Special Report

Steroids Help Severely Ill COVID-19 Patients

This summer, an international team of clinician-scientists led by the University of Pittsburgh's Derek Angus confirmed that inexpensive, widely available steroids improve the odds of recovery from COVID-19. In response, the World Health Organization updated its treatment guidelines to note that patients with COVID-19 who are on ventilators or oxygen and under intensive care should be given corticosteroids.

The study pooled data from 121 hospitals in eight countries and was reported in JAMA with Angus, chair of Pitt's Department of Critical Care Medicine, as the lead author on an article in a four-article package. Angus is also Pitt's associate vice chancellor for health care innovation and chief health care innovation officer at UPMC.

"It is relatively rare in medicine that you find drugs where the evidence of their effectiveness in saving lives is so consistent," says Angus. "This is, in many respects, the single clearest answer we've had so far on how to manage terribly ill COVID-19 patients."

Before COVID-19 emerged, Angus and several international collaborators had developed REMAP-CAP (Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia). The platform was designed to find optimal treatments for severe pneumonia. When the COVID-19 pandemic began, they adapted REMAP-CAP to incorporate additional treatment regimens specifically targeting the SARS-CoV-2 virus.

Between March and June, a REMAP-CAP corticosteroid trial randomized 403 adult COVID-19 patients admitted to an intensive care unit to receive the steroid hydrocortisone or no steroids. The trial found a 93% probability that giving patients a seven-day intravenous course of hydrocortisone would result in better outcomes than not giving the steroid. The results were consistent across age, race and sex.

"This gives physicians like me, who treat the sickest of the sick, hope," says Bryan McVerry, coauthor of the study and associate professor of pulmonary, allergy and critical care medicine at Pitt. "We are beginning to get a handle on the deadly side of this disease."

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Cows, Vaccines, Warp Speed

At last count, Pitt people were engaged in more than 400 studies related to COVID-19 and the novel coronavirus. A little update here.

A cow makes an awful lot of antibodies, buckets more than your average human. And when you're trying to fight a virus, that could be a lifesaver.

William Klimstra, University of Pittsburgh associate professor of immunology and member of the Center for Vaccine Research, is working on a project that started with the Department of Defense's interest in protecting soldiers from infectious diseases. The DOD is backing a company called SAB Biotherapeutics, in Sioux Falls, South Dakota, to breed cows with humanized immune systems to generate antibodies against the novel coronavirus. They've already had success with antibodies for MERS, a similar virus. It's hoped the new antibody therapy (called SAB-185) could be used to both treat COVID-19 and prevent it in frontline workers and in military personnel. In August, SAB-185 was injected into healthy volunteers for a phase 1 safety study.

Klimstra is also advancing a synthetic RNA-based novel coronavirus vaccine. (That's a third SARS-CoV-2 vaccine candidate for Pitt, in case you are keeping track. See "Science Champions" story on page 4.) On that vaccine project, Klimstra is partnering with Tiba, a small Boston tech firm. The Tiba pilot is in early stages, but the technology is worth talking about now. It uses programmable RNA designed to trick the body into thinking that it's come into contact with SARS-CoV-2.

That's a bit like the experimental vaccine called mRNA-1273 developed by Moderna and the National Institute of Allergy and Infectious Diseases (NIAID), which is in phase 3 trials. The Tiba vaccine uses a different molecular delivery method.

Sources for this special section include Pitt and UPMC reports.

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Speaking of Moderna, as part of Operation Warp Speed, Pitt/UPMC has been chosen as a site for both the Moderna and the AstraZeneca vaccine trials. "Participating in Operation Warp Speed is a huge honor," said Judy Martin (Res '94, Fel '98) in a July news conference. Martin is Pitt codirector of the Pittsburgh Vaccine Clinical Trials Unit and professor of pediatrics. She is directing the Pittsburgh site for the Moderna vaccine clinical trial. Her colleague Sharon Riddler (Fel '94), associate professor of medicine, will be leading the Pittsburgh AstraZeneca trial; that experimental vaccine was developed at the University of Oxford.

The Big Screen: Pitt's Clinical and Translational Science Institute (CTSI) has been called into action by the National Institute of Allergy and Infectious Diseases. Chancellor Patrick Gallagher's June report to the Board of Trustees described how that unfolded:

On April 10, NIAID called for volunteers. The goal: Screen the nation for coronavirus antibodies—every region, from urban to rural. And determine the scope of the pandemic by finding asymptomatic carriers with antibodies in their blood. NIAID approached Pitt because coordinating volunteer participants in clinical research is what our CTSI does—and frankly, nobody does it better. . . . [By June] they'd already recruited half the 10,000 participants NIAID needs. (The University of Alabama-Birmingham is responsible for another 4,500.) They distributed finger-prick kits to those participants. Blood samples came in from all over the nation for analysis.

