A RACE AGAINST THE CLOCK

BY PHOEBE HALL
PHOTOGRAPH BY KAREN PHILIPPI

In sepsis, every second counts. But the hunt for a sure-fire cure seems to be stuck on the starting line.

Until January 2014, Victoria Morrone, RN, had always been pretty healthy. As a CNA and nursing school student at the time, she knew about sepsis, but it was the last thing on her mind when she caught a cold. She remembers downplaying her illness, reassuring her husband, Joe, even as she was being loaded into an ambulance to the hospital, "I'll be fine."

SURVIVING SEPSIS
Vicky Morrone lost her right leg to sepsis in 2014. Now a nurse, she hopes to one day work in critical care. "I feel like that's where I should be," she says.

Morrone is blond and petite, with a warm smile. She's straightforward as she recalls that winter when everything changed. She was 30 years old and on break from school, enjoying time at home in Westerly, RI, with her infant son and two older kids, when she was diagnosed with an upper respiratory infection. She and her doctor didn't want to harm her breast milk supply, and elected to treat it with amoxicillin. It didn't work.

"It was very, very quick," she says of her decline. At the local emergency department Morrone was diagnosed with pneumonia and acute respiratory distress syndrome (ARDS), and put in a coma. She tells what happened next as though she's narrating someone else's story: the failed first attempt to place a central line, which missed and punctured her lung; the four chest tubes; the femoral line in her right leg. As her blood pressure cratered she was packed into an advanced life support ambulance and rushed through a snowstorm to Providence. A priest was called to give last rites. Her little brother, who was serving in Afghanistan, was flown home to say goodbye.

In the Rhode Island Hospital ICU the medical team found her right leg was in rigor. A fasciotomy stabilized her vitals, but it couldn't save her limb. "It was dead and it was taking me with it," Morrone says. "They called my husband because he was with our kids at the time, and asked for permission to take my leg. And they said if they don't take my leg, I will die. And if they take my leg, I may still die." With Joe's consent, surgeons amputated her right leg above the knee in the ICU. "They couldn't stabilize me enough to bring me to the OR," she says.

Three years later, Morrone became the first person in the state to graduate from a nursing program with a prosthetic leg. She's working at a nursing and rehab center, and she and Joe celebrated their 10th anniversary in August, on Marco Island in Florida. "It was beautiful," she says. "But it's, you know, that could have not happened." Their kids are 9, 6, and 4 now. "My oldest has almost PTSD. Every time I leave, he needs to know when I'm coming back," Morrone says. "My daughter, every once in awhile, will start to get teary and say, Mom, you almost died and I didn't have a mom."

The many weeks away from the baby, Oliver, during her illness and recovery, still weigh heavily on her. He might never have known his mother, she reflects, her eyes filling with tears. "But he doesn't—for him, he doesn't know any different," she says. "Mom just puts on her leg every day."

EQUAL OPPORTUNITY KILLER

Morrone says no one knows exactly when sepsis set in: whether the infection began in her lungs before she went to the hospital (doctors later determined she'd had H1N1 flu, not a cold), or in her leg after the femoral line was placed, or somewhere in between. But that chain of events—healthy young mother gets a lung infection and loses a limb—was a tragically familiar one to Professor of Medicine Mitchell Levy, MD, MCCM, FCCP, who, as the director of the medical ICU at Rhode Island Hospital, was part of the team that cared for her. "People get sepsis from cutting their hand. Young kids die," he says. "No one's immune from the ravages of sepsis."

Sepsis isn't a disease; it's not caused by a single agent, nor does it affect any one organ. It's a physiological condition, a dysfunctional response to an infection—usually bacterial, but sometimes caused by a fungus, virus, or parasite—in which the immune system turns on itself, damaging tissues and organs. There's no simple test for sepsis, yet if it's not rapidly identified, or treatment is administered too slowly, organs fail, blood pressure plummets, and death quickly follows.

For decades, its prevalence, and its lethality, were underappreciated; the NIH didn't even fund sepsis research until recently, Levy says. In the US alone it sickens 1.6 million people annually and kills more than a quarter million of them; it's the No. 1 killer of hospital patients, and the third leading cause of death overall. As the population ages, it will only get worse: the elderly, along with newborns and other immunocompromised people, are most vulnerable to sepsis, but it can, and does, strike anyone.

At first glance it seems there's no rhyme or reason to who gets sepsis. Most of us can get the flu, or a nick while shaving, and be just fine; but in an unfortunate few, the immune system overreacts, taking organs down like dominoes. But why? Researchers believe it's an ideal case for personalized medicine: if they can find genetic clues that indicate individual susceptibility to sepsis and, furthermore, the most effective therapy for each patient, maybe they could stop sepsis before it starts.

