MEDICAL DISPATCH

WHAT WE DON'T KNOW ABOUT THE CORONAVIRUS

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The Mysteries Perplexing Doctors About the Coronavirus

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COVID-*19 has been shown to damage multiple organ systems, including the lungs, the heart, the kidneys, and the brain.*

We think of COVID-19 as a disease of the respiratory tract. When future generations look back on this pandemic, its iconic symbol will probably be the ventilator. But, although respiratory problems are at the core of the disease,

COVID-19 has revealed itself to be more than a straightforward viral pneumonia. Doctors around the world—including in the emergency department where we work, at Mount Sinai Hospital, in Manhattan—have learned the hard way that the coronavirus doesn't confine its ravages to the lungs. COVID-19 can push kidneys into failure, send the body's immune system into catastrophic overdrive, and cause blood clots that impede circulation to the lungs, heart, or brain. It's a disease of remarkable complexity, which even the most experienced doctors are struggling to understand.

On blogs, podcasts, and #medtwitter, members of the medical community have been trading stories and theories about COVID-19's intricacies. Often, their conversation has followed the methodology of critical-care doctors. Physicians who work in I.C.U.s tend to talk not about symptoms or diseases—chest pain, diabetes—but about organ systems, which can malfunction and interact in complex ways. System by system, a picture of COVID-19 is emerging. Clarifying it may mean the difference between life and death for thousands of people in the months to come.

The shortness of breath that's most characteristic of COVID-19 is reasonably well understood. It originates in the gossamer air sacs of the lungs, called alveoli, where blood and air are separated by such thin membranes that oxygen and carbon dioxide can pass into and out of the bloodstream, respectively. Between them, the lungs have somewhere in the neighborhood of six hundred million alveoli. Severe COVID-19 causes many of them to either collapse or fill with fluid. The virus attacks the cells lining the alveoli; our overactive immune systems, in trying to fight the virus, may be damaging them as well. The result is that not enough oxygen gets into the blood.

Doctors trying to solve this problem have two basic tools at their disposal: oxygen and pressure. They can give patients concentrated oxygen beyond the usual twenty-one per cent that is found in normal air. Alternatively, using a CPAP machine or ventilator, they can create a kind of sustained air pressure within the lungs—"positive end-expiratory pressure," or PEEP—which keeps the alveoli open, and thus more receptive to oxygen, at moments when the lungs would ordinarily be emptier of air. (Imagine breathing in and out while leaning through the window of a moving car: that lungs-full-of-air feeling is PEEP.) Doctors have also been improving oxygenation by "proning" patients—that is, periodically turning them onto their stomachs. Such positioning takes advantage of gravity to match areas of air-filled lung with areas of higher blood flow.

All this makes straightforward mechanical sense. Still, mysteries hover around the certainties. Doctors track the "oxygen saturation" of patients with COVID-19—they monitor the percentage of hemoglobin molecules in the bloodstream that are currently carrying oxygen. Ordinarily, in patients with healthy lungs, an oxygen-saturation level below ninety per cent is cause for grave concern: when vital organs such as the heart and brain become starved for oxygen, the risk of death skyrockets. But doctors are finding, bizarrely, that some COVID-19 patients can remain subjectively comfortable even when their saturation levels fall far below these ranges. This "silent hypoxemia" is frightening for physicians, who associate such low numbers with imminent death. And it's deeply mystifying, since the numbers seem implausible.

Is silent hypoxemia a sign that, even though a patient feels relatively well, the bottom is about to drop out? Or is the virus somehow interfering with the blood's hemoglobin, or with the parts of the brain that warn us when we need more oxygen? Theories abound. Meanwhile, silent hypoxemia complicates the decision to intubate. In the early days of COVID-19 treatment, low oxygen saturation that failed to improve was generally seen as an indication that intubation was necessary right away. But in early March reports of comfortable patients with discordantly low saturation rates began spreading rapidly among doctors online. One particularly arresting image, posted on Twitter by a New York City emergency-medicine physician, shows a patient calmly reading on her phone while her overhead monitor reveals a saturation rate of just fifty-four per cent. Until we better understand the physiology behind silent hypoxemia, and why some people experience it and others do not, we will have no choice but to live with the mystery, scrutinizing some patients who have oxygen levels in the seventies and eighties, and whom we might have rushed to intubate in the past.

