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IMMUNE COMPROMISE IN ASTRONAUTS

Physical and psychological stresses cause immune alterations, and these factors may be significant contributors to a compromised immune state associated with spaceflight. Data from studies of students during examination periods and military cadets during training, as well as studies of individuals participating in Antarctica winter-over missions, indicate significant immune effects from psychological stress.2-4 A vast evidence base demonstrates that dysregulation of the human immune system is associated with spaceflight.5,6 T cell, natural killer cell, monocyte, and neutrophil function diminish during and/or after spaceflight.7-11 Stress hormone levels are elevated after flight and correlate strongly with mission duration.12,13 Altered cytokine
production patterns and a potential Th2 shift have been observed during or after spaceflight.\textsuperscript{14-16} The reactivation of latent herpes viruses has been demonstrated to occur during spaceflight\textsuperscript{17,18} and correlates with dysregulated plasma cytokine levels, thus confirming a direct linkage between immune dysregulation and latent herpes virus reactivation.\textsuperscript{19} During long-duration flight, \textit{in vivo} cell-mediated immunity is reduced in some subjects.\textsuperscript{20} Although not a widespread clinical concern for astronauts, epidemiological studies of astronaut medical records have revealed incidence of some specific clinical events that could relate to altered immunity.\textsuperscript{21} A case study of an ISS astronaut further supports a linkage between immune dysregulation, latent virus reactivation (ie, Epstein-Barr virus [EBV], varicella-zoster virus [VZV], and herpes-simplex-1 [HSV-1]), and adverse clinical outcomes.\textsuperscript{22} Given that various physiological stressors associated with spaceflight are likely to increase during planned deep-space exploration missions, thereby increasing crew clinical risk, a discussion of immunological countermeasures for spaceflight has ensued.\textsuperscript{23,24}

**EVIDENCE-BASED AUGMENTATION TO POST-FLIGHT QUARANTINE**

Crewmembers returning from space reside in crew quarters at JSC for medical observation, with limited contacts. However, they do interact with family members, medical personnel, researchers conducting biomedical experiments, and media members on occasion. From the study of ISS and Shuttle crews post-flight, there is no evidence of an increased incidence of respiratory or other viral infections over pre-flight rates. However, the SARS-CoV-2 pandemic is without precedent with regard to risk for hospitalization and severe illness. Therefore, an abundance of caution is necessary in managing post-flight crews, to limit their exposure to those with the potential to transmit SARS-CoV-2. On recommendation from specialists in infectious disease, specialists providing care in pandemic-affected areas, and specialists in spaceflight immunology, NASA implemented enhanced precautionary measures to shield the recently returned ISS astronauts (Soyuz 61S) from SARS-CoV-2.

Astronauts returning from the ISS via the Russian Soyuz land in Kazakhstan. NASA works closely with the Russian medical and search and rescue (SAR) teams, weeks ahead of landing to organize logistical support of retrieving returning astronauts and cosmonauts. NASA deploys a team on a NASA-operated Gulfstream aircraft to a staging area in the country the week before the proposed landing date to finalize and rehearse the landing operation with their Russian counterparts. The NASA landing team, also known as the Direct Return team, comprises flight surgeons, ISS Program representatives, an Astronaut Office representative, aircrew, and their backups. In preparation for the Soyuz 61S landing, special precautions were taken by the landing team to minimize risk of exposure to SARS-CoV-2. These precautions included strict home quarantine beginning 14 days before departure from Houston to Kazakhstan by all team members and backups, temperature checks and symptom screening twice daily, and optimizing sleep, diet, and daily exercise. On arrival at the Houston airport, and throughout the duration of the 5-day astronaut retrieval mission, all Direct Return team members donned personal protective equipment (PPE), per CDC-recommended protocols. The interior surfaces of, and the equipment aboard, the Gulfstream aircraft were sanitized according to a CDC-recommended method.

The US crew surgeons did not know whether the Russian SAR and medical teams practiced the same precautionary measures as the US team. However, in Kazakhstan, all personnel that the US landing party encountered donned Tyvek white suits, facemasks, face shields, gloves, and practiced physical distance. The gear and luggage were sanitized with a dilute bleach solution. The vehicle drivers that accompanied the US team to the landing site wore PPE. Fifteen kilometers from the Baikonur Cosmodrome (the spaceport facility), armed Russian military personnel, donning PPE, performed body temperature checks of the US team via infrared forehead scans, and requested proof of a recent negative SARS-CoV-2 polymerase chain reaction (PCR) test, as well as diplomatic papers attesting they had been in quarantine for 14 days before arrival. Before the space crews’ deorbit and return to Earth, the briefings between the Russian and US SAR teams proceeded by video conference. On the day of landing, before deploying the Russian Mi-8 helicopters, the Russianambulances that would be used to transport the US astronauts to the NASA jet in Kyzlorda, 4 hours away, were certified to comply with measures preventive for infectious diseases. At the spacecraft-landing site, all personnel donned facemasks and gloves (Figure 1). The American flight surgeons were assured that all Russian aircrew and support personnel had performed a 14-day quarantine and tested negative for SARS-CoV-2 immediately before landing. To this day, none of the US or Russian landing teams, surgeons, or returning astronauts have ever exhibited symptoms of COVID-19 or tested positive for SARS-CoV-2 infection, following the landing operation.