But here's the trick: can this be done really, really fast?

Because clinicians have minutes, not hours or days, to diagnose sepsis and begin treatment. "We know there is a pattern of genomic response," Levy says. But without a rapid diagnostic, all this genetic know-how won't save the patient. "They say in cardiology, time is muscle," Levy says. "The same thing is true for sepsis. We say time is tissue."

NEEDLE IN A HAYSTACK

Talk to a sepsis specialist and at some point they'll tell you how much they envy people who study and treat other disorders. A heart attack has a discrete beginning and end. Flu has a definitive agent. Cancer can be biopsied. But no one goes into sepsis research because it's easy.

"It's the Bermuda Triangle" of drug research, says Steven Opal, MD, a professor of medicine. It's financially too risky for small pharmaceutical companies; larger ones have gotten cold feet after high-profile failures and plummeting stock values. "A company needs to be very brave, very silly, or have lots of money in order to do these studies," he says.

As the codirector, with Levy, of the Ocean State Clinical Coordinating Center (OSCCC) in Providence, Opal has shepherded a number of potential sepsis drugs through clinical trials, only to see them all flame out. "It's a little depressing," he says. "There's been some spectacular failures." He was lead author of a 2014 paper in *Critical Care Medicine* that called for overhauling the approach to sepsis drug research and testing. "Hundreds of millions of dollars have been expended enrolling over 30,000 patients in clinical trials," the authors wrote. "Yet, not a single agent has convincingly proven to be consistently efficacious in clinical trials. There are no new drugs on the market to show for all this effort."

With its constellation of symptoms, sepsis is difficult to diagnose precisely and, thus, to define a clear patient cohort across centers in large clinical trials. With no one pathogen, there's no one thing for a drug to attack. Anti-endotoxin drugs, immunomodulators, and anticoagulants all have failed. Though inflammation is a hallmark of sepsis, no anti-inflammatory agent has panned out. Activated protein C, the only drug ever approved to treat septic shock, was taken off the market after 10 years when the results of the first phase 3 trial couldn't be duplicated.

Yet Opal is relentlessly optimistic. "We've been able to slowly convince Big Pharma that this is still an important unmet medical need and needs to be solved," he says. He has high hopes for three international drug trials that OSCCC is managing, including two potential therapies for complications of septic shock, both in phase 3; and a small phase 1 trial for a Bristol-Myers Squibb immunotherapy drug, nivolumab, that's had some success in cancer patients by using programmed cell death 1 (PD-1) antibodies to activate T cells. "We're all excited about it," Opal says.

> "They say in cardiology, time is muscle. The same thing is true for sepsis: time is tissue."

Alfred Ayala, PhD, a professor of surgery (trauma) (research), has been trying to understand why some people are predisposed to immunosuppression and sepsis since he was a postdoc at Michigan State. Some of his findings in the 2000s about PD-1, which is a type of immune checkpoint protein, formed the basis for the development of nivolumab and one other immunotherapeutic. Ayala says that while in certain cancers the cell death processes of PD-1 stop the uncontrolled division of tumor cells, in sepsis, where the immune system is dangerously hyperactive, it acts as a brake on T cell responsiveness. "The downside is … all branches of the immune system are affected by these agents," Ayala says. "It's not a panacea."

Checkpoint proteins like PD-1 have another interesting

SEPSIS IN THE US

#1

CAUSE OF DEATH IN HOSPITALS

Kills
1 person
every
2 minutes

#1

COST OF HOSPITALIZATION

$24 billion
PER YEAR

1.6 million
PEOPLE INFECTED

258,000
DEATHS PER YEAR

Common infections that lead to sepsis

LUNG INFECTION	**35%**
UTI	**25%**
GUT INFECTION	**11%**
SKIN INFECTION	**11%**

58%
OF ADULTS HAVE HEARD OF SEPSIS—LESS THAN EBOLA

38
AMPUTATIONS PER DAY RESULT FROM SEPSIS

#3
CAUSE OF ALL DEATHS, MORE THAN PROSTATE CANCER, BREAST CANCER, AND AIDS COMBINED

SOURCES: SEPSIS ALLIANCE, CDC

attribute: Ayala says they seem to be overexpressed in the sickest patients, and may point to biomarkers that could someday help clinicians identify a predisposition for sepsis, or if they're already sick, what therapy might work best. "There seem to be families of genes that are being altered and dysregulated, as well as cell populations within the immune system that seem to be altered," he says. His lab is investigating what role checkpoint proteins play in that immune dysregulation, and on what cells they're expressed. "Understanding these various immunosuppressive agents made many of us think these things may be changing because of the impacts of something outside the gene itself," Ayala says—that is, epigenetic factors like diabetes, high blood pressure, aging, and other stressors that might alter gene expression and predispose someone to immune dysfunction and sepsis. "Now, we don't understand what all those predispositions are," he adds. "Otherwise, we wouldn't have this conversation and I wouldn't be here."

