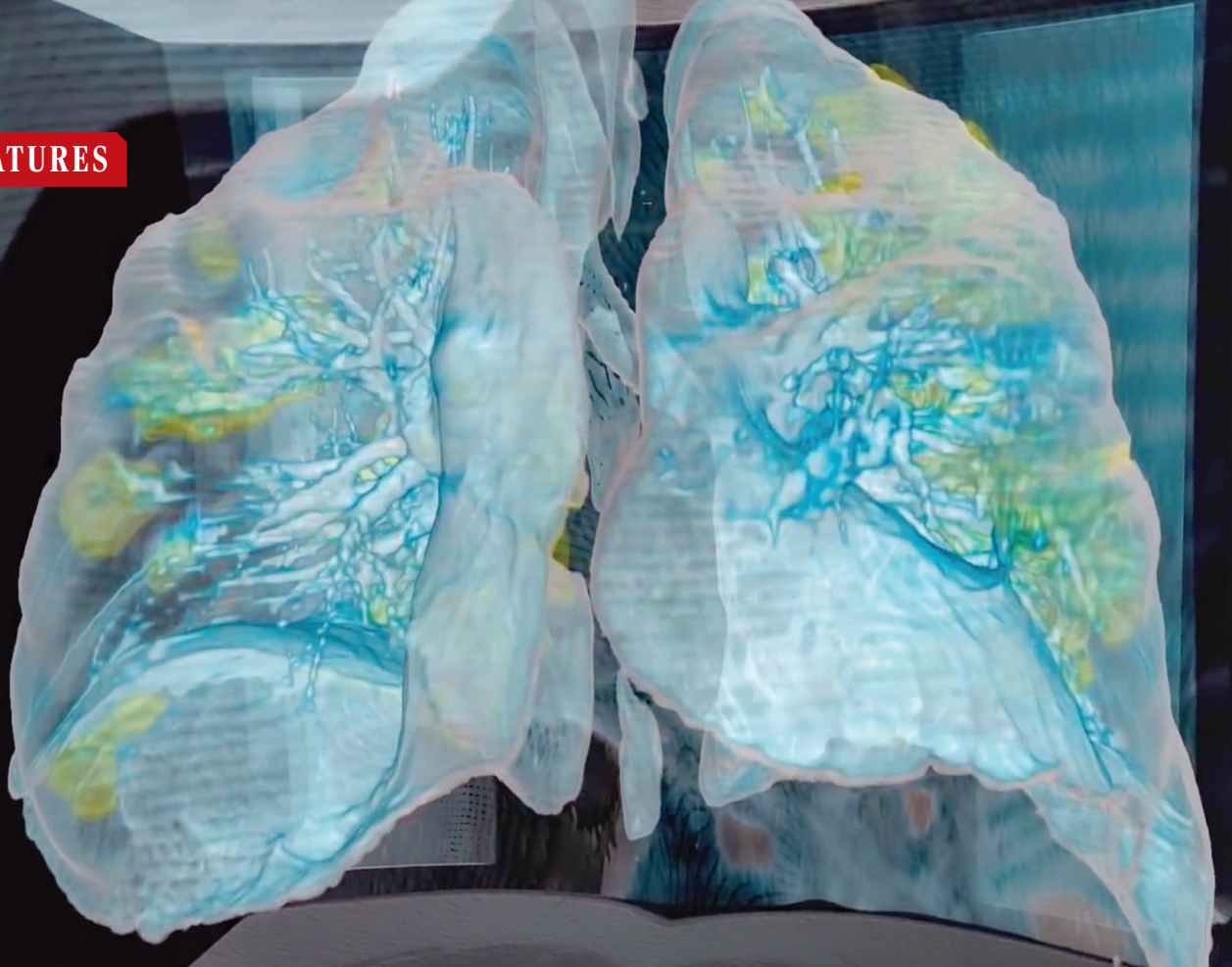




A RAMPAGE THROUGH THE BODY

The lungs are ground zero, but COVID-19 also tears through organ systems from brain to blood vessels