COVID-*19 is a disease of remarkable complexity, which even the most experienced doctors are struggling to understand.* Photograph by Sergio Perez / Reuters

Within hours of a viral invasion, the body's immune system swings into action. The "innate" immune system, which recognizes protein structures common to many pathogens, reacts first, by releasing a family of chemical distress signals called cytokines. They spread from the site of the infection, instructing the body to raise its temperature and divert blood flow to the affected area; they also activate other immune-system cells, which begin developing antibodies specifically targeting the invaders. Without cytokines, the immune system would slumber while infections wreak havoc. But the cytokine system has a weakness. Some pathogens can provoke it in a perverse way, so that it goads the immune system as a whole into overdrive. In what's known as a cytokine storm, fever and inflammation spike out of control. It's unclear why some patients might experience this phenomenon while others do not.

Faced with a cytokine storm in a patient, a doctor can try to modulate the immune system's response. The problem is striking the right balance. While some patients may benefit from a degree of medically induced immunosuppression, there are others for whom such an intervention could cause great harm. Some hospitals have begun cautiously administering steroids or drugs that inhibit the cytokine IL-6. But high-quality clinical-trial data about such treatments won't be ready for a long time. Moreover, even if early results are encouraging, we will still have to distinguish between those patients who will benefit from immunosuppression and those who won't. In the past, physicians have interpreted elevated blood levels of the protein ferritin as a sign that a cytokine storm is in progress. Some are now using that analysis in the treatment of COVID-19. Only time will tell if they're right.

It's not only the immune system that must maintain a delicate balance. The bloodstream, too, exists in a perpetual tug-of-war between bleeding and clotting. Too much bleeding, and the smallest trauma can cause hemorrhage, even to the point of death (the danger faced by people with hemophilia); too far in the other direction, and clots will form in the absence of trauma, potentially obstructing blood vessels and causing lethal damage if they travel to the heart, lungs, or brain.

By measuring a blood protein called D-dimer, doctors can get a rough sense of how much excess clotting is happening in the bloodstream. Many infections cause a rise in clotting. But in some COVID-19 patients doctors are seeing jaw-dropping spikes. A few patients appear to have widespread pathologic clotting. One of our patients, a healthy man in his fifties, arrived in our hospital's I.C.U. with a D-dimer level of a thousand—elevated but unremarkable. But when a doctor attempted to put an I.V. into one of the man's femoral veins—the largest veins in the legs—he discovered, through use of a bedside ultrasound, that it was filled with clots. The second D-dimer test, performed just hours after the first, registered a level of over ten thousand. The man died several hours later.

It's possible that cytokine storms are causing overactive clotting. But, whatever the cause turns out to be, clinicians face a challenge. Doctors often give small doses of anticoagulant medication to patients who are admitted to the hospital, simply because laying in bed for an extended period makes clotting more likely. But more extreme levels of clotting demand more aggressive anticoagulation—and doctors must figure out when to administer it and to whom. These medications carry their own risks. The patient suffering from femoral clotting was immediately put on aggressive anticoagulation medication. Yet his death, and the rapid increase in his D-dimer, suggest that successful anticoagulant interventions in other patients may need to come earlier.

Doctors often test critically ill patients for cardiac-specific troponins—proteins in the bloodstream that are normally found only in the muscles of the heart. The presence of such proteins in blood suggests heart damage. Some severe COVID-19 patients have elevated troponin levels; their hearts appear to be damaged. We're not entirely sure what's causing the damage, though, and so we don't know exactly how to treat it.

