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COVID-19 DIGEST

From the Cross-Campus Infectious Diseases COVID-19 Task Force

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Letter from the Editors

Welcome to our November issue of the COVID-19 ID Digest. The pace of new information and developments in the field remains at a frenetic pace. We have new information on COVID-19 vaccines for the pediatric population, and information on a new investigational oral drug (molnupiravir) that can reduce risk to progress to serious disease for person who are newly infected. Have you heard about "PASC"? If not, or even if you have, you are in for a treat from our UCSF experts (Drs. Michael Peluso, Lekshmi Santhosh, and Steven Deeks) on the latest information on this syndrome. Enjoy the issue!

The Editors,

Brian Schwartz and Diane Havlir

UPDATES ON POST-ACUTE SEQUALAE OF COVID-19 (PASC) – "Long COVID"

What is the definition of post-acute sequelae of COVID-19 (is that the same as Long COVID?)? How common is the syndrome? How is it impacted by disease severity?

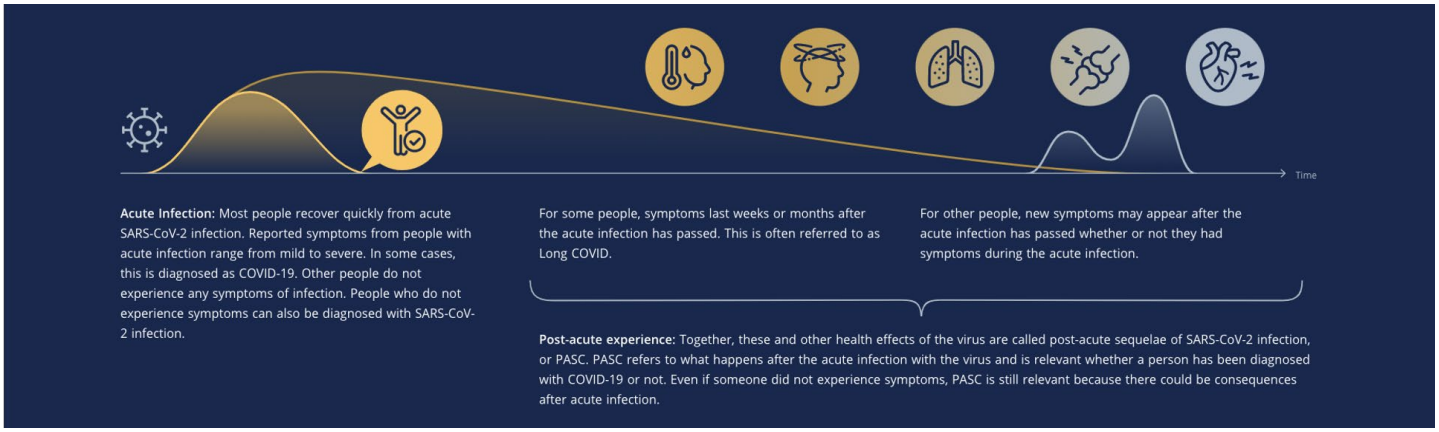
Post-acute sequelae of COVID-19 (PASC) is an umbrella term comprising many symptoms following SARS-CoV-2. Other common terms are "Post-Acute COVID-19 Syndrome," "Long COVID" or "Long-Haul COVID."

WHO defines PASC as those who are "3 months from the onset of COVID-19 with symptoms that last for at least 2 months that cannot be explained by an alternative diagnosis." This definition is inclusive, though non-specific. In well-controlled cohorts, new symptoms were approximately twice as common in patients with COVID-19 versus those who didn't have COVID-19, or in those with other viral infections.

Different studies use different case definitions, so incidence varies quite widely, from 2 to 90%. Studies focused on hospitalized patients or patients referred for specialty care may overestimate prevalence. Large population-based epidemiologic studies have found the prevalence to be ~5-20%. More severe acute disease and female sex have been found to be consistently associated with a higher risk of PASC.

What is the natural history of the symptoms?

There is no one "Long COVID experience," and each individual patient should be evaluated uniquely. Some people with symptomatic COVID-19 demonstrate rapid recovery and remain well. Others have a prolonged tail of recovery but eventually return to baseline. Still, others exhibit a waxing and waning recovery. It is not yet known whether each of these recovery trajectories represents the same or different pathobiology (see figure).



In our local COVID-19 recovery cohort (LIINC), about half of our volunteers have persistent COVID-19-attributed symptoms 4-8 months after they had COVID-19. Importantly, disabling symptoms like those often described in the media do occur, but are very uncommon (less than 5% of patients).

What is the proposed pathogenesis of Long COVID? Can any intervention during COVID infection reduce risk of Long COVID?