By **Meredith Wadman, Jennifer Couzin-Frankel, Jocelyn Kaiser, and Catherine Maticic**

On rounds in a 20-bed intensive care unit one recent day, physician Joshua Denson assessed two patients with seizures, many with respiratory failure, and others whose kidneys were on a dangerous downhill slide. Days earlier, his rounds had been interrupted as his team tried, and failed, to resuscitate a young woman whose heart had stopped. All of the patients shared one thing,

says Denson, a pulmonary and critical care physician at the Tulane University School of Medicine. “They are all COVID positive.”

As the number of confirmed cases of COVID-19 approaches 2.5 million globally and deaths surpass 166,000, clinicians and pathologists are struggling to understand the damage wrought by the coronavirus as it tears through the body. They are realizing that although the lungs are ground zero, the virus’ reach can extend to many

organs including the heart and blood vessels, kidneys, gut, and brain.

“[The disease] can attack almost anything in the body with devastating consequences,” says cardiologist Harlan Krumholz of Yale University and Yale-New Haven Hospital, who is leading multiple efforts to gather clinical data on COVID-19. “Its ferocity is breathtaking and humbling.”

Understanding the rampage could help doctors on the front lines treat the roughly

The coronavirus wreaked extensive damage (yellow) on the lungs of a 59-year-old man who died at George Washington University Hospital, as seen in a 3D model based on computed tomography scans.

5% of infected people who become desperately and sometimes mysteriously ill. Does a dangerous, newly observed tendency to blood clotting transform some mild cases into life-threatening emergencies? Is an overzealous immune response behind the worst cases, suggesting treatment with immune-suppressing drugs could help? And what explains the startlingly low blood oxygen that some physicians are reporting in patients who nonetheless are not gasping for breath? “Taking a systems approach may be beneficial as we start thinking about therapies,” says Nilam Mangalmurti, a pulmonary intensivist at the Hospital of the University of Pennsylvania (HUP).

What follows is a snapshot of the fast-evolving understanding of how the virus attacks cells around the body. Despite the more than 1500 papers now spilling into journals and onto preprint servers every week, a clear picture is elusive, as the virus acts like no pathogen humanity has ever seen. Without larger, controlled studies that are only now being launched, scientists must pull information from small studies and case reports, often published at warp speed and not yet peer reviewed. “We need to keep a very open mind as this phenomenon goes forward,” says Nancy Reau, a liver transplant physician who has been treating COVID-19 patients at Rush University Medical Center. “We are still learning.”

WHEN AN INFECTED PERSON expels virus-laden droplets and someone else inhales them, the novel coronavirus, called SARS-CoV-2, enters the nose and throat. It finds a welcome home in the lining of the nose, according to a recent arXiv preprint, because cells there are rich in a cell-surface receptor called angiotensin-converting enzyme 2 (ACE2). Throughout the body, the presence of ACE2, which normally helps regulate blood pressure, marks tissues potentially vulnerable to infection, because the virus requires that receptor to enter a cell. Once inside, the virus hijacks the cell’s machinery, making myriad copies of itself and invading new cells.

As the virus multiplies, an infected person may shed copious amounts of it, especially during the first week or so. Symptoms may be absent at this point. Or the virus’ new victim may develop a fever, dry cough, sore throat, loss of smell and taste, or head and body aches.

If the immune system doesn’t beat back

SARS-CoV-2 during this initial phase, the virus then marches down the windpipe to attack the lungs, where it can turn deadly. The thinner, distant branches of the lung’s respiratory tree end in tiny air sacs called alveoli, each lined by a single layer of cells that are also rich in ACE2 receptors.

