SARS-CoV-2 Pandemic Impacts on NASA Ground Operations to Protect ISS Astronauts

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NASA implements required medical tests and clinical monitoring to ensure the health and safety of its astronauts. These measures include a pre-launch quarantine to mitigate the risk of infectious diseases. During space missions, most astronauts experience perturbations to their immune system that manifest as a detectable secondary immunodeficiency. On return to Earth, after the stress of re-entry and landing, astronauts would be most vulnerable to infectious disease. In April 2020, a crew returned from International Space Station to NASA Johnson Space Center in Houston, Texas, during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Post-flight quarantine protocols (both crew and contacts) were enhanced to protect this crew from SARS-CoV-2. In addition, specific additional clinical monitoring was performed to determine post-flight immunocompetence. Given that coronavirus disease 2019 (COVID-19) prognosis is more severe for the immunocompromised, a countermeasures protocol for spaceflight suggested by an international team of scientists could benefit terrestrial patients with secondary immunodeficiency. **(J Allergy Clin Immunol Pract 2020;8:3247-50)**

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On Wednesday, March 18, 2020, in response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the executive leadership at NASA Johnson Space Center (JSC) decreed a mandatory telework policy, effectively imposing a self-quarantine on its workforce. Until further notice, all work would continue remotely, except for mission-essential personnel, defined as those required for the protection of life or property, or critical to the completion of a flight-related objective. It was a bold decision, considering at the time there were no confirmed cases of coronavirus disease 2019 (COVID-19) at JSC, the caseload in Houston was far less dramatic than in other American cities, and Texas Governor Greg Abbott had not issued any social restrictions officially (his shelter-in-place decree occurred on March 31, nearly 2 weeks after JSC's decision). NASA medical personnel began mapping an Agency response in February 2020, culminating in a 4-stage strategy: level 1—status quo, with recommended precautionary measures; level 2—recommended telework policy; level 3—mandatory telework policy, except for mission essential work; level 4—a complete shutdown of operations. The Agency leadership team stated that their decision to escalate the response through the various stages of the strategy would be guided by the local conditions—the number of local cases reported by symptoms, the number of confirmed cases, and area hospital capacity. However, given the rapid spread of the virus across the United States (by March 17, all 50 states reported confirmed cases of infections and COVID-19 morbidity),[1] and the CDC's warning on March 15 against holding or attending gatherings larger than 50 people,[1] JSC management decided to transition to the strict stage 3 telework policy. Clearly, the JSC leadership team acted ahead of the local curve. Still, SARS-CoV-2 was rampant. With an astronaut crew returning from the International Space Station (ISS) on April 17, 2020, the urgent task was now to augment standard operating procedures to ensure the health and safety of the astronauts from SARS-CoV-2 infection and morbidity.

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

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

production patterns and a potential Th2 shift have been observed during or after spaceflight.[14-16] The reactivation of latent herpes viruses has been demonstrated to occur during spaceflight[17,18] and correlates with dysregulated plasma cytokine levels, thus confirming a direct linkage between immune dysregulation and latent herpes virus reactivation.[19] During long-duration flight, *in vivo* cell-mediated immunity is reduced in some subjects.[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.[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.[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.[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 Russian ambulances 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-

FIGURE 1. An astronaut who returned from the International Space Station on Soyuz 61S is cared for by support personnel wearing face masks, as part of the precautions in response to the COVID-19 global pandemic. NASA ID: NHQ202004170035. Photo Credit: NASA/GCTC/Andrey Shelepin.

19 threat, the flight surgeons requested specific immunological assessments at landing, as well as 3 and 7 days after landing. This strategy enabled the surgeons to define the immune competence of the astronauts more quickly, before releasing them to home quarantine.

T cell frequency and function was the focus of the post-flight testing augment because the early literature describing the immunology of patients with COVID-19 suggests T cells play a vital role in the defense against SARS-CoV-2. Severe COVID-19 prognosis correlates highly with reductions (at initial presentation) of absolute T cell (CD4 and CD8) counts,[25] and a low frequency of CD3+ CD8+ T cells (<75 cells/μl) is a predictor of mortality, based on the study of 179 patients with COVID-19.[26] Furthermore, the lower the absolute value of CD4+ T lymphocytes, the longer the virus persists.[27] Of mechanistic interest, central memory CD4+ and CD8+ T cell subsets of patients with COVID-19 displayed a phenotype of exhaustion.[28] Thus, low numbers of T cells appear to correlate with sensitivity to COVID-19 disease progression; T cells are an obvious target for therapeutic intervention and a useful measure for immune surveillance.

Immune compromise of NASA astronauts has been defined by the measurement of absolute leukocyte number, the frequency of lymphocyte subsets (CD4:CD8, central memory, senescent, etc.), and T cell function in response to mitogenic polyclonal stimulation—the induction of cellular activation antigens (CD69 and CD25).[10,18] Given the overlap in the immune correlates of spaceflight-induced immune dysfunction and COVID-19 prognosis, we used multi-parametric flow cytometry to quantify these analytical endpoints from the blood samples of the returning 61S astronauts. In addition, reactivation and shedding of EBV, VZV and HSV-1 DNA in saliva, an excellent biomarker for immune compromise, was determined by quantitative PCR.