The CTSI team will soon start another nationwide serostudy recruitment effort for the agency.

Little Antibody Goes Long Way

It's tiny. And that has advantages.

Pitt scientists have isolated the smallest biological molecule to date that completely and specifically neutralizes the SARS-CoV-2 virus. This antibody component, which is 10 times smaller than a full-size antibody, has been used to construct a potential therapeutic against SARS-CoV-2 that may also prevent infection, notes John Mellors, chief of the Division of Infectious Diseases at Pitt and UPMC.

The researchers reported in the journal Cell that the drug, called Ab8, is highly effective at both preventing and treating SARS-CoV-2 infection in mice and hamsters. Its tiny size helps it diffuse in tissue to subdue the virus; it also makes it possible to administer the drug by inhalation or other routes. Most monoclonal antibodies in development would be administered intravenously through an IV drip.

Dimiter Dimitrov, senior author of the Cell paper and director of Pitt's Center for Antibody Therapeutics, was one of the first to discover neutralizing antibodies for the original SARS coronavirus in 2003. Starting in February, Wei Li, assistant director of the antibody center and colead author, sifted through hundreds of billions of antibody component candidates and found Ab8 in record time.

The Pitt researchers partnered with scientists from the University of North Carolina at Chapel Hill, University of Texas Medical Branch at Galveston, University of British Columbia and University of Saskatchewan.

The drug does not bind to human cells—a good sign that it won't have negative side-effects in people. And it can be produced in mass quantities. Abound Bio, a newly formed UPMC-backed company, has licensed Ab8 for worldwide development.

Science Champions

Pittsburghers are rooting for a homegrown COVID-19 vaccine.

"Nothing great in life is ever achieved alone," **Heather Lyke**, Pitt's athletic director, said in a recent news release. **So the families of four leaders in Pitt Athletics donated a combined $500,000 in support of Pitt's Center for Vaccine Research (CVR) as it advances a potential COVID-19 vaccine.** Those leaders are Lyke, football coach Pat Narduzzi, men's basketball coach Jeff Capel and women's basketball coach Lance White. Donations of $100,000 each were added by the Penguins, the Pirates and the Steelers—for a total of $800,000.

"We are stunned by the generosity and support the Pittsburgh community has shown for our center," said **Paul Duprex**, CVR director.

"The issues in medicine and bioscience are broad issues for improving the human condition," notes another Pittsburgher, **Ashok Trivedi**, managing partner at SWAT Capital and founder of Ashoka University in India. "The COVID-19 pandemic makes these points very clear. Not only is it infecting millions of people, it's bringing entire societies to a halt."

The Trivedi Family Foundation has given a significant gift to support the development of PittCoVacc, a vaccine platform invented by Lou Falo, chair of dermatology, and Andrea Gambotto, associate professor of surgery. PittCoVacc uses a low-cost microneedle patch—"a very effective method for delivering medications to millions," says Trivedi.

Henderson

With a Trace

Contact tracing is key to preventing COVID-19's spread. However, as several University of Pittsburgh students discovered this spring, this vital task relies on the work of case investigators, who line up the dots for the tracers to connect.

Minorini

When a new case of COVID-19 is reported to the Allegheny County Health Department, an investigator calls that person and asks about their symptoms, when they sought care, demographic information and the names of recent close contacts. The case investigator logs the answers into Pennsylvania's National Electronic Disease Surveillance System (PA-NEDSS) database, and the list of the patient's recent close contacts is passed to a contact tracer, who then reaches out to them.

A close contact is someone who has been within 6 feet of that person for 15 or more minutes starting at 48 hours before that person experienced symptoms of COVID-19.

"I'm really comfortable cold-calling people," says Andrew Henderson, who worked as a political organizer, calling potential voters in Virginia, before enrolling at Pitt Med. In March, he became one of 35 Pitt Med students who signed up as case investigators for the Health Department. Three students from the Graduate School of Public Health also worked as investigators.

With clinical rotations delayed because of the coronavirus, the work filled an educational void. For some Pitt Med students, it served as an elective, while others, like Henderson, volunteered at the beginning of the pandemic, and then received course credit the longer they remained on the job.