Normally, oxygen crosses the alveoli into the capillaries, tiny blood vessels that lie beside the air sacs; the oxygen is then carried to the rest of the body. But as the immune system wars with the invader, the battle itself disrupts healthy oxygen transfer. Front-line white blood cells release inflammatory molecules called chemokines, which in turn summon more immune cells that target and kill virus-infected cells, leaving a stew of fluid and dead cells—pus—behind (see graphic, p. 358). This is the underlying pathology of pneumonia, with its corresponding symptoms: coughing; fever; and rapid, shallow respiration. Some COVID-19 patients recover, sometimes with no more support than oxygen

breathed in through nasal prongs.

But others deteriorate, often suddenly, developing a condition called acute respiratory distress syndrome. Oxygen levels in their blood plummet, and they struggle ever harder to breathe. On x-rays and computed tomography scans, their lungs are riddled with white opacities where black space—air—should be. Commonly, these patients end up on ventilators. Many die, and survivors may face long-term complications (see sidebar, p. 359). Autopsies show their alveoli became stuffed with fluid, white blood cells, mucus, and the detritus of destroyed lung cells.

Some clinicians suspect the driving force in many gravely ill patients’ downhill trajectories is a disastrous overreaction of the immune system known as a “cytokine storm,” which other viral infections are known to trigger. Cytokines are chemical signaling molecules that guide a healthy immune response; but in a cytokine storm, levels of certain cytokines soar far beyond what’s needed, and immune cells start to attack healthy tissues. Blood vessels leak, blood pressure drops, clots form, and catastrophic organ failure can ensue.

Some studies have shown elevated levels of these inflammation-inducing cytokines in the blood of hospitalized COVID-19 patients. “The real morbidity and mortality of this disease is probably driven by this out of proportion inflammatory response to the virus,” says Jamie Garfield, a pulmonologist who cares for COVID-19 patients at Temple University Hospital.

But others aren’t convinced. “There seems to have been a quick move to associate COVID-19 with these hyperinflammatory

states. I haven’t really seen convincing data that that is the case,” says Joseph Levitt, a pulmonary critical care physician at the Stanford University School of Medicine.

He’s also worried that efforts to dampen a cytokine response could backfire. Several drugs targeting specific cytokines are in clinical trials in COVID-19 patients. But Levitt fears those drugs may suppress the immune response that the body needs to fight off the virus. “There’s a real risk that we allow more viral replication,” Levitt says.

Meanwhile, other scientists are zeroing in on an entirely different organ system that they say is driving some patients’ rapid deterioration: the heart and blood vessels.

IN BRESCIA, ITALY, a 53-year-old woman walked into the emergency room of her local hospital with all the classic symptoms of a heart attack, including telltale signs in her electrocardiogram and high levels of a blood marker suggesting damaged cardiac muscles. Further tests showed cardiac swelling and scarring, and a left ventricle—normally the powerhouse chamber of the heart—so weak that it could only pump one-third its normal amount of blood. But when doctors injected dye in her coronary arteries, looking for the blockage that signifies a heart attack, they found none. Another test revealed the real cause: COVID-19.

How the virus attacks the heart and blood vessels is a mystery, but dozens of preprints and papers attest that such damage is common. A 25 March paper in *JAMA Cardiology* found heart damage in nearly 20% of patients out of 416 hospitalized for COVID-19 in Wuhan, China. In another Wuhan study, 44% of 36 patients admitted to the intensive care unit (ICU) had arrhythmias.

The disruption seems to extend to the blood itself. Among 184 COVID-19 patients in a Dutch ICU, 38% had blood that clotted abnormally, and almost one-third already had clots, according to a 10 April paper in *Thrombosis Research*. Blood clots can break apart and land in the lungs, blocking vital arteries—a condition known as pulmonary embolism, which has reportedly killed COVID-19 patients. Clots from arteries can also lodge in the brain, causing stroke. Many patients have “dramatically” high levels of D-dimer, a byproduct of blood clots, says Behnood Bikdeli, a cardiovascular medicine fellow at Columbia University Medical Center.

“The more we look, the more likely it becomes that blood clots are a major player in the disease severity and mortality from COVID-19,” Bikdeli says.