One major cause of heart damage is oxygen starvation: it's what happens in a heart attack, when the sudden obstruction of a coronary artery prevents oxygen from reaching heart muscle. Starvation can also occur when failing lungs prevent oxygen

from entering the bloodstream, or when sepsis causes such a drop in blood pressure that even properly oxygenated blood can't get to the heart fast enough. These problems are significant, and, in broad terms, doctors know how to respond to them. There are, however, other possibilities. Perhaps runaway clotting is choking off circulation vessel by vessel. Early reports from China, meanwhile, suggested that the coronavirus could be attacking the heart muscle directly, causing a syndrome known as myocarditis. No one knows for sure what the best treatment for this form of myocarditis might be. Some doctors have reported that steroids can help—and yet steroids also act as an immunosuppressant. In critical care, it's often hard to bring one organ system into balance without destabilizing another.

A similar story appears to be unfolding around the kidneys. Kidneys serve as filters for the blood, weeding out certain compounds and excreting them in urine, while regulating the precise composition of electrolytes that allow cells to function. Complete kidney failure is a death sentence if it's not quickly addressed. Unfortunately, many critically ill COVID-19 patients are developing it. Just as ventilators are substituting for failing lungs, so dialysis machines are taking over for failing kidneys. The hardest-hit areas of the country are facing shortages of the resources needed for dialysis: dialysis machines, the fluid used in the dialysis process, and dialysis-trained nurses.

We don't yet know how kidney injury plays out in COVID-19 patients. It's likely that some people will recover their kidney function, while others could lose it permanently. We also don't know why people are going into kidney failure in the first place. As with the heart, it's possible that oxygen starvation is the problem. But some clinicians argue that the virus is attacking kidney cells directly—and there is biopsy data out of China that supports this thesis, too.

Still other organ systems may be involved in COVID-19. The ACE-2 receptor protein, which is used by the coronavirus to enter human cells, resides not just in the respiratory tract but also on cells in the stomach, intestines, liver, kidneys, and brain. There are reports of coronavirus patients with encephalitis—a potentially fatal inflammation of the brain—and signs of an increased incidence of stroke. In our hospital, we have seen several COVID-19 patients suffering from a severe complication of diabetes called diabetic ketoacidosis, despite having no history as diabetics.

Last month, we screened for COVID-19 by asking about fever and cough. Now we know that the disease manifests in other ways, or sometimes proceeds with no symptoms at all. One patient recently arrived in the E.R. reporting three days of watery diarrhea and a day of nausea and vomiting; she said that she felt weak but hadn't experienced fevers, chills, sweats, or respiratory symptoms. Her oxygen saturation was in the low nineties; her chest X-ray was consistent with COVID-19.

For us, and for many doctors we know, cases like these have become subjects of consuming fascination. During our few free moments, we share patients' sky-high D-dimer levels and swap theories about the sources of their discordant oxygen readings. In the absence of data from randomized, prospective trials, we search for answers on colleagues' Twitter accounts, in interviews with Chinese or Italian physicians, and in our patients' charts. Our colleagues at Mount Sinai are actively embarking on dozens of research projects, ranging from ventilator-management strategies to social determinants of COVID-19 mortality, but months will pass before these projects give us objective insight into the disease. The desperate desire for clarity

is evident at every level of the medical profession. Earlier this month, *The New England Journal of Medicine* published an observational, fifty-three-patient study of the antiviral drug remdesivir; many observers criticized the journal for publishing it, because the trial had neither a control group nor randomization, and so no meaningful statistical conclusions could be drawn from its results. (Even its authors noted that actual measurement of the drug's efficacy would require "ongoing randomized, placebo-controlled trials.")

And yet, as the historian of science Lorraine Daston writes in a recent essay, it's natural to cast about for answers at the dawn of a pandemic. "At moments of extreme scientific uncertainty," Daston writes, "observation, usually treated as the poor relation of experiment and statistics in science, comes into its own." Confronting a new disease, doctors have no choice but to turn to "suggestive single cases, striking anomalies, partial patterns." Slowly, as our ideas about "what works and what doesn't" help tell us "what to test, what to count," the picture clarifies. Until then, "we are back in the seventeenth century, the age of ground-zero empiricism, and observing as if our lives depended on it." One patient at a time, we have to work our way into the present.

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