LOCATING SEPSIS

MICHIGAN REDEFINES SEPSIS CARE AND SURVIVAL

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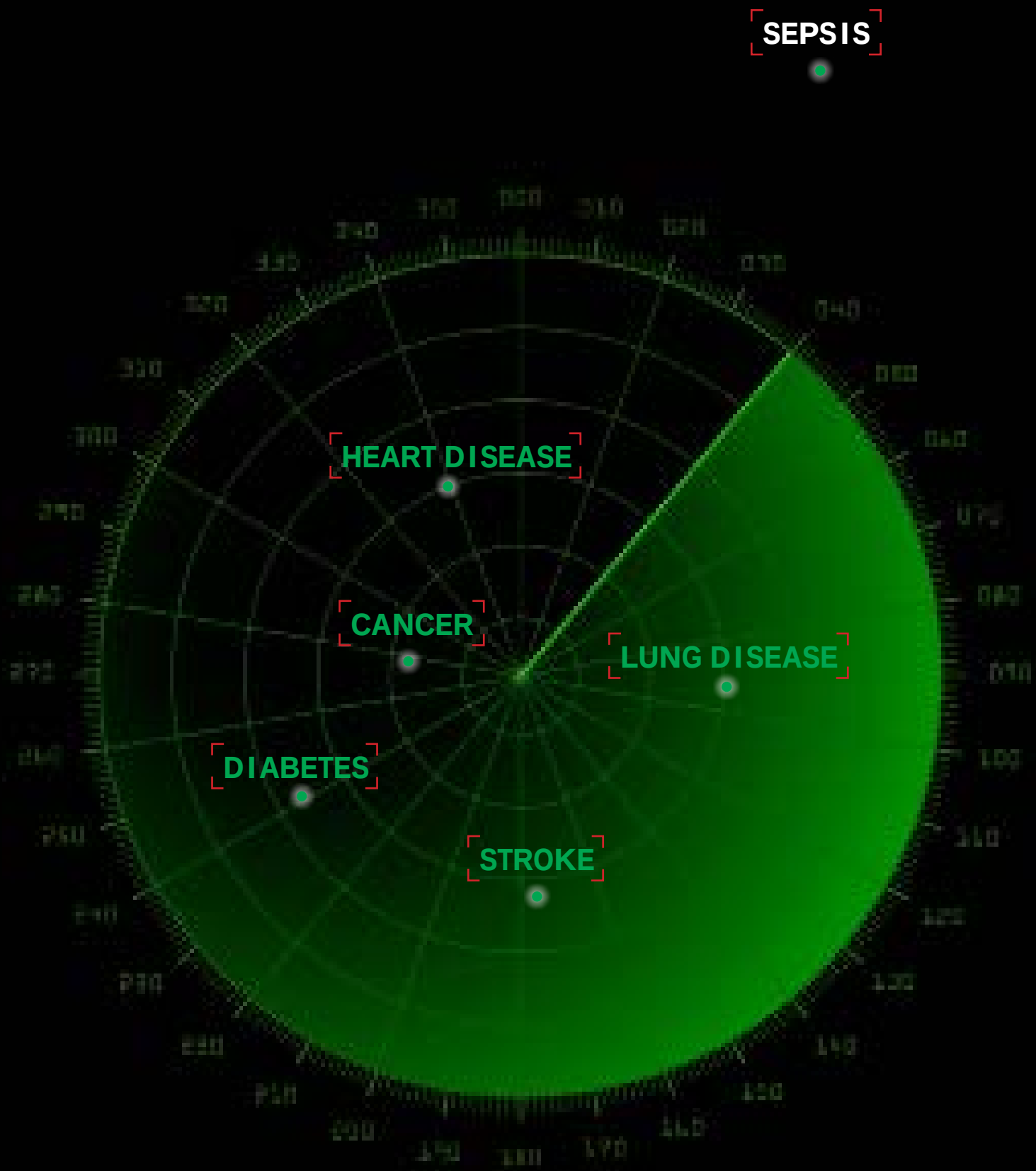
There's a medical condition that strikes a million Americans a year, killing a quarter of those it sickens. It saddles many survivors with cognitive disabilities and steals their independence — even their limbs. It is notoriously hard to treat. Yet this ubiquitous disease flies largely under the radar. Doctors can easily miss it, especially in its early stages. Public awareness is low, with no lapel ribbons or massive pledge walks. Fewer than half of all Americans have ever even heard of it.