Several mechanisms are under investigation. First, the virus can cause tissue damage. During the acute stage, cardiac damage, cerebrovascular events and mucosal disruption (a "leaky gut" syndrome) could all result in sustained symptoms. Although the virus is assumed to be cleared immunologically within weeks, sustained virus replication may occur, as has been demonstrated in immunocompromised people. Even in the absence of active replication, viral nucleic acid and proteins can be found in tissues months after infection. Second, inflammation can persist after the acute infection resolves. In the UCSF-based LIINC cohort, higher levels of certain markers like IL-6 were associated with an increased risk of developing PASC. Third, endotheliitis and microvascular thrombosis contributes to disease during the acute phase and might persist in the post-acute period. Finally, autoreactive immunity are highly prevalent in acute infection and could lead to PASC.

These biologic pathways are not occurring in isolation. Socioeconomic factors are likely shaping people's experiences in complex ways. There are some early data suggesting that underserved communities might be at higher risk for developing PASC.

Is the risk of Long COVID less among vaccinated persons who have breakthrough infections?

This is an ongoing area of study. The suggestion that breakthrough cases could experience PASC was initially made by an Israeli study that demonstrated that approximately 20% of individuals with breakthrough infection experienced symptoms beyond 6 weeks. Notably, this was before the Delta surge. One study found decreased incidence of PASC symptoms among vaccinated patients with breakthrough infections. We are following several previously vaccinated people who had breakthrough infection with persistent symptoms, but it is too soon to know whether their symptoms will persist long enough to be considered PASC.

We do not yet know whether interventions during acute COVID-19 will have an impact on the occurrence of PASC, but this is an area of active investigation. The identification of early interventions that mitigate the risk of developing PASC could provide clues to the relevant biologic pathways.

If a patient is diagnosed with Long COVID are there any treatments that can be useful?

Because there is no one "long COVID-19 experience," treatments are individualized. For example, patients with cough, dyspnea, and wheezing that persist after COVID-19 may be treated with inhalers and/or pulmonary rehabilitation, similar to treatment of asthma/COPD patients. Patients with depression, anxiety, and/or PTSD may be treated with cognitive-behavioral therapy or antidepressant medications. Patients with chronic headaches may be treated with

therapies typically used for migraines. There are a few clinical trials with previously available medications, and teams at UCSF are working toward implementing studies of novel therapeutics using our existing clinical trials infrastructure.

In our experience, patients experiencing PASC must contend with substantial stigma related to their ongoing symptoms and challenges returning to their normal home and work responsibilities. It is important to validate their experience and the uncertainty associated with this condition. Especially in the first year of the pandemic, many patients faced challenges in the healthcare system recognizing and legitimizing their experience of illness.

What resources at UCSF are available for patients diagnosed with Long COVID?
UCSF is fortunate to have a post-COVID-19 clinic, and many such clinics are being developed all over the country. The UCSF OPTIMAL clinic is a multidisciplinary clinic that sees patients who were hospitalized with COVID-19 at UCSF or elsewhere. For patients who were not hospitalized who have persistent pulmonary symptoms, there are OPTIMAL specialists in the General Pulmonary clinic. The OPTIMAL clinic works with faculty champions in Divisions like Cardiology, Psychiatry, Integrative Medicine, and Primary Care. There is a team pharmacist, social worker, and physical therapist embedded in the clinic. In addition, some patients with primarily neurocognitive symptoms have been seen at the Memory and Aging Center.

In terms of research, individuals can be referred to the LIINC study (www.liincstudy.org), which is based at SFGH and enrolls adults with prior COVID-19 regardless of whether they have persistent symptoms. Several teams from UCSF have also been participating in the NIH Researching COVID-19 to Enhance Recovery (RECOVER) Initiative, a national COVID-19 recovery consortium funded by the NIH (www.recovercovid.org).

FREQUENTLY ASKED QUESTIONS

1. **It's almost here! What do we know about the efficacy and safety of the Pfizer/Biotech vaccine for children ages 5-11?**
   Promising data about Pfizer/Biotech BNT162b2 in children 5 to 11 years were presented to the FDA on 10/26/21. These children were given a 10 mcg dose whereas adults have been given a 30 mcg dose. Among 264 children who received the vaccine, they found a 99.2% serologic response rate, with neutralizing antibody levels comparable to those from 30 mcg dose given to those 16-25 year (n=253), and 90.7% (95% CI: 67.7-98.3) efficacy. Vaccinees (n=1518) in the placebo-controlled primary safety cohort experienced side effects similar to those reported in young adults, but generally lower in frequency and severity. There were no cases of anaphylaxis, myocarditis, death, or other vaccine-attributed serious events through ~3 months of follow up. Results were similar in a supplemental safety cohort (n=1591 vaccinees). **Conclusion**: While rare safety events cannot be excluded, these data suggest the 10 mcg dose of BNT162b2 has struck a good balance of immunogenicity and reactogenicity in children 5 to 11 years old. Elementary school-age children made up a significant portion of cases in the recent Delta-driven surge (10% in the week of 10/10/21). Following a favorable vote by the CDC's Advisory Committee on Immunization Practices, it has been approved by CDC Director Dr. Walensky and doses will be available to children this week.