After return to Houston, the astronaut crew, flight surgeons, and immediate family support—who performed a home quarantine, and documented temperature and symptom checks twice daily for the 14 days leading up to landing—proceeded to a strict quarantine facility onsite at JSC, with limited outside contact for a 7-day period after landing. The limited medical and research laboratory personnel that interacted with the crew had performed a strict 14-day home quarantine and donned full PPE in the presence of the crewmembers.

**ADDITIONAL POST-FLIGHT MONITORING OF IMMUNE STATUS**

Typical immunologic research investigations at NASA surveil crewmembers at single or multiple time points before flight, in flight, at landing, and after flight, anywhere from 30 to 90 days in order to determine immune recovery. Because of the COVID-

### Abbreviations used

- COVID-19: Coronavirus disease 2019
- EBV: Epstein-Barr virus
- HSV-1: Herpes-simplex-1
- ISS: International Space Station
- JSC: NASA Johnson Space Center
- PCR: Polymerase chain reaction
- PPE: Personal protective equipment
- SAR: Search and rescue
- SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
- SC: Subcutaneous
- VZV: Varicella-zoster virus
A recent study indicates that some already-deployed diet and exercise biomedical countermeasures induce a positive effect on immunity in astronauts. If the pandemic persists, this immunological evaluation protocol could be considered for routine use before and after flight.

**BOOSTING IMMUNOCOMPETENCE**

Because future deep-space exploration missions will endure for an unprecedented amount of time, with increased magnitude of mission-associated stressors, it is reasonable to expect a higher incidence of morbidities. To this end, NASA published a comprehensive review of potential countermeasures to obviate the immune “problem” associated with spaceflight. Subsequently, NASA published a specific and personalized immune countermeasure prescription for prospective astronauts embarking on deep-space voyage. This protocol consists of various nutritional supplements (vitamin D, a probiotic), a specific exercise protocol that maintains fitness similar as was achieved aboard ISS using specifically designed aerobic and resistive devices, the use of daily stress-relieving breathing exercises via a virtual reality—based guided protocol, and pharmacological interventions. Continuous use pharmacological options to augment the medical kit for deep-space missions include antivirals and antihistamines, whereas as-needed options to “reset” immunity include subcutaneous (SC) interleukin-2, SC polyclonal IgG, and granulocyte colony-stimulating factor (G-CSF). SARS-CoV-2 infection frequency and COVID-19 development and prognosis are markedly more severe for patients with an underlying condition of immune compromise. We hypothesize that the “immune boosting” protocol designed for astronauts has a terrestrial utility—to augment standard therapy of patients with secondary immunodeficiency, including those with COVID-19.

**OTHER CONSIDERATIONS**

A need to reduce the risk of infectious disease for astronauts has been recognized since the Apollo program and the initiation of the NASA Health Stabilization Program (pre-mission quarantine). The SARS-CoV-2 pandemic represents an unprecedented medical crisis. The precautionary procedures implemented for this Soyuz landing to protect astronaut health will be reviewed, and possibly both pre- and post-mission protocols may be enhanced for future space missions (ISS and lunar).

It is essential that the ISS be protected from SARS-CoV-2. This virus aboard station could have profound operational impacts, including required deorbit of the entire crew. SARS-CoV-2 is also a real threat to the goal of deep-space exploration in this next decade. An expansion of the current pre-flight quarantine could be considered, as SARS-CoV-2 is a persistent virus with a long incubation period. The quarantine should span comfortably the contagious state of the virus, which for SARS-CoV-2 is a minimum of 14 days. An expanded quarantine could prevent the virus from doing a “slow burn” through the crew, with overlapping incubation periods exceeding in their sum the length of the quarantine period. It could also be beneficial to consider testing the astronauts at strategic time points for the presence of virus and for immune responsiveness to assure that the quarantine was successful. Monitoring could occur at the start of the true quarantine and close to launch, at a minimum.
Implementation of any new pre-flight medical requirements would not happen until proper vetting by the appropriate NASA medical board and international partner space agencies. As the SARS-CoV-2 prognosis is far more serious for immunocompromised individuals, immunological monitoring of crews after landing may afford an evidence-based approach to reduce crew risk during normal post-flight contacts and to determine optimal time for home release of crewmembers. Careful planning and decisive action by NASA at JSC prevented a crisis for returning crewmembers in April 2020, but the virus continues to ravage humanity around the world, and there is no effective therapy or vaccine within reach. In all likelihood, NASA will have to contend with this threat as a “new normal.” Consideration of enhanced medical protection procedures, some having been triaged during the recent Soyuz 61S landing, could have definite benefits to protecting ISS astronaut health. Coupled with a suite of translational “immune countermeasures,” they should afford increased protection for the planned deep-space missions.

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