding Oxygen. Hydrogen is vented to space

Water testing

- Colorimetric assay for coliforms performed periodically on potable water. None detected to date. Means for speciation not available if detected.
- Quantitative assay performed for cell counts only. Recent elevations in colony counts led to the detection of ***Wautersia sp***. in potable water plumbing. High resistance to silver.

Significance of Wautersia in ISS

- Although not dangerous, is not supposed to be present at all. Ubiquitous in terrestrial water. Commonly found in plumbed water supplies, bottled water, swimming pools.
- Origin terrestrial, but precise path to ISS and route of spread in ISS plumbing hard to track even after extensive evaluation. Evaluation slowed by infrequent sample transport opportunities, relative lack of microbiological assets on board.
- Demonstrates principle that generic numerical thresholds for bacterial colony counts serve at best as a marker. Actual hazard will vary with species.
- Ecological niches tend to get filled. Microbes may move "under the radar" en route to niches.

Food

Food

- Food: generally processed terrestrial, occasionally fresh fruit.
- Food is tested for bacteria periodically.
- Commercial food supply chain issues poses theoretical hazard in the event contaminated food got to orbit.

Host Changes in Space

Cephalad fluid shifts as venous elasticity persists in absence of high fluid column—facial edema, sinus congestion.

Axial loading forces gone—muscle mass drops in absence of replacement exercise. Bone mass drops in part due to persistence of normal remodeling in response to "new" load.

Calcium excretion rises from bone loss. Risk of kidney (and therefore of obstructive UTI) rises.

Drug effects—early in flight space adaptation sickness is treated with phenergan with potential for urinary retention.

Sleep cycle disruption with possible effect on immunity.

Lung perfusion zones blend together

Normal flora remain normal—humans are a mobile environment

Normal flora example: Does Staph go into Space?

Yes. It has been found on the ISS. Individual strains have been tracked from date of arrival across more than one expedition. This was not associated with disease. Antibiograms were obtained, there was no sign of MRSA.

V.A. Castro, A.N. Thrasher, M. Healy, C.M. Ott,and D.L. Pierson. 2003. Microbial Characterization During the Early Habitation of the International Space Station. Microbial Ecology 47: 119-126.

CA-MRSA risk

The eventual appearance of CA-MRSA in Space seems plausible, given three assumptions:

(A) *Staph* goes to Space (already shown)

(B) CA-MRSA is spreading on Earth

(C) Space isolates reflect a sampling of the "action on the ground"