Henderson, now a fourth-year at Pitt Med, was a case investigator for nine weeks.

"I really enjoyed talking to patients about their symptoms, learning about the disease course," he says. Henderson, 33, was surprised when a few patients indicated that their first symptom was pain in their eyes.

"That's been reported nationally, but it's a rare symptom."

Henderson, who had been slated for a pediatrics rotation at UPMC Children's Hospital of Pittsburgh, felt sidelined after the pandemic hit. When he learned about the opportunity to volunteer at the Health Department through a med school-wide email, he reached out to several classmates and urged them to join him.

Rebecca Minorini also stepped up: "This felt like a direct way to help; and even though it wasn't face-to-face, it felt good to interview patients, give them guidance and answer their questions."

Minorini, a fourth-year med student doing a family medicine rotation before the pandemic hit Allegheny County, built a rapport with several patients. "A lot of people had follow-up questions," she says. "I called some people maybe six times over the course of the four weeks I was there. I became their contact person for this."

Minorini, 30, described how patients expressed a range of fears: from worry about when they could return to work to concern about getting food delivered. When a patient was in the ICU and too sick to talk, she spoke to a family member.

"It was a little scary to be on our side of it and not really know how to approach [each case] when you don't know the severity of each person going into it," she says.

The investigators also go over isolation protocols.

Debra Bogen, an MD and director of the Health Department, said Pitt students who worked as case investigators helped contain the spread of the novel coronavirus in Allegheny County. "And they saved lives."

—Gavin Jenkins

Disease Detectives

Nancy Glynn volunteered to be a contact tracer with the Health Department this spring. "It seemed like a great way to contribute to helping stem the spread of coronavirus," she says.

Glynn

And as an epidemiologist, she feels that being a disease detective is in her blood.

"It involves teaching health literacy, which I love," says the associate professor of epidemiology in Pitt's Graduate School of Public Health. "And piecing together the contacts' timeline and understanding one's exposure history can be a puzzle and enjoyable to me."

Contact tracers like Glynn call people who have been exposed to someone who tested positive for COVID-19; the tracers receive the information on close contacts from case investigators. Tracers instruct the people they call to self-quarantine for 14 days, and they discuss symptoms. "I expected people to be resistant," she says. "But most people are very appreciative of the call and the Health Department's effort, and they agree to remain in quarantine."

Sometimes, people did not believe the person calling was a tracer.

"At the beginning of the pandemic, a lot of people thought [it] was a scam," says Vivian Feng, a Pitt Public Health student.

Feng served as a contact tracer and then as a case investigator for the Health Department. Both roles require empathy, she notes.

"I try my best to lessen [people's] worries and answer all their questions and needs."

Both jobs have played such a crucial role in preventing COVID-19's spread that Pitt's Graduate School of Public Health launched a course on them this summer. Taught by Lauren Orkis, an adjunct assistant professor in epidemiology, the class has 20 Pitt Public Health students.

"We not only want to prepare students to serve as case investigators and contact tracers but also want to prepare them to serve as applied epidemiologists managing these types of operations," Orkis says. *—GJ*

Lean on Me, Virtually

It's April: Medical teams in New York City have been stretched thin by a surge of COVID-19 cases, and physicians with limited critical care experience are handling ICU patients. At Weill Cornell Medical Center in Manhattan, those physicians include hospitalists, doctors normally dedicated to the general care of hospital patients.

Sitting behind his desk in Pittsburgh at UPMC Montefiore, Ian Barbash stares at his computer. On the screen—a live view of an ICU at Weill Cornell. Barbash is able to see this because a Weill hospitalist is carrying a tablet. Barbash, medical director of UPMC TeleICU and Pitt assistant professor of medicine, virtually attends rounds with a team caring for COVID-19 patients.

The camera follows the hospitalists as they walk down the ICU hallway. Nurses have written each patient's vital signs and ventilator settings on the window to each room, saving the physicians from unnecessary trips inside that might further spread the virus. At each window, Barbash (Fel '16) discusses the patient inside with the team. The patients are sedated, lying on their bellies—a method called proning that allows oxygen to easily reach the lungs.

For more than two weeks in the spring, when New York–Presbyterian Hospital's medical centers (of which Weill Cornell is part) were overwhelmed, more than two dozen Pitt Med critical care physicians assisted them virtually through UPMC's TeleICU program. (In April, Allegheny County recorded 1,289 COVID-19 cases compared to more than 109,000 in New York.)

As a thank-you, New York-Presbyterian Hospital published a full-page advertisement in the Pittsburgh Post-Gazette saluting UPMC "Healthcare Heroes." (See ad on the right.)

