

A new treatment that might keep COVID-19 patients off the ventilator

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A new treatment is among the first known to reduce the severity of acute respiratory distress syndrome caused by the flu in animals, according to a new study.

Tests in [mice](#) infected with high doses of influenza showed that the treatment could improve [lung function](#) in very sick mice and prevent progression of disease in mice that were pre-emptively treated after being exposed to the flu.

The hope is that it may also help humans infected with the flu, and potentially other causes of acute respiratory distress syndrome (ARDS) such as SARS-CoV-2 infection.

Specific [cells](#) in mice are less able to make key molecules after influenza invades the lungs, reducing their ability to produce a substance called surfactant that enables lungs to expand and contract. The shortage of surfactant is linked to ARDS, an illness so serious that it typically requires mechanical ventilation in an ICU.

Researchers bypassed the blocked process in mice by re-introducing the missing molecules alone or in combination as an injected or oral treatment. The results: normalized [blood oxygen levels](#) and reduced inflammation in mouse lungs—effects that could make a person well enough for hospital discharge.

"The most important and impressive thing in this study is the fact that we have benefits even when we treat late in the disease process. If we could develop a drug based on these findings, you could take somebody who's going to have to go on a ventilator and stop that completely," said Ian Davis, professor of veterinary biosciences at The Ohio State University and senior author of the study. "There's nothing out there now that can do this for ARDS that will bring them back to that degree, and certainly not for flu."

ARDS can also result from infections, cancer, trauma and many other ailments. Though this therapy has been tested in the context of the flu, Davis said its reliance on fixing a broken cell function in the host rather

than killing the virus suggests it has potential to treat virtually any [lung injury](#).

The study was published online recently in the *American Journal of Respiratory Cell and Molecular Biology*.

The [experimental treatment](#) consists of molecules known as liponucleotides, which are essential for making surfactant in the lungs. Davis analyzed lung cells from flu-infected mice and determined that the pathway to surfactant production was disrupted, with one of the two necessary liponucleotides completely undetectable.

"The thinking before was that the reason there was less surfactant in mice with flu-related ARDS was because cells are dying. This defect is in some ways better—if cells are dying, there's not much you can do, but if there's a problem with the cell's metabolism, maybe you can fix it," Davis said.

And fix it—in mice—he did, developing therapies containing the missing liponucleotide molecule alone or combined with one or two others.

Davis and colleagues inoculated mice with high doses of H1N1 influenza and then treated some mice with liponucleotides once daily for five days and others just a single time five days after exposure. The mice receiving daily treatment were protected from getting seriously ill, and the very sick mice treated on the fifth day, whose severe blood-oxygen loss and lung inflammation had cause ARDS, showed significant improvement.

"Obviously that's what you need in someone with severe influenza—we want to take someone who is already in the ICU and help them get out faster, or head going to the ICU off at the pass," Davis said.

Liponucleotides don't kill the flu virus—which is the point.

"I've always been interested in finding new therapies to treat lung injury," he said. "The problem with anti-viral drugs is you probably need a different drug for every virus. Also, many viruses can quickly mutate to become resistant to these drugs.

"Our approach is to fix the patient. Once the virus has caused the injury—the inflammation—it doesn't really matter if it stays or goes away."

There's still a lot to learn. The agents have a strong anti-inflammatory effect, but don't fully restore the surfactant-production process—and Davis isn't sure why that is. Studies so far have been based on findings in a single type of lung cell, but the scientists haven't confirmed that those cells are the ones responding to the therapy—any number of other cells in the immune system, blood vessels or heart could also play a role.

Despite the unknowns, Davis said that because the missing liponucleotides naturally exist in mammals, including humans, they are considered safe and unlikely to cause side effects, even if they go unused in the body.

More information: Lucia E Rosas et al. Post-exposure Liponucleotide Prophylaxis and Treatment Attenuates ARDS in Influenza-infected Mice, *American Journal of Respiratory Cell and Molecular Biology* (2021). [DOI: 10.1165/rcmb.2020-0465OC](https://doi.org/10.1165/rcmb.2020-0465OC)

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