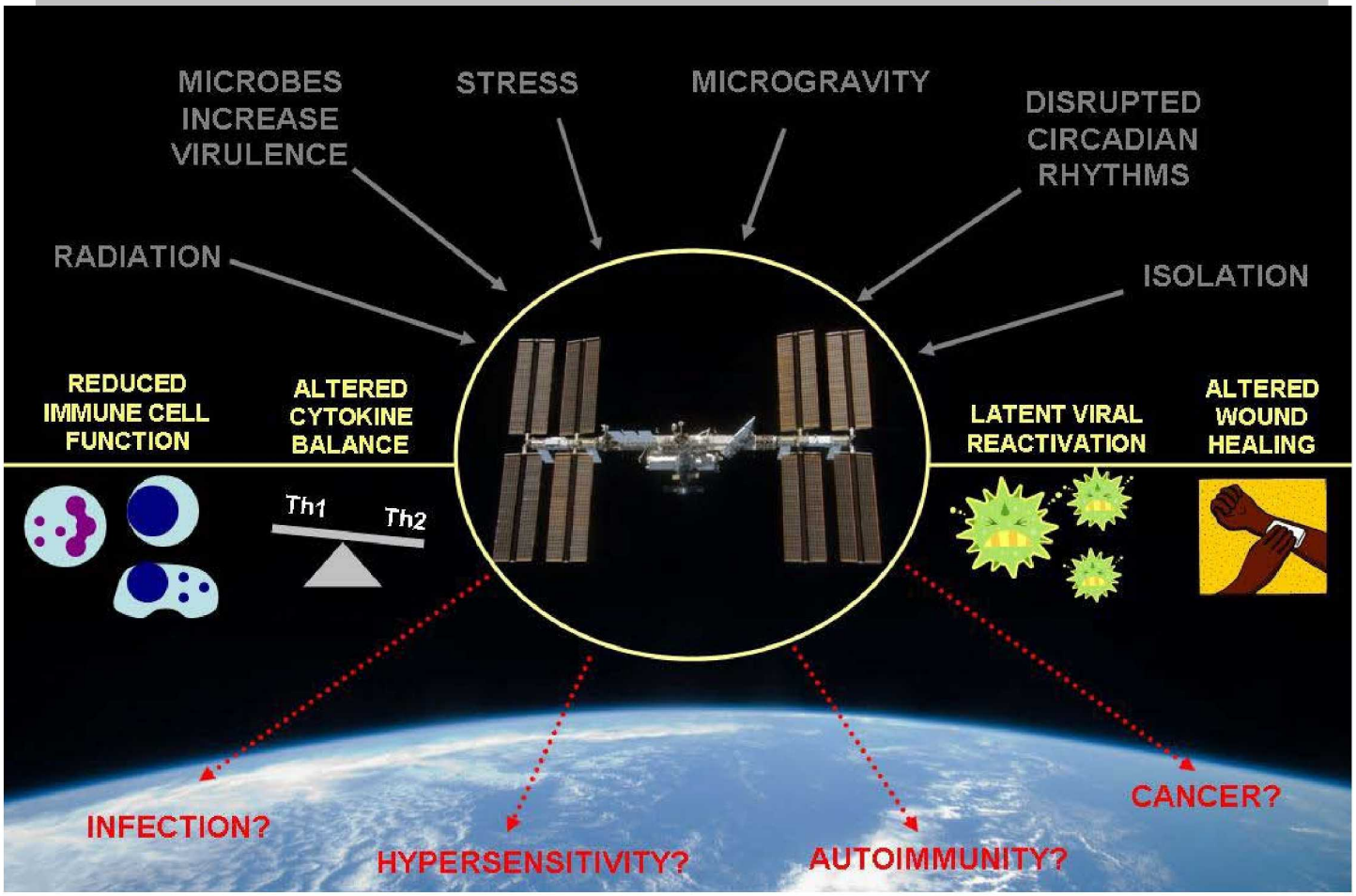
CA-MRSA Exercise

- Short of not launching anybody, what reasonable precautions could be taken to prevent launching CA-MRSA into space?
- What degree of (un)certainty is acceptable?
- Objectively, how bad might the consequences be, and what is most likely?
- Under what circumstances would you allow it?
- What on-orbit resources should be available in the event CA-MRSA successfully reaches orbit?
- Do potential changes in host immunity undermine the usefulness or reliability of predictions and planning?

Crucian, et al., space immunity

- "In-flight testing of humans has revealed that latent herpes viruses reactivate to a high level during short-duration spaceflight, but it is currently unknown whether this phenomenon would persist or intensify during extended duration flight, or eventually resolve itself. During long duration flight, cell-mediated immunity has been demonstrated to be reduced in some subjects, and there may be a relationship between the observed in-flight immune changes and reactivation of latent viruses. Postflight human testing has revealed severely depressed T cell function following 6 months of flight, but unaltered function following short-duration flight. Altered cytokine production patterns and potentially a shift to the Th2 pattern have been observed following spaceflight. Natural killer (NK) cell, monocyte, and neutrophil function have all been found to be reduced following spaceflight. Stress hormone levels have been found to be elevated following flight, heavily dependent on mission duration. Various animal studies have demonstrated similar findings either during or after flight."

Immune System in Space



Pierson, et al, Viral re-activation

- Stress-induced subclinical reactivation of varicella zoster virus in astronauts. J Med Virol 2004;72;174-9
- Varicella Zoster in the Saliva of Patients with Herpes zoster JID 2008:197 (1 March)

Varicella-Zoster Virus in the Saliva of Patients with Herpes Zoster

Satish K. Mehta,[1] Stephen K. Tyring,[3] Donald H. Gilden,[4,5] Randall J. Cohrs,[4] Melanie J. Leal,[1] Victoria A. Castro,[1] Alan H. Feiveson,[2] C. Mark Ott,[2] and Duane L. Pierson[2]

[1]Enterprise Advisory Services, Inc., [2]Space Life Sciences, National Aeronautics and Space Administration, Lyndon B. Johnson Space Center, and [3]University of Texas Health Science Center, Houston; Departments of [4]Neurology and [5]Microbiology, University of Colorado Health Sciences Center, Denver

(See the editorial commentary by Breuer and the article by Lopez et al., on pages 635–7 and 646–53, respectively.)

