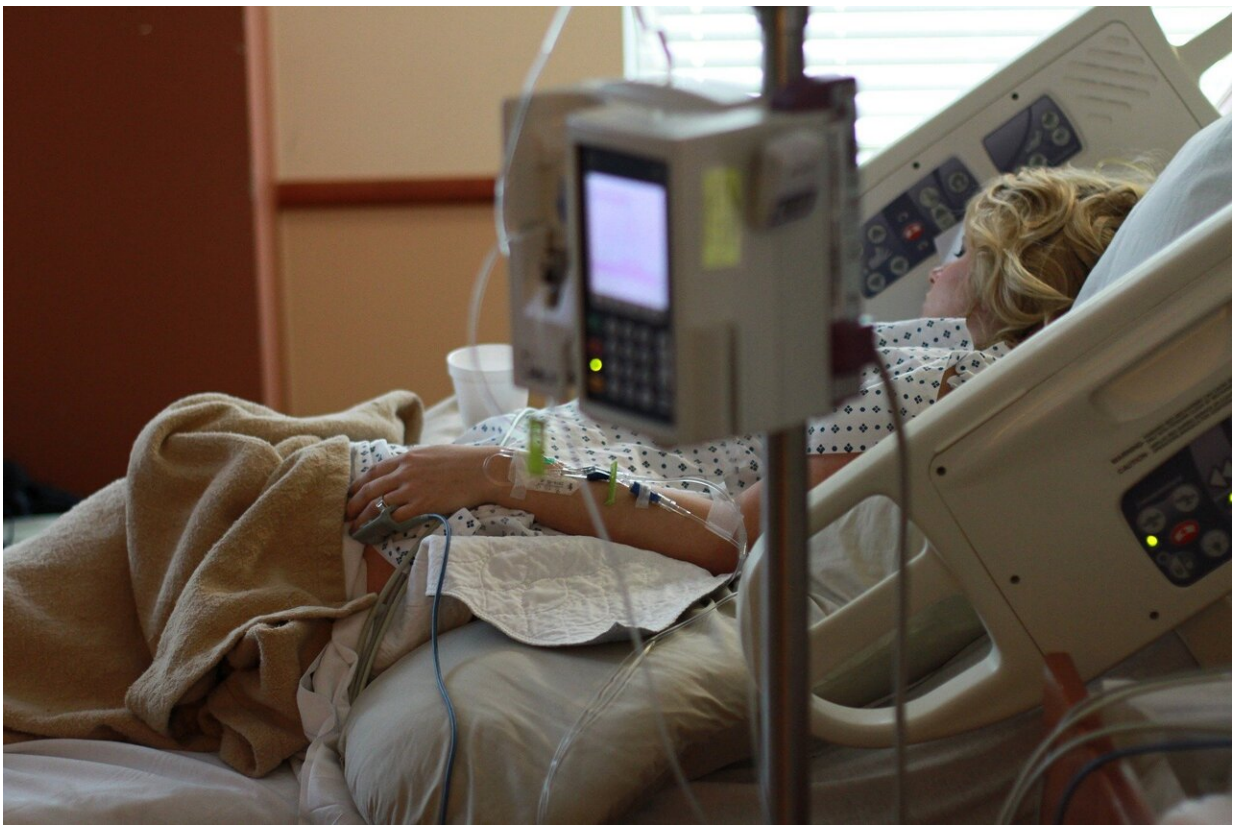
COVID patients can be overwhelmed with inflammation. Doctors are learning to calm that 'storm'

July 13 2020, by Tom Avril, The Philadelphia Inquirer



Credit: CC0 Public Domain

In the millions of tiny air sacs tasked with absorbing oxygen in Brett Breslow's lungs, the scene was chaos.

Some of the sacs were swollen with fluid that had leaked from surrounding blood vessels. Others had simply collapsed. The grim result: the Cherry Hill man was starved of oxygen, leading doctors at Cooper University Hospital to put him on a ventilator for 19 days.

Breslow was suffering from a massive bout of inflammation—a catch-all description for the damage in many of the sickest patients with COVID-19. In addition to the assault on his lungs, the disease was harming his liver and kidneys, as well as causing him to form abnormal blood clots.

"It really attacked every organ in the body," said his wife, Amy.

Physicians have known for decades how to treat inflammation. In 1950, the Nobel Prize was given to researchers who found that in people with rheumatoid arthritis, inflammation could be calmed with steroids (not the kind used illegally by some athletes, but synthetic versions of a different class of hormones). Later that year, steroids were used to treat asthma, another widespread inflammatory condition.

And in June, researchers reported that dexamethasone, an inexpensive, generic steroid, improved the odds of survival for COVID-19 patients on ventilators.

But steroids are a brute-force approach. Though inflammation can be harmful, it also is one way the immune system fights off disease. From the start of the pandemic, physicians warned that if steroids were used to tamp down the collateral damage from inflammation, patients might be less able to fight off the initial cause of the problem: the coronavirus.