SEPSIS
HEART DISEASE
CANCER
LUNG DISEASE
DIABETES
STROKE

That condition is sepsis, a dangerous immune response to infection or damaged tissue that can pose a greater risk than the infection itself. A kind of inflammatory overkill, sepsis can lead to a complex and deadly chain of events that causes multi-organ failure and death in victims of any age.

Sepsis has risen dramatically in recent years. As a hospital-discharge diagnosis, it jumped an alarming 57 percent between 2007 and 2011, according to a 2014 report by the Center for Healthcare Research & Transformation. That increase comes in part because hospitals are getting better at spotting and reporting the condition. But it's also an ironic mark of medical success because sepsis often picks off vulnerable survivors of stroke, cancer and heart disease — people who until recently might not have lived long enough to contract sepsis. Now, though, this out-of-control infection response is the No. 1 reason that Medicare and Medicaid patients are hospitalized. It kills more children than cancer does. Among hospital patients, it's involved in up to half of all deaths. University of Michigan sepsis researcher Theodore "Jack" Iwashyna, M.D., Ph.D., associate professor of internal medicine, puts it simply: "Sepsis is an important part of the story of how people die now."

Iwashyna — also a member of the U-M Institute for Healthcare Policy and Innovation, or IHPI — and his colleagues are working to improve sepsis treatment and research at the bedside, in the lab and on the policy level, at diagnosis and after recovery. Their efforts are fostering collaboration and innovation across multiple specialties and disciplines at the U-M, including: emergency medicine, physical therapy, computer science, information technology and engineering. Together, these specialists are creating new sepsis-focused facilities and technologies, while establishing a new framework for understanding and treating sepsis.

A NEW CRITICAL CARE

It's a complex battle, to say the least. For all kinds of reasons, sepsis is a wily foe. Early recognition and treatment are crucial, yet there is no good lab test. There's no obvious way to spot a septic patient, who might be a tired-looking elderly man, a shivering middle-aged woman or a teenager with flu-like symptoms. There are countless ways to get sepsis: The offending bacteria enter through a surgical wound, an IV line, a birth canal, a trace of stool in the urine or bacterial pneumonia. There is no specific drug treatment, and the decades-long unsuccessful search for an effective sepsis drug has begun to seem almost quixotic. Septic patients need tailored antibiotics, yet not knowing which bug is involved often forces physicians to resort to the broad-spectrum type, which leads to resistance, side effects and immune compromise. There isn't even a very good way to monitor the patient to see if treatment is helping.

Though doctors have long viewed sepsis with resignation, offering supportive measures and hoping for the best, the last major clinical advance arrived with a landmark 2001 study that appeared in *The New England Journal of Medicine* and offered

THERE'S GREAT UNDERSTANDING OF SEPSIS AND WHAT TO DO ABOUT IT, AND WE'RE TRYING TO TO TRANSLATE IT INTO THE POLICY WORLD.

grounds for optimism that serve for the advancements of today. Nicknamed the Rivers Trial after its principal investigator, Emanuel Rivers, the study suggested that a fast, rigorous, algorithmic approach to care could reduce the sepsis death rate. Nothing had helped before, so the Rivers study caused a sensation. Follow-up studies found that "protocolized" therapy does help, even as work continues to identify a more effective protocol.

There's nothing glamorous about this approach. It consists of early diagnosis, then aggressive support with antibiotics, intravenous fluids and blood pressure agents while keeping a close watch on the patient's vital signs and blood tests. Still, rapid and sustained therapy is hard to deliver in a hospital ward or emergency department. It requires costly resources and a degree of vigilance more typical of an intensive-care unit.

