8 October 2020

BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

An early hopeful for an effective covid-19 therapy comes up short in a major trial.

Lopinovir-ritonavir is a combination of antiviral medications that was proposed as a potential treatment for SARS-CoV-2 as laboratory data demonstrated that the medication stopped the virus from replicating. The RECOVERY group from the United Kingdom have now reported the results in *The Lancet* from a randomized controlled trial in which 1,616 patients were randomized to receive lopinavir-ritonavir plus standard care and 3,424 patients were randomized to standard care alone. The study was open-label, meaning both the patients and clinicians were aware of the treatment patients received. Most patients were on oxygen (70 pecent) and very few were mechanically ventilated (4 percent). There was no difference in 28-day mortality between the groups – 23 percent of patients allocated to lopinavir-ritonavir died and 22 percent of those allocated to standard care died. Researchers analyzed several groups to assess for any effects among specific cohorts; there was no difference in mortality based on age, sex, ethnicity, time from symptom onset, degree of respiratory support, or baseline risk. An earlier trial also found no clear benefit to the medication. This larger study confirms that this medication does not change important outcomes in patients with covid-19. This study is an important reminder that treatments that appear effective in the laboratory setting often do not translate into effective therapies in the real-world setting. *—Lauren Westafer, DO, MPH*

Long-term effects of SARS-CoV-2 Infection: Heart and Mind.
SARS-CoV-2 infection may have long term-effects. Even after appearing to "clear" the infection (see below for our Glossary for more on this problematic term) some patients report prolonged difficulty concentrating, persistent shortness of breath, and cough, weakness, fatigue, and pain.

Long-Haulers and Post-viral Syndromes. A *long-hauler* is someone whose symptoms began after a confirmed COVID-19 infection and persisted after a subsequent negative test or resolution of other symptoms. The term *postviral syndrome* refers to a wide variety of poorly understood symptoms that often occur after viral infections, ranging from fatigue and "brain fog" to pain (e.g. after herpes or shingles), anemia (after parvovirus infection), thyroid hyperactivity or underactivity (caused by almost any virus). Some post-viral effects, such as anemia or thyroid dysfunction, self-correct but may require treatment in severe cases. It is important to distinguish whether the persistent symptoms reflect an insidious infection, damage only now being appreciated, or a counterproductive reaction by the body. An insidious infection might respond to antivirals or a vaccine booster, but not the other possible causes.

Brain Fog. **Surveys of those who had covid-19 symptoms** and then recovered noted persistent difficulty concentrating, fatigue, pain, and loss of smell. Difficulty concentrating and fatigue may reflect thyroid dysfunction or a "pre-diabetic state." Persistent shortness of breath, cough, or weakness could arise from damage to the lungs, deconditioning from hospitalization, or complications from mechanical ventilation.

Heart Dysfunction. MRI images of the hearts of 100 patients with confirmed infection and clearing of covid-19 showed a decrease in the ability of heart to pump blood, leading to heart

failure and fluid buildup in the lungs. Covid-19 is associated with an increased risk of blood clots in the lungs and could conceivably be associated with blood clots in the extremities (which could lead to persistent pain), in the brain (i.e. a stroke), and in the coronary arteries (i.e. a heart attack). Covid-19 is also associated with a hyperinflammatory state. The walls of blood vessels weaken when inflamed, sometimes ballooning out into an aneurysm. This has been seen in children with covid-19, where it is termed MIS-C (multisystem inflammatory system-children).

The overall message is that, as with other viruses, SARS-CoV-2 infection may have long term-effects. We do not fully understand which people are prone to what effects. We remarked in a prior brief that SARS-CoV-2 causes illness directly by infecting cells and indirectly by provoking the infected person's body to retaliate in a self-destructive manner. Until we understand the biology behind each of SARS-CoV-2's effects, healthcare providers should assiduously investigate persistent effects so that we may eventually learn how to treat them.

Glossary. *Clearing an infection*. Physicians describe a patient as "clearing an infection" when the patient's health improves, and laboratory tests demonstrate no or gradually diminished levels of the bug causing the infection. Laboratory tests may not test all places an infection can hide. HIV can, for example, hide in the kidneys and wall itself off from the immune system leading to an apparent improvement and undetectable viral load for decades. Herpes and chickenpox (shingles) can hide in the nervous system.

—Michael Chary, MD PhD.

POLICY BRIEFING

FDA prevails in vaccine requirements.

For the past several weeks the White House has been fighting the release of vaccine guidelines developed by the Food and Drug Administration (FDA), calling them too restrictive. On the other side, a joint letter from more than sixty public health experts and physicians (including the editor-in-chief of *Brief19*) called for stricter requirements, including two months of monitoring after trials for all vaccine candidates.

Amidst this, the White House's budget office on Tuesday released the final Emergency Use Authorization (EUA) guidelines. In addition to requiring applicants to have completed a Phase III trial showing efficacy, the recommendations emphasize continuing data collection for two months after vaccine administration before applying for EUA approval. *The Food and Drug Administration*

—Joshua Lesko, MD