

Focus on the Postacute Phase: Consideration for Optimizing Outpatient Antivirals to Mitigate the Long-term Impact of COVID-19

Introduction

Dr. Yohei Doi (University of Pittsburgh): Thank you for joining the COVID-19 Playbook: Purposeful Strategies for Mitigating the Disease Burden in High-Risk Populations, capsule three.

Today, I'll be talking about long COVID or post-acute sequelae of SARS-CoV-2 infection and where antivirals do or do not fit into management. Even though acute COVID-19 outcomes have improved dramatically, long COVID remains one of the most common reasons that patients continue to seek care months after infection. Here, we'll focus on practical take-home points you can use in clinic.

Faculty and Disclosures

I'm Yohei Doi, an Infectious Disease Physician and Professor of Medicine at Fujita Health University in Japan and at the University of Pittsburgh in the United States. And I'll be guiding the discussion for this capsule.

Learning Objective

The goal of this capsule is pretty straightforward. It is to help you translate the growing body of long COVID data into evidence-based outpatient management, especially for higher-risk patients. In particular, we will focus on what we can do early during acute infection to reduce downstream burden.

Patient Case 1

So let's start with a patient case. Here we have a 64-year-old woman with diabetes and COPD. She has severe COVID-19 requiring hospitalization. And now, six months later, presents with ongoing fatigue and brain fog. A very reasonable question she asks is, "Is there an antiviral that I can take to make this better?"

Based on what we know today, there is no role for starting an antiviral, including molnupiravir, remdesivir, or nirmatrelvir/ritonavir at this point. We also would not defer vaccination. The best answer is, therefore, to manage symptoms and focus on prevention of future infection.

Burden of COVID-19 Severe Disease

We know from the CDC and IDSA guidelines, and also from our own practice, that patients with older age, diabetes, COPD, and other chronic conditions are at higher risk for severe COVID-19. What's important here is that these same risk factors also increase the likelihood of long COVID, especially after moderate or severe infection requiring hospitalization. So long COVID isn't random. Rather, it disproportionately affects the patients we already worry about most.

Long COVID

Long COVID is defined clinically. Symptoms start weeks to months after infection, last at least two months, and interfere with daily life. The WHO defines long COVID as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation.

Symptoms of long COVID can fluctuate, overlap with post-ICU syndromes, and often don't come with objective lab abnormalities, which is part of what makes these visits challenging.

One of the key messages is that long COVID is not a single-organ problem. We see neurologic symptoms, cardiac injury, pulmonary disease, metabolic complications, renal issues, and thromboembolic events. That diversity helps explain why a single effective treatment hasn't emerged.

US Prevalence of Long COVID

How common is long COVID? A meta-analysis from earlier in the pandemic estimated that about 45% of patients who survived COVID-19 reported persistent symptoms. A more recent study quotes a prevalence of approximately 36%. The reassuring news is that most patients improve within about six months, but a smaller group, around 1% to 5%, remain chronically symptomatic. When you scale that to the population level, it's still a very large number of patients with ongoing disability, and even a modest reduction in incidence would translate into substantial public health impact.

Potential Causes of Long COVID

As suggested by the diverse clinical presentation, long COVID is likely not a single disease, but rather a syndrome that can arise from multiple overlapping mechanisms. One leading hypothesis is viral persistence, or residual viral antigens, where fragments of the virus may continue to stimulate inflammation even after acute infection has resolved. This provides biologic plausibility for why early antiviral treatment may help prevent long COVID.

But also explains why antivirals haven't worked well once long COVID is established, as we will discuss later.

Another major contributor is immune dysregulation, including chronic inflammation and, in some patients, features suggestive of autoimmunity. Importantly, immune profiles appear heterogeneous, which likely contributes to the wide range of symptoms we see clinically.

There is also growing evidence for endothelial and microvascular dysfunction, which may explain symptoms like exertional intolerance, dyspnea, and chest discomfort despite normal routine testing.

Finally, in patients who are hospitalized or critically ill, long COVID often overlaps with post-critical illness syndromes and residual organ injury, particularly involving the lungs, heart, and nervous system. Taken together, this has helped explain why no single treatment has emerged and why symptom-directed, individualized care remains central to management.

