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Risk of severe COVID-19 infection in International Space Station astronauts despite routine pre-mission measures

To the Editor:

In the article "SARS-CoV-2 Pandemic Impacts on NASA Ground Operations to Protect ISS Astronauts,"[1] recently published in the *Journal of Allergy and Clinical Immunology: In Practice*, Makedonas et al addressed current medical tests and clinical monitoring procedures that ensure the health and safety of National Aeronautics and Space Administration astronauts, including a prelaunch quarantine (to decrease infectious disease risk), the issue of immune system dysregulation during the mission, and post-mission astronauts' vulnerability to infectious disease as well as post-mission quarantine protocols. They also highlighted the risk associated with poor COVID-19 prognosis in immunocompromised individuals such as postflight astronauts. Although the article by Makedonas et al can be considered a significant contribution to the field of space medicine in the COVID-19 pandemic era, it has a major omission. We believe that the authors are overly focused on postflight issues, whereas the cardinal issue is severe infection during the mission, as addressed in recent publications.[2,3] In this commentary, we provide evidence indicating that even with the most reliable pre-mission screening and quarantine strategies, astronauts with a latent (hidden, inactive, or dormant) SARS-CoV-2 infection can inadvertently be sent to space. Although according to some early studies, the rate of asymptomatic infections was as high as 81%,[4] a meta-analysis that included 13 studies involving 21,708 individuals reported asymptomatic presentation in 17% of the population.[5] Accordingly, when there is a dormant infection in these individuals, not only they are unaware of the infection, it is likely that they could successfully pass all prelaunch medical tests. The findings of new studies clearly support the key idea discussed in our article, "Can Reactivation of SARS-CoV-2 Decrease the Chance of Success of Future Deep Space Missions?"[2]. Regarding reactivation, a recent study[6] showed that among 109 patients, 29 experienced reactivation (27%), and seven of these were symptomatic (24%). Given this consideration, during a long-term space mission, when the immune system starts to weaken, the dormant infection may progress to a severe infection. This issue is of paramount importance because it directly affects the chance of success of any mission. Further studies are warranted to clarify the different aspects of this issue.

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Reply to "Risk of severe COVID-19 infection in International Space Station astronauts despite routine pre-mission measures"

To the Editor:

We thank Mortazavi et al[1] for their interest in our article.[2] In their commentary, the salient point raised is that risk for SARS-CoV-2 reactivation during spaceflight is a concern that was unaddressed in our original article.

The point of the article was to share how the National Aeronautics and Space Administration (NASA) adjusted protocols to reduce risk for returning astronauts during the initial stages of the pandemic. Returning astronauts manifest a defined pattern of immune dysregulation, and the early-pandemic crews returned through a unique set of vehicle transfers (International Space Station [ISS] to Houston, via Kazakhstan) making clinical care a unique challenge. The article details all of the protocols put in place to protect crewmembers who are perceived to be more vulnerable to a serious prognosis if infected immediately after landing. The protocols span various operational impacts, including limiting contacts, adjusting postflight schedules, and for the first returning crew, monitoring of immune status before release from quarantine.

The commentary authors speculate that SARS-CoV-2 infection is challenging to detect ("hidden, inactive, or dormant"), and therefore an astronaut may launch to space with an asymptomatic but active infection that would worsen owing to immune compromise during flight. In fact, our article did not address protections for launching crewmembers; it was specific to returning crewmembers. The launch and landing clinical care scenarios are very different, and even more so because most American astronauts will now launch from US soil on a *SpaceX Dragon* capsule. Nevertheless, the commentary supposition is interesting and certainly worth considering. NASA protocols, including some specific for SARS-CoV-2, are designed to protect crews before launch. They should mitigate to the maximum extent possible the risk for an astronaut launching with an asymptomatic

case. These protocols include (1) a health stabilization program, essentially a preflight quarantine in place since Apollo and extremely effective at reducing crew infectious disease; (2) enhanced isolation protocols specific for SARS-CoV-2; (3) vaccination for SARS-CoV-2 and documented induction of protective antibody, and (4) frequent polymerase chain reaction tests for the crew and all crew contacts. During the pandemic, crews launching on Soyuz before vaccine was available were given a polymerase chain reaction test before launch, and no related clinical incidence was observed during the mission. This package of protections makes it extremely unlikely that future crews will launch with active infection, asymptomatic or otherwise.