Infection may also lead to blood vessel constriction. Reports are emerging of isch-

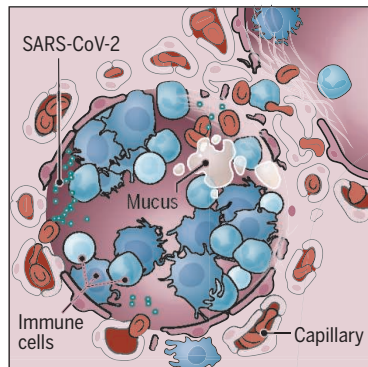
Science’s
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An invader's impact

In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body's response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

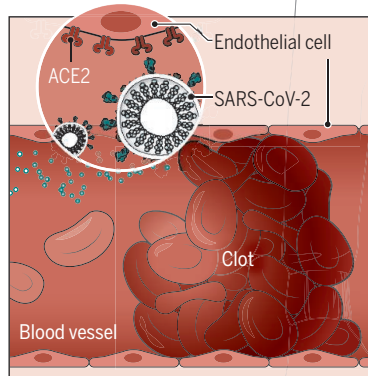
1 Lungs

A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.



2 Heart and blood vessels

The virus (teal) enters cells, likely including those lining blood vessels, by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.



emia in the fingers and toes—a reduction in blood flow that can lead to swollen, painful digits and tissue death.

In the lungs, blood vessel constriction might help explain anecdotal reports of a perplexing phenomenon seen in pneumonia caused by COVID-19: Some patients have extremely low blood-oxygen levels and yet are not gasping for breath. In this scenario, oxygen uptake is impeded by constricted blood vessels rather than by clogged alveoli. “One theory is that the virus affects the vascular biology and that’s why we see these really low oxygen levels,” Levitt says.

If COVID-19 targets blood vessels, that could also help explain why patients with pre-existing damage to those vessels, for example from diabetes and high blood pressure, face higher risk of serious disease. Recent Centers for Disease Control and Prevention (CDC) data on hospitalized patients in 14 U.S. states found that about one-third had chronic lung disease—but nearly as many had diabetes, and fully half had pre-existing high blood pressure.

Mangalmurti says she has been “shocked by the fact that we don’t have a huge number of asthmatics” or patients with

other respiratory diseases in her hospital’s ICU. “It’s very striking to us that risk factors seem to be vascular: diabetes, obesity, age, hypertension.”

Scientists are struggling to understand exactly what causes the cardiovascular damage. The virus may directly attack the lining of the heart and blood vessels, which, like the nose and alveoli, are rich in ACE2 receptors. By altering the delicate balance of hormones that help regulate blood pressure, the virus might constrict blood vessels going to the lungs. Another possibility is that lack of oxygen, due to the chaos in the lungs, damages blood vessels. Or a cytokine storm could ravage the heart as it does other organs.

“We’re still at the beginning,” Krumholz says. “We really don’t understand who is vulnerable, why some people are affected so severely, why it comes on so rapidly ... and why it is so hard [for some] to recover.”

THE WORLDWIDE FEARS of ventilator shortages for failing lungs have received plenty of attention. Not so a scramble for another type of equipment: kidney dialysis machines. “If these folks are not dying of

lung failure, they’re dying of renal failure,” says neurologist Jennifer Frontera of New York University’s Langone Medical Center, which has treated thousands of COVID-19 patients. Her hospital is developing a dialysis protocol with a different kind of machine to support more patients. What she and her colleagues are seeing suggests the virus may target the kidneys, which are abundantly endowed with ACE2 receptors.

According to one preprint, 27% of 85 hospitalized patients in Wuhan had kidney failure. Another preprint reported that 59% of nearly 200 hospitalized COVID-19 patients in China’s Hubei and Sichuan provinces had protein in their urine, and 44% had blood; both suggest kidney damage. Those with acute kidney injury were more than five times as likely to die as COVID-19 patients without it, that preprint reported.

“The lung is the primary battle zone. But a fraction of the virus possibly attacks the kidney. And as on the real battlefield, if two places are being attacked at the same time, each place gets worse,” says co-author Hongbo Jia, a neuroscientist at the Chinese Academy of Sciences’s Suzhou Institute of Biomedical Engineering and Technology.