But Ayala does know there won't be a single biomarker that identifies all potential sepsis patients: just as sepsis is marked by a constellation of symptoms, there will be a constellation of biomarkers that, taken together, indicate someone's level of risk. "One of the big challenges with this field is that understanding the backgrounds of individuals also plays a role, in that your immune responsiveness or your organ responsiveness is all selectively individualized," he says.

Sepsis shares some of the complexities of cancer, Ayala says. Cancer used to be thought of as one disease; now "we understand that cancer is a constellation of diseases. We are beginning to wrap our heads around that in sepsis," he says. "Sepsis of a neonate may not be sepsis of an older person, may not be sepsis of a young person in between. … Even as we understand it, as we personalize it, then maybe we can understand our models better and put them into better context."

That's why he believes, as with cancer, personalized medicine is poised to play a huge role in his field. "I would be happy if anything we did could help even a few people. That would be nice," Ayala says. "As excited as I am about some of the proteins and gene targets we're looking at, we still need to know what patient will best respond to this agent. … Right now, those tools are a little beyond us." More specific patient recruitment for clinical trials could be one way to move drugs forward. Nivolumab, for instance, may only help septic patients who express high levels of the PD-1 target, Ayala says; but until there's a rapid genetic test to identify those individuals, researchers can't be sure why the drug did or didn't work.

Opal agrees. "The current thinking is that if you pick the patient population just right, then you could show these things could work," he says. "The idea that every septic patient is going to behave the same as the next is pretty much passé."

One thing that is the same across all patients is sepsis happens fast—in hours, even minutes. Patient survival depends on clinicians figuring out why they're sick and just as quickly administering the appropriate therapy. Tools for rapid, precise molecular phenotyping and diagnostics, to predict the patient's immune response, identify the infectious agent or injured organ, and choose the correct treatment, are in development, and Opal believes they'll be in clinical use within the decade.

"This is a great unmet medical need," he says. "We, as sepsis researchers and ICU docs, are actually adding to the [antibiotic] resistance problem. We are encouraging em-

"The idea that every septic patient is going to behave the same as the next is pretty much passé."

piric antibiotics because we know it saves people's lives." Getting a culture report in an hour, not a day, could take the guesswork out of antibiotic selection, and give the patient a better chance.

BE ALARMED

Absent a cure, or diagnostics, or personalized medicine, prompt identification and treatment are the best hope for sepsis patients. Levy cofounded the Surviving Sepsis Campaign, an international effort to raise awareness, improve clinical care, and reduce sepsis deaths, in 2002. They called for routine screening of all patients, published guidelines for sepsis management, and developed treatment bundles—essentially, checklists of evidence-based practices that were designed to simplify care of a complex and fast-moving condition. A study published in the *New England Journal of Medicine* in June, of which Levy was senior author, found that for every hour it took clinicians to complete the first treatment bundle, the risk of death went up 4 percent.

"The most important thing is the initial management of the septic patient. Ensuring they get the appropriate testing and antibiotics and fluids earlier is the best thing that we can do to improve their risks and mortality," says Nathan Hudepohl, MD, MPH, the director of Quality and Patient Safety for the University Emergency Medicine Foundation. He credits improvements in sepsis diagnosis and treatment in the Rhode Island Hospital emergency department, where he practices, to education; a new series of best practice alerts (BPAs), implemented last year, that pop up in the electronic medical record; and workflow changes, including a physician stationed in public triage, who can identify at-risk patients while they're still in the waiting room. "That has had an impact on how rapidly we assess and treat patients with sepsis," Hudepohl says.

The system is far from perfect. Every patient who arrives at the emergency department is checked for abnormal vital signs and, if they meet two or more criteria, they're flagged as being at risk for sepsis. The provider then must complete the first treatment bundle within three hours: order blood cultures, administer fluids and antibiotics, and measure lactate level, which indicates whether tissues are getting enough oxygen. (If there are no signs of improvement, the BPA prompts clinicians to start the six-hour septic shock bundle.) But, Hudepohl notes, "there are other possibilities for why this person is dizzy or why their blood pressure is low. Sometimes it's hard to parse out whether it's due to a systemic infection or something else."