Fifty-four patients with herpes zoster were treated with valacyclovir. On treatment days 1, 8, and 15, pain was scored and saliva examined for varicella-zoster virus (VZV) DNA. VZV DNA was found in every patient the day treatment was started and later disappeared in 82%. There was a positive correlation between the presence of VZV DNA and pain and between VZV DNA copy number and pain ($P < .0005$). VZV DNA was present in 1 patient before rash and in 4 after pain resolved and was not present in any of 6 subjects with chronic pain or in 14 healthy subjects. Analysis of human saliva has potential usefulness in the diagnosis of neurological disease produced by VZV without rash.

Microbe changes in space

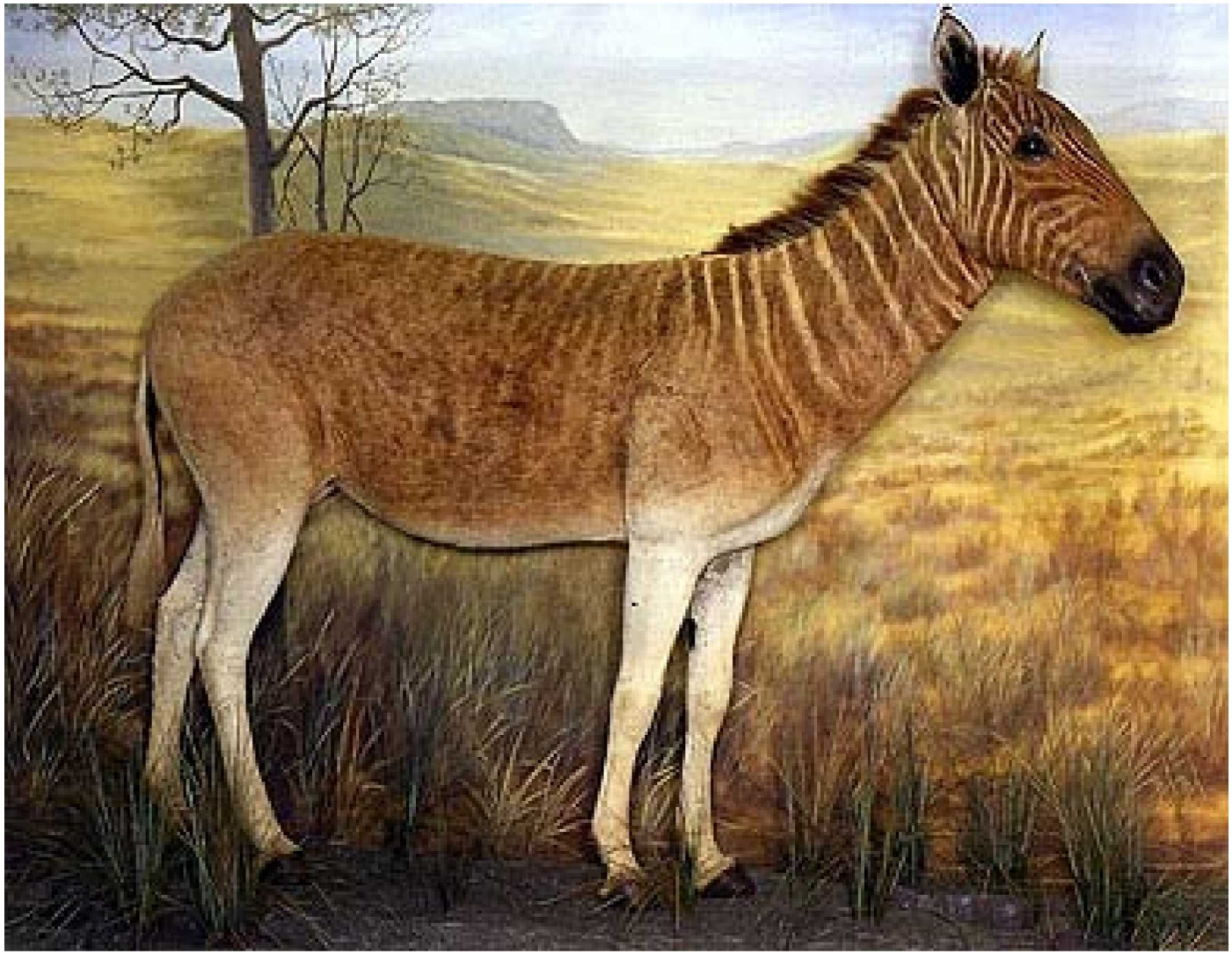
- ***Normal flora travel with us.***
- ***Intuitively, one might reason that a microbe would not change in space. How would it "tell" where it was? There is no fluid column to speak of, nor a vestibular system. No reason to think that evolution has produced an organelle that detects orbital velocity or a subtle change in the curve of space.***
- ***But that turns out not to be the point…***