2. **How much of COVID-19 in San Francisco over the last 4 months has been in fully vaccinated patients and is this surprising?**
   The delta variant led to a surge in new cases of COVID-19 among both unvaccinated and fully vaccinated individuals, peaking in San Francisco on August 2, with a 7-day average of 310 new cases/day. At the time of this peak, 71% of the city's population were fully vaccinated, and fully vaccinated individuals accounted for approximately 60% of new infections. While the case rate was higher among unvaccinated (49.7 vs 31.4 per 100,000), the case rates were much more similar than seen across California, where, during this time period the case rate among unvaccinated was approximately 7x higher compared to fully vaccinated. It is not surprising to see a significant proportion of new cases among vaccinated persons when the majority of the population is vaccinated. The case rate among vaccinated persons was likely partly due to an increased close contact among vaccinated adults as restrictions were eased,

waning antibodies among those vaccinated >6 months ago, and the highly transmissible delta variant. However, the hospitalization and death rate remained consistently low among vaccinated persons. **Conclusion**: The majority of recent COVID-19 cases in San Francisco have been in vaccinated persons, which is not surprising since vaccination rates are so high in the city. Hospitalization rates remain very low for vaccinated patients who get infected with COVID-19. COVID-19 boosters are now available for all adults offering opportunity to mitigate waning immunity and increased risks for illness.

3. **What do we know about the utility of Molnupiravir for the treatment of COVID-19?**
   Molnupiravir (MOV) is an oral ribonucleoside analog, that blocks SARS-CoV-2 replication by inducing errors in RNA replication. The Phase 3 MOVe-OUT study evaluated MOV 800 mg BID x 5 days vs. placebo in outpatients within 5 days of COVID-19 diagnosis and with one or more risk factors for severe COVID-19, such as age >60, diabetes, and obesity. The combined endpoint of all cause hospitalization and death was 7.4% with MOV vs. 14.1% with placebo (p=0.0012), leading to early study termination by the DSMB. While this relative risk reduction (~50%) is lower than the 70-85% reduction in hospitalization/death seen with recent monoclonal antibodies, the convenience of an oral treatment would significantly improve access to outpatient therapy. MOV will likely need to be given very early after symptom onset and to those with only mild COVID-19 infection, as a lack of efficacy has been reported in hospitalized COVID-19 patients and in moderate outpatient disease (O_2 sat 90-93%). **Conclusion**: MOV appears to be an effective treatment for high-risk outpatients with COVID-19 to prevent hospitalization and death. The FDA will be reviewing MOV next month for possible EUA.

4. **I have read about SARS-CoV-2 antibodies as anti-spike, anti-RBD, anti-nucleocapsid, and neutralizing, what does this mean and how do I use that information when caring for my patients?**
   In response to SARS-CoV-2 infection, a diversity of antibodies are generated, each targeting different sites on the coronavirus—spike, nucleocapsid, or other viral proteins. SARS-CoV-2 vaccines specifically induce antibodies against the spike protein, and thus people who have been vaccinated (but not infected) will only have detectable anti-spike antibodies; whereas those infected will have antibodies detectable to multiple viral proteins, including spike. Commercially available tests to assess for spike antibody are not known to correlate with protective immunity. A subset of antibodies—called neutralizing antibodies—are capable of effectively inhibiting viral infection in the laboratory. These antibodies target the spike protein receptor binding domain (RBD), a specific region essential for binding to the receptor used by the virus to infect cells. The FDA has approved some tests with this capability. **Conclusion:** At present, antibody testing to assess SARS-CoV-2 immunity is not routinely performed due to the limitations of the assay. Newer tests are coming to market which may be more useful to determine immunity to SARS-CoV-2 infection.

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UCSF Hospital Epidemiology and Infection Prevention COVID-19 webpage:
https://infectioncontrol.ucsfmedicalcenter.org/ucsf-health-covid-19-resources

San Francisco DPH link: https://www.sfcdcp.org/infectious-diseases-a-to-z/coronavirus-2019-novel-coronavirus

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Previous digests can be found: hividgm.ucsf.edu/covid-19
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