Amid the din of beeps and phones and chatter, Hudepohl, an assistant professor of emergency medicine, settles in at a nursing station and pulls up the current emergency department patient roster. One patient has been flagged for showing some signs of sepsis. "They probably have unstable vital signs that may be related to their trauma, like their blood pressure was a little bit low when they came in, and they probably have an elevated respiratory rate because they're in pain," he says. Regardless, clinicians initiated the three-hour bundle. "At this point, it's the best screening that we have."

The BPAs, which are used throughout the hospital, are another work in progress. The protocol, which Hudepohl helped develop with Levy and others, prompts providers to consider ordering more tests or treatment depending on a patient's vitals. "The problem is, sometimes the alerts fire too frequently and providers get a little bit overwhelmed, or just flat out ignore them," Hudepohl says. "We're trying to figure out how to refine some of them so they don't pop up so excessively."

It's a classic case of the boy who cried wolf, Levy says. "Caregivers are so busy. They want electronic alerts, because it's a way of reminding them, hey, pay attention to Mrs. Jones. On the other hand, if there's this constant voice that goes off, then you just stop listening." But more than three-quarters of sepsis patients in the US are identified in emergency departments. "You want to identify every patient with sepsis. But if the alerts trigger on too many people, you don't take the alarm seriously anymore," Levy says.

And that's concerning, because despite a drop in mortality of around 25 percent as compliance with the bundles has gone up, sepsis still kills more than one in five patients diagnosed with it. It's also the most expensive inpatient ticket item in the nation, costing $24 billion annually. With an eye on spiraling health care costs and an aging populace, in 2015 the Center for Medicare and Medicaid Services announced new accountability measures that codify the Surviving Sepsis Campaign screening and treatment protocols into federal law. While the regulations are well received in some corners, other physicians chafe. Levy, who helped write them, is well aware of the criticism.

"The era of performance measures and public reporting

is really unsettling for a lot of physicians. And there are problems with it; I don't in any way mean to imply that it's a perfect system. But this is another case of not letting perfect be the enemy of the good," Levy says. If you administer antibiotics and fluids to a patient who turns out not to be septic, he says, you're unlikely to harm them. As for antibiotic resistance, yes, clinicians should be concerned—but early, appropriate antibiotics and antibiotic stewardship can go hand in hand. "If you have any question, just give the antibiotics," he says. "But as soon as you give that first dose, you should start asking yourself, do they need another dose?"

Some critics argue that it can't be proved that regulations have improved survival. Levy counters that because the standard of care has changed, there is no longer a good basis for comparison. "People identify septic patients much earlier. People get antibiotics more quickly in hospitals" than they did before the Surviving Sepsis Campaign, he says. "It would be impossible to do a randomized controlled trial now, because everybody agrees: you have to identify these folks early. You have to measure lactate. You have to give them antibiotics quickly. So what are you going to test? Ignoring them?"

What the criticism boils down to, Levy believes, is this: some doctors think regulations impede their clinical judgment. But "we are not at the point where we can truly tailor therapy," he says. "It's true, one size does not fit all. There is some validity to that. However, we are here because docs are too busy. We often forget to do the right thing. We sometimes even forget to wash our hands. And so reminders and regulations and holding physicians' feet to the fire is a good idea."

Tracy Madsen, MD RES'12 F'14 ScM'14, an assistant professor of emergency medicine, has always worked under the Surviving Sepsis Campaign guidelines, which were first published in 2004 and have been revised three times. "The guidelines have been appropriately changed over the years to match what the data are saying," Madsen says. The BPAs haven't reduced her to an automaton—she still exercises her clinical judgment. But they raise a red flag, and in a chaotic emergency department, that's a good thing. "We know that septic patients need fluid, hydration, they need antibiotics, they need blood cultures. We also know that, in general, the faster these things happen for septic patients, the better. That's evidence based," she says. "I'm happy to do whatever is best for the patient."

Critics argue there's no proof that regulations have improved survival. But the standard of care has changed.

AMONG THE LIVING

As a survivor of sepsis, Vicky Morrone's outlook is sunny. "I'm just so happy to wake up every day," she says. Kids love her prosthesis—she has to tell them, no, they don't actually want one. With a wry laugh, she points out that the recurring cyst on her right knee will never bother her again.

It's been a professional boon, too. When she was a nursing student she had a pediatric patient who also had lost a leg. "I was able to help the family so much: look, this doesn't have to negatively impact their lives," she says. Morrone appreciates her special rapport with patients who've been in the ICU. "It gives me an entirely different outlook," she says. "I sympathized but I didn't get it before. I get it now."

And when patients complain about the tests and rechecks and alerts, Morrone can speak with an authority that few clinicians can summon. "I don't think [some patients] understand how severe it can be," she says. "We're not coming in to check on them to bother them. We're coming in to check on them to make sure that nothing is changing, especially in a hospital setting. You're so acute that an hour could change everything."