The assessment panel was performed on both returning US crewmembers. For interpretive purposes, all findings reported to Flight Medicine were compared with previously established normal ranges. The returning crewmembers demonstrated a typical pattern of immune dysregulation associated with spaceflight,[10] which trended to resolution by 3 to 7 days after landing. Previous studies have revealed that for ISS crewmembers, such compromise can persist for up to 30 days after landing.[10] A recent study indicates that some already-deployed diet and exercise biomedical countermeasures induce a positive effect on immunity in astronauts.[29] 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.[23] Subsequently, NASA published a specific and personalized immune countermeasure prescription for prospective astronauts embarking on deep-space voyage.[24] 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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REFERENCES

1. Schumaker E. Timeline: How coronavirus got started. ABC News. September 22, 2020. Available from: https://abcnews.go.com/Health/timeline-coronavirus-started/story?id=69435165. Accessed May 5, 2020.
2. Glaser R, Pearson GR, Bonneau RH, Esterling BA, Atkinson C, Kiecolt-Glaser JK. Stress and the memory T-cell response to the Epstein-Barr virus in healthy medical students. Health Psychol 1993;12:435-42.
3. Feuerecker M, Crucian BE, Quintens R, Buchheim JI, Salam AP, Rybka A, et al. Immune sensitization during 1 year in the Antarctic high-altitude Concordia Environment. Allergy 2019;74:64-77.
4. Tingate TR, Lugg DJ, Muller HK, Stowe RP, Pierson DL. Antarctic isolation: immune and viral studies. Immunol Cell Biol 1997;75:275-83.
5. Guéguinou N, Huin-Schohn C, Bascove M, Bueb JL, Tschirhart E, Legrand-Frossi C, et al. Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit? J Leukoc Biol 2009;86:1027-38.
6. Makedonas G, Chouker A, Mehta SK, Simpson RJ, Stowe RP, Sams CF, et al. Mechanistic clues to overcome spaceflight-induced immune dysregulation. Curr Pathobiol Rep 2018;6:185.
7. Cogoli A. The effect of space flight on human cellular immunity. Environ Med 1993;37:107-16.
8. Sonnenfeld G, Shearer WT. Immune function during space flight. Nutrition 2002;18:899-903.
9. Borchers AT, Keen CL, Gershwin ME. Microgravity and immune responsiveness: implications for space travel. Nutrition 2002;18:889-98.
10. Crucian B, Stowe RP, Mehta S, Quiriarte H, Pierson D, Sams C. Alterations in adaptive immunity persist during long-duration spaceflight. NPJ Microgravity 2015;1:15013.
11. Bigley AB, Agha NH, Baker FL, Spielmann G, Kunz HE, Mylabathula PL, et al. NK cell function is impaired during long-duration spaceflight. J Appl Physiol (1985) 2019;126:842-53.
12. Stowe RP, Sams CF, Pierson DL. Effects of mission duration on neuroimmune responses in astronauts. Aviat Space Environ Med 2003;74:1281-4.
13. Stowe RP, Sams CF, Pierson DL. Adrenocortical and immune responses following short- and long-duration spaceflight. Aviat Space Environ Med 2011; 82:627-34.
14. Sonnenfeld G, Miller ES. The role of cytokines in immune changes induced by spaceflight. J Leukoc Biol 1993;54:253-8.
15. Sonnenfeld G. Effect of space flight on cytokine production. Acta Astronaut 1994;33:143-7.
16. Crucian BE, Zwart SR, Mehta SK, Uchakin P, Quiriarte HD, Pierson D, et al. Plasma cytokine concentrations indicate that in vivo hormonal regulation of immunity is altered during long-duration spaceflight. J Interferon Cytokine Res 2014;34:778-86.
17. Pierson DL, Stowe RP, Phillips TM, Lugg DJ, Mehta SK. Epstein-Barr virus shedding by astronauts during space flight. Brain Behav Immun 2005;19: 235-42.
18. Mehta SK, Laudenslager ML, Stowe RP, Crucian BE, Feiveson AH, Sams CF, et al. Latent virus reactivation in astronauts on the international space station. NPJ Microgravity 2017;3:11.
19. Mehta SK, Crucian BE, Stowe RP, Simpson RJ, Ott CM, Sams CF, et al. Reactivation of latent viruses is associated with increased plasma cytokines in astronauts. Cytokine 2013;61:205-9.
20. Taylor GR, Janney RP. In vivo testing confirms a blunting of the human cell-mediated immune mechanism during space flight. J Leukoc Biol 1992;51: 129-32.
21. Crucian B, Babiak-Vazquez A, Johnston S, Pierson DL, Ott CM, Sams C. Incidence of clinical symptoms during long-duration orbital spaceflight. Int J Gen Med 2016;9:383-91.
22. Crucian B, Johnston S, Mehta S, Stowe R, Uchakin P, Quiriarte H, et al. A case of persistent skin rash and rhinitis with immune system dysregulation onboard the International Space Station. J Allergy Clin Immunol Pract 2016;4: 759-762.e8.
23. Crucian BE, Chouker A, Simpson RJ, Mehta S, Marshall G, Smith SM, et al. Immune system dysregulation during spaceflight: potential countermeasures for deep space exploration missions. Front Immunol 2018;9:1437.
24. Makedonas G, Mehta S, Chouker A, Simpson RJ, Marshall G, Orange JS, et al. Specific immunologic countermeasure protocol for deep-space exploration missions. Front Immunol 2019;10:2407.
25. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620-9.
26. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55:2000524.
27. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl) 2020;133:1039-43.
28. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol 2020;17: 533-5.
29. Crucian BE, Makedonas G, Sams CF, Pierson DL, Simpson R, Stowe RP, et al. Countermeasures-based improvements in stress, immune system dysregulation and latent herpesvirus reactivation onboard the International Space Station—relevance for deep space missions and terrestrial medicine. Neurosci Biobehav Rev 2020;115:68-76.