Microbe Changes in Space

- Shear forces are altered in free-fall, and bacteria have had in their history opportunity to experience environments with variable shear forces. So the effect of orbital free-fall is to bring out one mode of terrestrial response. Even within a host, shear forces vary by region and tissue. Such as between brush border microvilli.

- CA Nickerson, JW Wilson, CM Ott, PNAS Oct 9, 2007, vol. 104 no. 41 16299-16304

When you hear hoofbeats…



Horses, Quaggas and Zebras

Given what we know about genomes, are you completely sure that horses don't carry genes for stripes?

That which looks new, may in fact be old, and may remain in play under certain conditions.

Nickerson, Ott, Wilson, et al

- "Space flight alters bacterial gene expression and virulence and reveals a role for global regulator Hfq"
- PNAS October 9, 2007, Vol. 104, no. 41 16299-16304

Space flight initially modeled with a rotating wall vessel (RWV) that allows bacterial cultures to grow with a minimum of shear forces.

" Specifically, S(almonella) typhimurium grown in…low-shear modeled microgravity (LSMMG) exhibited increased virulence, increased resistance to environmental stresses (acid, osmotic and thermal), increased survival in macrophages, and global changes in gene expression at the transcriptional and translational levels."

The experiment was repeated aboard STS-115 using a carefully structured Fluid Processing Apparatus while parallel cultures obtained on the ground. Results consistent with previous studies using Rotating Wall Vessel.

"The space flight environment imparts a signal that can induce molecular changes in bcterial cells. Furthermore, these results also provide direct evidence that this signal can alter the virulence of a microbial pathogen."

Significant differences in space-grown Salmonella

167 genes differently expressed (+/- 2x expression)

73 proteins at different levels

Decreased LD50 in mice, lower rate of survival and earlier death

Extracellular material expression consistent with biofilm.

Nickerson, Wilson, Ott, et.al PNAS 104;41;16299-16304

Meet the new bug, Same as the old bug

- ***The changes in behavior and virulence seen in Salmonella typhimurium are widespread and reproducible.***
- ***This is not what a mutating organism would be expected to show, with variable changes in individual genes.***
- ***Rather, the bacterium, placed in a novel environment, is consistently expressing a pre-existing package, one that is appropriate for normal low-shear environments to which the bacterium is well adapted.***

Space Changes Suggest a New Target for Terrestrial Therapy

- A two-fold change in Salmonella virulence does not change the fact that you didn't want to be ingesting Salmonella in Space one way or the other.
- The point is that these changes may occur in terrestrial contexts, such as with the formation of biofilms, and provide an opportunity to interrupt virulence mechanisms in normal settings.

Effects of the Space Environment on terrestrial microbes

- How common and how extensive?
- What are the likely mechanisms of the observed changes?
- What is the operational relevance? What if nobody actually gets sick?
- Should changes be made accordingly in pre-launch screening and eradication efforts, in the orbital pharmacy, or in orbital environmental assays?

Current ISS approach to Preventing, Mitigating and Treating Flight-Related Infectious Disease

Infection Control: Longitudinal View, preflight

- Healthy crew: MED Vol A, condition at selection
- MED Vol B condition at mission assignment
- Specific immunity to and/or demonstrated absence of pathogens and/or absence of overt disease.
- Prophylactic treatment and/or vaccination
- Quarantine pre-launch.

Specific Entities Screened

MED Vol A: Syphilis (VDRL or RPR), HIV, Hepatitis A,B,C, *H. pylori* (Urea breath test, serology, or biopsy), TB (skin test, quantiferon), MRSA (nasal cultures only).