At the center of much of Michigan's sepsis research is the Department of Emergency Medicine, which has tackled this problem by bringing the ICU into the ED. In February, a new nine-bed area within the department called the Joyce and Don Massey Family Foundation Emergency Critical Care Center, or EC3, began accepting septic and other critically ill patients. The first center of its kind in the nation, the EC3 will dedicate critical care-trained physicians and nurses

With five resuscitation/trauma bays and nine patient rooms, the Emergency Critical Care Center provides an ICU-level environment for patients' initial diagnoses and stabilization. Dedicated emergency physicians and nurses also provide protocolized sepsis care.

to protocolized sepsis care that may change the course of the illness and save lives. This "hyperacute" critical care unit will share common protocols with traditional units elsewhere in the hospital, easing a patient's transfer to such a unit if that becomes necessary. The EC3 will offer intensivists-in-training a chance to care for patients as soon as they come to medical attention, as well as bring far more patients into research studies.

"You don't have 24 hours of them brewing in their own illness before we enroll them — we can do it right when they come into the ED," says Kyle Gunnerson, M.D., associate professor in the departments of emergency medicine, anesthesiology and internal medicine, who helped spearhead the EC3.

The new unit is not just an ED innovation. Gunnerson says intensivists all over the hospital have collaborated to plan the EC3. "I have the medical directors from the medical ICU, the neuro ICU, the cardiac surgery ICU, the surgical ICU, the burn/trauma ICU [involved]," Gunnerson says. "They have all worked very well with the ED and my team on this project."

On a statewide scale, Marianne Udow-Phillips is working to call lawmakers' attention to the high prevalence of sepsis in Michigan hospitals. Udow-Phillips is director of the Center for Healthcare Research & Transformation, or CHRT, a nonprofit affiliate of the university. Last June, CHRT released a brief detailing a steep rise in rates of hospitalization for septicemia, a cause of severe sepsis, at both Michigan and nationwide hospitals. CHRT is encouraging Michigan's Department of Community Health to create a state-sponsored coalition of sepsis centers analogous to existing trauma centers.

"There's great understanding of sepsis and what to do about it, and we're trying to create that partnership to translate it into the policy world," says Udow-Phillips, a lecturer at the U-M School of Public Health and an IHPI member.

ENGINEERING NEW SOLUTIONS

Those kinds of efforts — from emergency care to policy — help set the stage for work at the University of Michigan Center for Integrative Research in Critical Care, or M-CIRCC. The center puts engineers, information scientists and basic scientists together with medical researchers and industry partners so they can collaborate to tackle critical illness and trauma. In its 2014 flagship initiative, the Sepsis Grand Challenge, M-CIRCC awarded grant money to six multidisciplinary teams to develop sepsis-related technolo-


Andy Odden


Colin Cooke


Kyle Gunnerson


Hallie Prescott

gies. The goal is to devise a "game-changer" solution to basic problems like early diagnostics and noninvasive monitoring.

One team, for instance, is developing an early detection gadget that will clip onto a finger and use signal-processing algorithms to analyze data from heart rate and blood pressure variability. These data ordinarily get filtered out when a monitor outputs a set of vital signs, but they contain valuable information that might tip caregivers off to early sepsis.

"It's just really awesome to see the fresh perspectives when you bring a biomedical engineer, an electrical engineer, a materials scientist, or a computer scientist into the mix," says Kevin Ward, M.D., M-CIRCC director and emergency medicine professor. "They start getting the ah-ha moments about how you can address [critical illness] from a technology standpoint."

Other winning Grand Challenge ideas include a device that analyzes endothelial cells in the bloodstream as a means of early detection, a device that uses ultrasound to gauge a patient's fluid status and a nanoparticle-based system to deliver the immune-boosting protein IL-15. Some of these may be piloted in the EC3, and Ward expects several to make an exit to industry in the near future.

Another challenge being undertaken by M-CIRCC involves creating algorithms to collect and sort through the hidden data within electronic vital signs and predict which hospitalized patients may be falling ill with sepsis. Created in partnership with IBM and the medical-technology company Airstrip, the technology is envisioned to be scalable to all hospital areas and even into the patient's home with the use of wearable sensors. Earlier detection before changes appear in vital signs should lead to earlier interventions and better outcomes as well as determine which patients are most at risk.

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LIFE AFTER SEPSIS

With the life-saving promise of EC3 and new devices, there could be more sepsis survivors than ever before. But what happens to sepsis patients who survive to hospital discharge? Do they go on with their lives as before? What Iwashyna has discovered has led him to, more or less, found the study of sepsis survivorship while completely overturning conventional wisdom, which held that most sepsis survivors return to their baseline level of health.