"They are like shotguns," Anita McElroy, a University of Pittsburgh infectious-disease specialist, said of the drugs. "They dampen all the immune response."

A new pair of studies from the University of Pennsylvania may offer a roadmap to a more targeted response. Researchers took blood samples from dozens of COVID patients and ran them through a boxy device called a flow cytometer, using laser beams to identify which kinds of immune cells had been activated to fight the disease.

The authors measured each patient's B-cells, which, if properly activated, make antibodies to fight the virus. They also measured various kinds of T-cells, including "helper" cells that play a role in marshaling the body's defenses, and "killer" cells, which destroy infected cells before the virus inside them spreads further. All cells were further categorized by molecular signatures that indicated their readiness to fight disease.

When it was all boiled down, people with COVID seemed to cluster into three broad "immunotypes," said E. John Wherry, director of Penn's Institute for Immunology. Loosely speaking, some patients' immune systems seemed to have overreacted to the virus, while others were slow to react. In a third group, the immune system did not seem to respond much at all.

The findings represent a first step toward identifying which patients might need to have certain inflammatory agents calmed down, and which might need other elements of the immune system dialed up, said Wherry, who led one of the studies.

"You might want to boost the immune system in a certain way, or you might want to take the edge off it, or shut it down a little bit," he said.

A key part of the puzzle might be apparent "perturbations" in what is called the innate immune system: a series of first-responder white blood cells that start fighting disease before more specialized T- and B-cells get to work, said Wherry's Penn colleague Michael R. Betts, who led the

other study.

"We've identified that there's something going on there," Betts said. "Now we have to figure out what does it mean."

Elsewhere, studies already are underway for several of the more-targeted anti-inflammatory drugs—including one called tocilizumab, marketed as Actemra.

But long before those studies could yield results, Brett Breslow needed help.

A drug cocktail

An engineer at Lockheed Martin, Breslow felt moderately ill for more than a week in mid-March. Then, as some other COVID-19 patients have experienced, he took a sudden turn for the worse. At Cooper, the 50-year-old was put in a drug-induced coma and had a breathing tube placed down his throat to deliver more oxygen to his fluid-filled lungs.

Three days after he was admitted to the hospital, Breslow's various "markers" of inflammation were elevated, including his levels of ferritin, a type of molecule that stores iron. That can mean two things, said Wherry, who was not involved in his care. Viruses need iron just like the humans they infect, so Breslow's body might have been trying to sequester it from the virus. Elevated iron storage also can be a sign of tissue damage.

Breslow got one dose of Actemra on March 23, followed by a second dose on March 28, said his wife, who used her iPhone to take copious notes on his daily progress. To her relief, his inflammation markers started to come down. Yet he stayed on the ventilator for 12 more days.

Did Actemra make the difference? Since then, evidence from studies of the drug has been mixed, but some researchers have theorized that it helps only when given to the right subset of patients.

Breslow received other drugs as well, including hydroxychloroquine, the drug touted by President Donald Trump, and Kaletra, an antiviral drug designed to treat HIV, as his doctors reviewed early evidence from virus hotspots in Italy and China. And because he was suffering from blood clots, the hospital gave him heparin, an anticoagulant.

"Basically, they were learning as they went," Amy Breslow said.

Some physicians have characterized the inflammatory state of severe COVID patients as being triggered by a "storm" of cytokines: a class of small proteins that serve as alarm signals for the immune system. But others have rejected that term, as overall cytokine levels are not that high in many severe patients.

Instead, the culprit could be a modest elevation in certain flavors of cytokines, said Wherry, a professor at Penn's Perelman School of Medicine. Actemra blocks just one type of cytokine, called interleukin-6.

Striking a balance

As the research on targeted therapies continues, the broader approach of steroids remains part of the plan for many COVID patients.

At Temple University Hospital, steroids have helped hundreds of severely ill COVID patients recover, said pulmonologist Sameep Sehgal.

When used judiciously, for a short period at a moderate dose, steroids can keep inflammation in check without suppressing the immune system

to the degree that patients cannot fight off infection, he said.

"It's a balancing act," Sehgal said. "The more practical question is, does this help save lives, and get patients out of the hospital quicker?"

Though Breslow did not get steroids to calm down his inflamed lungs in the hospital, doctors prescribed them to him later to improve function in another organ: his kidneys.

His kidneys started to fail while at Cooper, prompting physicians to place him on dialysis. He continued with the filtering treatments afterward, at Magee Rehabilitation Hospital in Philadelphia.

But his levels of creatinine, a waste product that the kidneys are supposed to remove, remained high, and doctors started talking about a transplant. As a last-ditch measure, one physician suggested that he try taking the steroid prednisone. Within a day or two, his kidney function improved.

Breslow has been home in Cherry Hill since May 27, yet is still not back to normal.

"It's a long road back," he said.

At first, he could barely get up the stairs. A week ago, his lungs looked normal on a chest X-ray. But he still tires easily, and will undergo another test of his lung function on Monday.

While the all-out, inflammatory assault of COVID-19 is Breslow's past, its aftereffects remain.