Other disqualifying entities: General mission-impacting, TB w/in last 2 years, LTBI untreated, malaria, AIDS, chronic hepatitis B,C, Lyme disease, MRSA carrier state, mission-impacting herpes simplex I, II, intestinal parasites, herpes zoster, active or post-herpetic neuralgia.

MED Vol B: Timing and Wrinkles

- ***H. pylori***. Testing at L-365/330. May use serology, UBT, stool serology or biopsy. If positive, treat and re-assess with UBT or Stool antigen. Persistent positives assessed on case-by-case basis.
- Wrinkle: Detection or conversion close to launch, otherwise without symptoms.
- ALARA philosophy

MED Vol B: Timing and Wrinkles

- Tuberculosis: some international variation in screening for LTBI. MED Vol A, B protocols include Quantiferon as means of reconciling protocols of several different nations. Timing: L-365/330

MED Vol B: Timing and Wrinkles

- MRSA Nasal cultures at L-45/30 days with topical mupirocin and anti-staphylococcal washes for 5 days. No follow-up culture mandated, intentionally. Aim is ALARA, recognizing that other risks emerge from removing asymptomatic crew close to launch. If symptomatic, a different rule is invoked.
- Wrinkle #1: Nasal swabs miss 25% of carriage
- Wrinkle #2: Potential exists for onset of carriage between L-30 and launch, especially as all contacts (1000's) in that period not screened.

Infection Control: Preflight confounders

Colonists and "normal flora" can become pathogens—risk not zero

True pathogens may have low risk that cannot be reduced to zero

Over-aggressive preventive interventions may cause harm or exclude valuable personnel

Risk assessment, "risk trough"

In-Flight Infectious Safeguards

- Skin care and preservation of skin barrier (harness fit, etc).
- Normalized exercise, sleep and nutrition
- Air filtration
- Food and Water processing (heating and biocides)
- Environmental microbial sampling
- Vaccination pre-flight may prevent secondary cases in flight, e.g., varicella pneumonia less likely upon exposure to another crewmember with dermatomal zoster.

In-Flight Infectious Safeguards

- To what extent is immunity compromised?
- How much of that compromise is relevant in the space working environment?
- To what extent can immunity be normalized?

In-Flight Infectious Safeguards

- Pharmacological agents fall into two categories:
- 1) Definitive treatment or suppression on orbit, without significant disruption of mission. Most of the topical and oral medications fall into this category
- 2) Temporizing treatment of more serious illnesses while evacuating to definitive care

Antibiotics on ISS

Antivirals

Topical:

Acyclovir ointment (Zovirax) 15 gm tube (1)

Oral:

Oseltamivir (tamiflu) 75 mg tablet (30)

Valacyclovir (valtrex) 1 gm tablet (21)

Antibiotics on ISS

- Parenteral antibacterial

Amikacin 250 mg/ml (2 ml unit) (4)

Ceftriaxone (1 gm) provided with xylocaine 1% (1)

In either case, essentially a one day supply.

Antibiotics on ISS

- Oral antibacterial

Amoxicillin 500 mg tabs (84)

Azithromycin 250 mg tabs (20)

Bismuth subsalicylate tabs (48) (*H. pylorii)*

Cefadroxil (duricef) 500 mg capsules (40)

Levofloxacin (levaquin) 500 mg tablet (30)

Metronidazole (flagyl) 250 mg (28 tabs)

Trimethoprim/Sulfamethoxazole 160/800 mg (56)

Vancomycin 250 mg capsule (4)

Antibiotics on ISS

- Topical Antibacterial

Bacitracin ointment 28 gm tube (1)

Ciprofloxacin Ophthalmic ointment 0.3% 3.5 gm tube (2)

Ciprofloxacin ophthalmic solution 0.3% 5 ml bottle (6)

Mupirocin ointment 2% 22 gm tube (1)

Polymyxin/Bacitracin ointment 28.3 gm tube (2)

Polymyxin B sulfate and Trimethoprim ophthalmic solution 10 ml (1)

Silver sulfadiazine cream 1% (20 gram tube) (2)

Tobramycin ophthalmic solution 0.3% 5 ml bottle (1)

Tobramycin/dexamethasone ophthalmic solution 5 ml (1)

Antibiotics on ISS

- Oral antifungal
- Fluconazole tablets 150 mg (3)

Antibiotics on ISS

- Topical anti-fungal

Clotrimazole cream (lotrimin)12 gm tube (2)