Long COVID Symptoms

When we talk about long COVID symptoms, two things are important to keep in mind. The range of symptoms is broad, and the course is often fluctuating. In this well-described cohort of hospitalized patients followed for one year, only about 22% were completely symptom-free at 12 months. Fatigue, dyspnea, cognitive issues, and sleep problems dominated. And these are the most commonly reported symptoms across studies. These are also the symptoms we hear most often in clinic, and the ones that tend to interfere most with daily functioning of our patients.

Long COVID and COVID-19 Vaccination

Vaccination doesn't eliminate long COVID, but it clearly reduces risk. Across multiple studies, vaccinated individuals have lower rates of neurologic, pulmonary, and systemic post-COVID complications. Quantitatively, two doses of SARS-CoV-2 vaccine have been associated with a roughly 30% to 50% reduction in the risk of developing long COVID, depending on the population studied and the outcome definition.

Even after a breakthrough infection, vaccination is associated with a lower hazard of multiple post-acute sequelae, including respiratory failure, cognitive symptoms and cardiovascular events.

So for now, vaccination remains our strongest, most consistent tool for long COVID prevention, even in the Omicron era we are in. I personally continue to take a SARS-CoV-2 vaccine once a year, and the primary motivation to do so is to manage the risk of long COVID in case I get infected. Importantly, vaccination is preventive. It does not reliably reverse established long COVID symptoms.

Antivirals as Prevention for Long COVID

Now, what about antivirals? When given early, within the first few days of infection, there's growing evidence that they may reduce the risk of long COVID. Retrospective studies with nirmatrelvir/ritonavir show lower long COVID rates in high-risk outpatients.

Large, real-world cohort studies from the United States suggest an approximately 20% to 30% relative risk reduction in long COVID among patients treated with nirmatrelvir/ritonavir, with the strongest signal seen in older adults and those with comorbidities.

Follow-up from the PANORAMIC randomized clinical trial conducted in the United Kingdom suggests that molnupiravir may improve longer term quality of life and symptom burden, particularly measures such as fatigue and ability to return to work. However, the magnitude of benefit with molnupiravir appears more modest and less consistent than with nirmatrelvir/ritonavir.

For remdesivir, some studies report protective effect, but the results are overall mixed. In short, less virus early in infection likely means fewer downstream problems.

Antivirals as Treatment for Long COVID

That said, using antivirals after long COVID is established has not panned out so far. Randomized trials like STOP-PASC and PAX LC, both of which compared 15 days of nirmatrelvir/ritonavir with placebo, did not show clear benefit with nirmatrelvir/ritonavir. Likewise, there is no convincing evidence that molnupiravir improves symptoms once long COVID is established.

Newer agents like ensitrelvir, a novel protease inhibitor, are being studied in clinical trials. But right now, antivirals are not recommended for treating long COVID once it is diagnosed.

Patient Case 1: Discussion

Let's go back to our patient, the 64-year-old woman with long COVID. The right approach here is symptom-based care. Evaluation for other contributing conditions, rehabilitation when appropriate and staying up-to-date on vaccination. It's also important to set expectations early. Improvement of symptoms is common, but it may be gradual rather than immediate.

Key Points

Let me close with a few key points. First, long COVID is real, but it's complicated. The definition is clinical. Symptoms are heterogeneous, and there is no single diagnostic test. So recognition and validation of patient symptoms are critical.

Second, the incidence of long COVID has decreased since the beginning of the pandemic. This likely reflects a combination of vaccination, prior immunity from infection, and improved acute management, but it has not gone away.

Third, and most importantly, prevention is where we have the strongest evidence. Vaccination reduces long COVID risk by roughly one-third to one-half, and early antiviral treatment, particularly with nirmatrelvir/ritonavir offers additional protection when given during acute infection.

And finally, while certain antivirals are being investigated for the treatment in the long-term phase, the data are still evolving, and none are recommended for routine treatment of established long COVID outside of clinical trials.

So for now, evidence-based prevention and symptom-directed care remain the foundation of management.

Go Online for More Coverage of COVID-19

For additional COVID-19 coverage, please visit the link provided here.

Thank you for your attention and for the care you provide to patients with long COVID.