

What really killed COVID-19 patients: It wasn't a cytokine storm, suggests study

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Secondary bacterial infection of the lung (pneumonia) was extremely common in patients with COVID-19, affecting almost half the patients who required support from mechanical ventilation. By applying machine

learning to medical record data, scientists at Northwestern University Feinberg School of Medicine found that secondary bacterial pneumonia that does not resolve was a key driver of death in patients with COVID-19. It may even exceed death rates from the viral infection itself.

The scientists also found evidence that COVID-19 does not cause a "[cytokine storm](#)," so often believed to cause death.

The study was recently published in the *Journal of Clinical Investigation*.

"Our study highlights the importance of preventing, looking for and aggressively treating secondary [bacterial pneumonia](#) in [critically ill patients](#) with severe pneumonia, including those with COVID-19," said senior author Dr. Benjamin Singer, an associate professor of medicine at Northwestern University Feinberg School of Medicine and a Northwestern Medicine pulmonary and critical care physician.

The investigators found nearly half of patients with COVID-19 develop a secondary ventilator-associated bacterial pneumonia.

"Those who were cured of their secondary pneumonia were likely to live, while those whose pneumonia did not resolve were more likely to die," Singer said. "Our data suggested that the mortality related to the virus itself is relatively low, but other things that happen during the ICU stay, like secondary bacterial pneumonia, offset that."

The study findings also negate the cytokine storm theory, said Singer, also the Lawrence Hicks Professor of Pulmonary Medicine at Feinberg.

"The term 'cytokine storm' means an overwhelming inflammation that drives organ failure in your lungs, your kidneys, your brain and other organs," Singer said. "If that were true, if cytokine storm were

underlying the long length of stay we see in patients with COVID-19, we would expect to see frequent transitions to states that are characterized by multi-organ failure. That's not what we saw."

The study analyzed 585 patients in the [intensive care unit](#) (ICU) at Northwestern Memorial Hospital with severe pneumonia and respiratory failure, 190 of whom had COVID-19. The scientists developed a new machine learning approach called CarpeDiem, which groups similar ICU patient-days into clinical states based on electronic health record data. This novel approach, which is based on the concept of daily rounds by the ICU team, allowed them to ask how complications like bacterial pneumonia impacted the course of illness.

These patients or their surrogates consented to enroll in the Successful Clinical Response to Pneumonia Therapy (SCRIPT) study, an observational trial to identify new biomarkers and therapies for patients with severe pneumonia. As part of SCRIPT, an expert panel of ICU physicians used state-of-the-art analysis of lung samples collected as part of clinical care to diagnose and adjudicate the outcomes of secondary pneumonia events.

"The application of machine learning and [artificial intelligence](#) to [clinical data](#) can be used to develop better ways to treat diseases like COVID-19 and to assist ICU physicians managing these patients," said study co-first author Dr. Catherine Gao, an instructor in pulmonary and critical care medicine at Feinberg and a Northwestern Medicine physician.

"The importance of bacterial superinfection of the lung as a contributor to death in patients with COVID-19 has been underappreciated because most centers have not looked for it or only look at outcomes in terms of presence or absence of bacterial superinfection, not whether treatment is successful or not," said study co-author Dr. Richard Wunderink, who

leads the Successful Clinical Response in Pneumonia Therapy Systems Biology Center at Northwestern.

The next step in the research will be to use [molecular data](#) from the study samples and integrate it with machine learning approaches to understand why some patients go on to be cured of [pneumonia](#) and some don't. Investigators also want to expand the technique to larger datasets and use the model to make predictions that can be brought back to the bedside to improve the care of critically ill patients.

More information: Catherine A. Gao et al, Machine learning links unresolving secondary pneumonia to mortality in patients with severe pneumonia, including COVID-19, *Journal of Clinical Investigation* (2023). [DOI: 10.1172/JCI170682](https://doi.org/10.1172/JCI170682)

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