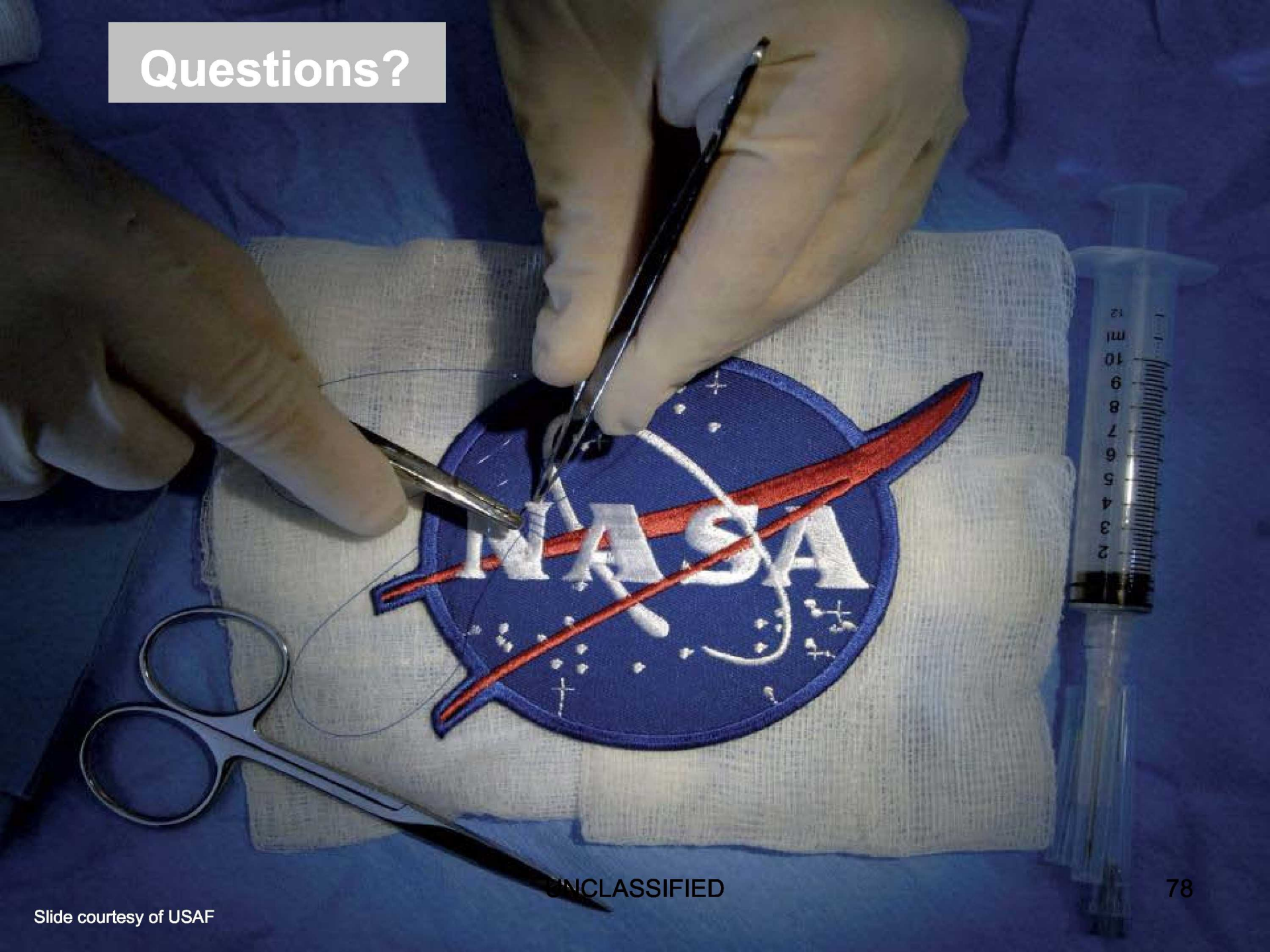
Antiseptics on ISS

- Isopropyl alcohol pads (35)
- Benzalkonium chloride wipes (58)
- Povidone iodine (betadine) swabs (15)

- Wound care items (including steri-strips and staples as well as sutures), barriers, dressings, drapes, oto-wicks, waste disposal bags.

"Mir cat"

Questions?



Slide courtesy of USAF