3 Brain

Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

4 Eyes

Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

5 Nose

Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose’s nerve endings and damage cells.

6 Liver

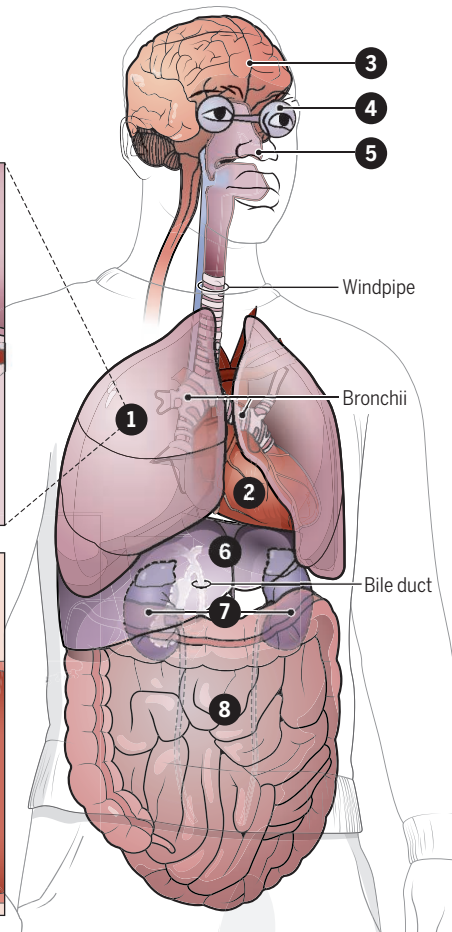
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

7 Kidneys

Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

8 Intestines

Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.



One study identified viral particles in electron micrographs of kidneys from autopsies, suggesting a direct viral attack. But kidney injury may also be collateral damage. Ventilators boost the risk of kidney damage, as do antiviral compounds including remdesivir, which is being deployed experimentally in COVID-19 patients. Cytokine storms can also dramatically reduce blood flow to the kidney, causing often-fatal damage. And pre-existing diseases like diabetes can increase the chances of kidney injury. “There is a whole bucket of people who already have some chronic kidney disease who are at higher risk for acute kidney injury,” says Suzanne Watnick, chief medical officer at Northwest Kidney Centers.

ANOTHER STRIKING SET of symptoms in COVID-19 patients centers on the brain and nervous system. Frontera says 5% to 10% of coronavirus patients at her hospital have neurological symptoms. But she says that “is probably a gross underestimate” of the number whose brains are struggling, especially because many are sedated and on ventilators.

Frontera has seen patients with the brain inflammation encephalitis, seizures, and a “sympathetic storm,” a hyperreaction of the sympathetic nervous system that causes seizurelike symptoms and is most common after a traumatic brain injury. Some people with COVID-19 briefly lose consciousness. Others have strokes. Many report losing their sense of smell and taste. And Frontera and others wonder whether, in some cases, infection depresses the brain stem reflex that senses oxygen starvation—another explanation for anecdotal observations that some patients aren’t gasping for air, despite dangerously low blood oxygen levels.

ACE2 receptors are present in the neural cortex and brain stem, says Robert Stevens, an intensive care physician at Johns Hopkins Medicine. And the coronavirus behind the 2003 severe acute respiratory syndrome (SARS) epidemic—a close cousin of today’s culprit—was able to infiltrate neurons and sometimes caused encephalitis. On 3 April, a case study in the *International Journal of Infectious Diseases*, from a team in Japan, reported traces of new coronavirus in the cerebrospinal fluid of a COVID-19 patient who developed meningitis and encephalitis, suggesting it, too, can penetrate the central nervous system.

But other factors could be damaging the brain. For example, a cytokine storm could cause brain swelling. The blood’s exaggerated tendency to clot could trigger strokes. The challenge now is to shift from conjecture to confidence, at a time when staff are focused on saving lives, and even neurologic assessments like inducing the

gag reflex or transporting patients for brain scans risk spreading the virus.