"[Pitt Med doctors] mainly helped me with management of sedation and ventilators for patients," says Michael Torres, a hospitalist at Weill Cornell. "Even though I had never met them in person, working and talking with them felt very natural."

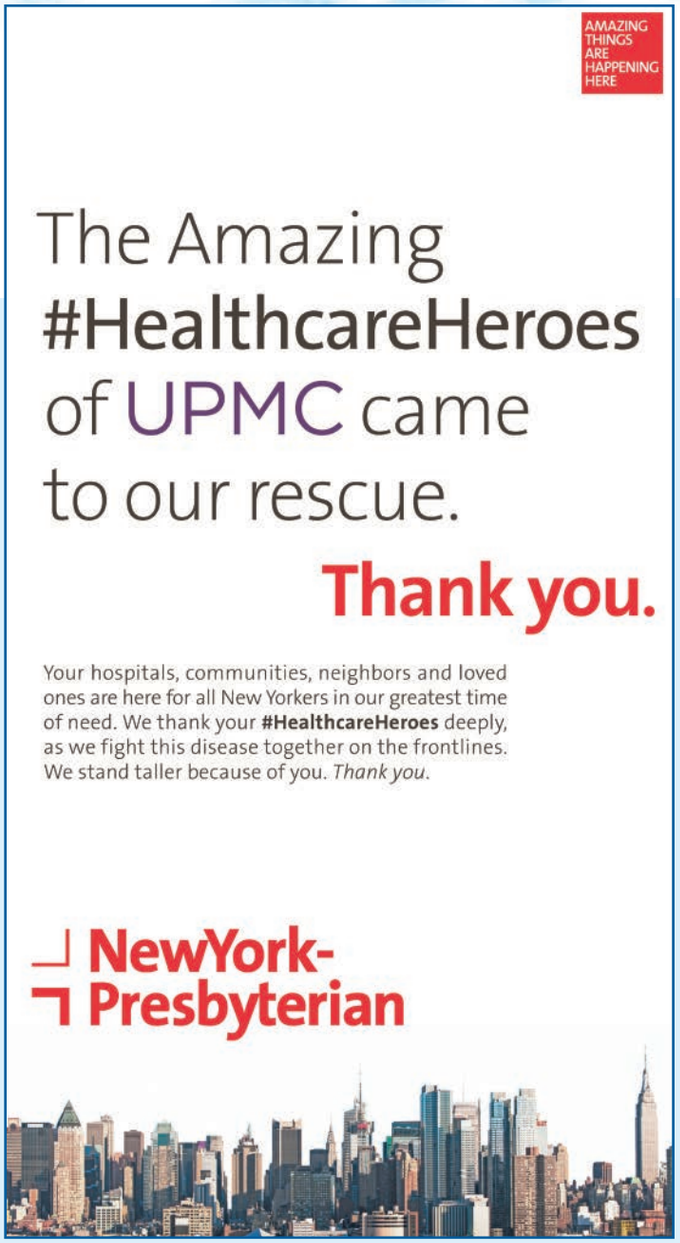
This spring, Corrine Kliment spoke on the phone with several physicians in New York who worked in a step-down unit—the last stop before the ICU. Kliment, an assistant professor of medicine, advised a few pediatricians on how to figure out dosages for adult patients.

"What I helped with was managing," Kliment says. "How you set a ventilator. What medications you should give. How you sedate the patient so they're comfortable."

Kliment and Barbash say that they spent a lot of time validating professionals who knew what they were doing but were stressed out.

Kliment says that the news on television did not fully capture what she heard on the phone, and Barbash describes what he saw through virtual rounds as "surreal."

"I saw a recovery unit for operating rooms that was completely transformed into an ICU and filled with coronavirus patients," he says.



This ad ran in the Pittsburgh Post-Gazette in the spring.

Critical care medicine docs here are now helping the U.S. Army Medical Research and Development Command's Telemedicine and Advanced Technology Research Center to create critical care telehealth and interdisciplinary staffing options for COVID-19 and other national emergencies.

Rachel Sackrowitz, an associate professor of critical care medicine and chief medical officer for the UPMC ICU Service Center, notes that telemedicine isn't really about technology.

"Telemedicine is about connecting people," she says. "Fundamentally, the connection is very old school: two or more people working together to try to solve a problem."

In that sense, Sackrowitz adds, being thanked in 2020 with a newspaper advertisement was quite apt. *–GJ*