The commentary authors are correct that crews manifest immune compromise during flight, and the pattern of dysregulation was found to be similar to that observed in zoster patients.[3] Recent evidence suggests that multisystem biomedical countermeasures already deployed to ISS benefit immunity.[4] However, because some of these ISS countermeasures do not readily translate to deep space missions, NASA and its international partners have embarked on the development of a countermeasure protocol that will benefit immunity and be compatible with deep space missions.[5] This international team of translational scientists created a protocol consisting of specific nutritional supplements, monitoring, stress-relieving techniques, specific duration and loads of aerobic and resistive exercise, and medications.[6] Immunity during deep space missions must be maintained regardless of SARS-CoV-2. Solar particle events, latent herpesvirus reactivation, mutagenic transformation, and increased microbial virulence within the vehicle microbiome will all require full crew immunocompetence. Planned research will validate countermeasures package to be effective at protecting deep space crewmembers during their transit phases of flight.

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The immunology of switching biologics in severe eosinophilic asthma patients

To the Editor:

We have read with interest the article by Eger and colleagues,[1] reporting four cases of symptomatic hypereosinophilia and sudden deterioration of asthma in patients switched from anti-IL-5/IL-5-R to anti IL-4-R-alfa. Because the cause is still to be determined, the authors speculated that a weaning-off effect not balanced by adequate oral corticosteroid (OCS) administration and the presence of a subclinical antineutrophil cytoplasmic antibodies-negative eosinophilic granulomatosis with polyangiitis might have contributed to the acute onset of eosinophilia and symptoms flare. Of note, one of the patients had stopped anti-IL-5 1 year before dupilumab administration, and OCS tapering had been cautious in all patients. For these reasons, other immunologic features may explain this peculiar adverse reaction.

First, the phase 2b randomized dose-ranging study demonstrated a 12-week recovery from complete eosinophil depletion after benralizumab suspension, even for dose regimens higher than approved for clinical practice (eg, 100 mg).[2] Second, post hoc analyses from phase 1, 2, and 3 studies demonstrated that benralizumab is significantly able to reduce not only blood and sputum eosinophils,[3] but also eosinophil granule proteins such as eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin.[4] On the contrary, serum IL-5, eotaxin/CCL11, and eotaxin-2/CCL24 levels were significantly increased after benralizumab administration.[4] In this context, although eotaxin levels could be markedly induced by IL-13, it is important to underline how (1) IL-5 levels do not depend strictly on the IL-4/IL-13 pathway; (2) CCL11 is constitutively expressed under homeostatic conditions; and (3) other cytokines, such as IL-3 and granulocyte-macrophage colony-stimulating factor, contribute to eosinophil maturation and activation.[5] Third, the presence of sinonasal symptoms, frequent severe exacerbations, OCS use, and high eosinophil levels in these patients is in line with the definition of severe eosinophilic asthma and the presence of an eosinophilic united airway disease.[6] In particular, a strict correlation among sinonasal thickening at computed tomography scans, the presence of nasal polyps, the levels of sputum eosinophils, and severity of asthma have been demonstrated.[6] Last but not least, eosinophil cationic protein levels in the LIBERTY ASTHMA QUEST study were substantially within normal levels (median baseline of 17.0 ng/mL), suggesting type 2 inflammation without eosinophil activation, at least in some patients. In this regard, blood eosinophilia occurred in 52 patients who received dupilumab (4.1%); eight needed to discontinue dupilumab treatment owing to this event.[7] Dupilumab was unable to decrease sputum eosinophils in patients with severe eosinophilic asthma.

In our opinion, all of these factors might have contributed to the sudden increase in eosinophil levels with the development of eosinophilic pneumonia and eosinophilic granulomatosis with