Last month, Sherry Chou, a neurologist at the University of Pittsburgh Medical Center, began to organize a worldwide consortium that now includes 50 centers to draw neurological data from care patients already receive. Early goals are simple: Identify the prevalence of neurologic complications in hospitalized patients and document how they fare. Longer term, Chou and her colleagues hope to gather scans and data from lab tests to better understand the virus’ impact on the nervous system, including the brain.

No one knows when or how the virus might penetrate the brain. But Chou speculates about a possible invasion route: through



A 58-year-old woman with COVID-19 developed encephalitis, with tissue damage in the brain (arrows).

the nose, then upward and through the olfactory bulb—explaining reports of a loss of smell—which connects to the brain. “It’s a nice sounding theory,” she says. “We really have to go and prove that.”

Most neurological symptoms “are reported from colleague to colleague by word of mouth,” Chou adds. “I don’t think anybody, and certainly not me, can say we’re experts.”

IN EARLY MARCH, a 71-year-old Michigan woman returned from a Nile River cruise with bloody diarrhea, vomiting, and abdominal pain. Initially doctors suspected she had a common stomach bug, such as *Salmonella*. But after she developed a cough, doctors took a nasal swab and found her positive for the novel coronavirus. A stool sample positive for viral RNA, as well as signs of colon injury seen in an endoscopy, pointed to a gastrointestinal (GI) infection with the coronavirus, according to a paper posted online in *The American Journal of Gastroenterology* (AJG).

Her case adds to a growing body of evi-

dence suggesting the new coronavirus, like its cousin SARS, can infect the lining of the lower digestive tract, where ACE2 receptors are abundant. Viral RNA has been found in as many as 53% of sampled patients’ stool samples. And in a paper in press at *Gastroenterology*, a Chinese team reported finding the virus’ protein shell in gastric, duodenal, and rectal cells in biopsies from a COVID-19 patient. “I think it probably does replicate in the gastrointestinal tract,” says Mary Estes, a virologist at Baylor College of Medicine.

Recent reports suggest up to half of patients, averaging about 20% across studies, experience diarrhea, says Brennan Spiegel of Cedars-Sinai Medical Center in Los Angeles, co-editor-in-chief of *AJG*. GI symptoms aren’t on CDC’s list of COVID-19 symptoms, which could cause some COVID-19 cases to go undetected, Spiegel and others say. “If you mainly have fever and diarrhea, you won’t be tested for COVID,” says Douglas Corley of Kaiser Permanente, Northern California, co-editor of *Gastroenterology*.

The presence of virus in the GI tract raises the unsettling possibility that it could be passed on through feces. But it’s not yet clear whether stool contains intact, infectious virus, or only RNA and proteins. To date, “We have no evidence” that fecal transmission is important, says coronavirus expert Stanley Perlman of the University of Iowa. CDC says that, based on experiences with SARS and with the coronavirus that causes Middle East respiratory syndrome, the risk from fecal transmission is probably low.

The intestines are not the end of the disease’s march through the body. For example, up to one-third of hospitalized patients develop conjunctivitis—pink, watery eyes—although it’s not clear that the virus directly invades the eye.

Other reports suggest liver damage: More than half of COVID-19 patients hospitalized in two Chinese centers had elevated levels of enzymes indicating injury to the liver or bile ducts. But several experts told *Science* that direct viral invasion isn’t likely the culprit. They say other events in a failing body, like drugs or an immune system in overdrive, are more likely causes of the liver damage.

This map of the devastation that COVID-19 can inflict on the body is still just a sketch. It will take years of painstaking research to sharpen the picture of its reach, and the cascade of effects in the body’s complex and interconnected systems that it might set in motion. As science races ahead, from probing tissues under microscopes to testing drugs on patients, the hope is for treatments more wily than the virus that has stopped the world in its tracks. ■

A rampage through the body

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