Not so, Iwashyna says. These patients often wind up right back in the hospital, with nearly one in five returning within 30 days. Moreover, they're not the people they were before. In a large-scale study of sepsis survivors 65 and older, Iwashyna found that even those with no trouble performing activities of daily living before they got sick lost, on average, one-and-a-half such activities afterward. Many developed cognitive impairments. Many lost their previous independence entirely.

"It's a new permanent deficit. They're not just kind of foggy for a while," Iwashyna says.

The deficits, Iwashyna found, appear to affect the brain and muscles most, so they may be amenable to cognitive rehab and physical therapy.

Part of the solution is preventing deterioration in the first place. Getting sick patients out of bed and walking is doable, and it's becoming more common in intensive-care units. But septic patients in regular hospital wards aren't necessarily asked to exercise. Andy Odden, M.D. (Residency 2010), is a U-M assistant professor of internal medicine and hospitalist studying the effects of mobilization on septic patients being treated on hospital wards — the first known researcher to do so. In a pilot study, these patients are receiving twice-daily physical therapy


Jack Iwashyna


Kevin Ward


Marianne Udow-Phillips


John Younger


Peter Ward

as a proactive intervention rather than the usual once-daily session prescribed after the patient develops a disability.

Guiding the physicians who care for sepsis survivors after discharge is the research interest of Hallie Prescott, M.D. (Fellowship 2014), internal medicine clinical lecturer. These doctors may have just a few minutes in the clinic to make sense of a patient's inches-thick chart, and they can miss opportunities to prevent future health problems.

Prescott has faced that daunting task many times herself. So she's developing a computing tool that will condense the masses of clinical data generated by a sepsis hospitalization into a brief report, one that should help doctors improve care for survivors. By estimating each patient's risk for hospitalization for recurrent infection — as well as for other serious conditions like heart failure, renal failure and aspiration pneumonitis — the report should show doctors where to direct their efforts to ward off further health disasters for these patients.

Modest steps, perhaps.

"If somebody wants to invent a magic bullet [to treat sepsis], that'd be awesome," says Iwashyna, who co-authored a review with Odden on getting septic patients mobilized. "I'll be the first in line to sign up for it. But until then, maybe we can just do the things we already know how to do, but don't do well."

Easier said than done. In an Oct. 8 editorial in *JAMA*, Iwashyna and Colin Cooke, M.D., assistant professor of internal medicine and IHPI member, called upon the Centers for Medicare & Medicaid Services to develop quality mandates for sepsis — just as it has for other serious illnesses like pneumonia. They warned that current methods of reimbursement may create a perverse incentive for hospitals to underreport sepsis and suggested better ways. Additionally, they advocated for regional-scale experimentation and called for a rapid response to new evidence.

A NEW METAPHOR

Experts at the U-M are beginning to discuss a paradigm shift in sepsis research, one that echoes the way we deal with cancer. Cancer isn't a monolithic entity. It's a collection of diseases, each of which we treat differently despite their similarities at the molecular level. Even subdividing one type of cancer — say, childhood leukemia — and treating each type differently can bring transformative treatment successes.

Similarly, intensivists need to taxonomize sepsis, argues John Younger, M.D., a professor of emergency medicine whose lab studies how bacteria adhere to medical devices.

"The war on cancer is not being won by attacking the entire illness as a single entity," Younger says. "What if the way we approach sepsis should be a lot like how we've made such headway in cancer? Divide it up into a lot of more specific types of diseases, say by location, duration, causative microorganisms or evidence of spread, and then start targeting it as a large collection of related illnesses, knocking down one at a time."

In that way, Younger argues, by finding treatments that work for small subsets of the illness, you might start meaningfully chipping away at the problem. The trick will be in establishing the best way to 'stage' sepsis as is currently done with cancer and getting the medical community acquainted with treatments that work fantastically in small groups of patients rather than in every patient that we treat.

Clinical trials in sepsis should use narrower selection criteria, says Peter Ward (M.D. 1960, Residency 1963), the Godfrey D. Stobbe Professor of Pathology. Ward has researched the molecular mechanisms of sepsis for decades, making the seminal discovery in the 1990s that the sepsis response involves the immune system's complement cascade. It's quicker and cheaper, he says, to study a small group of patients with pneumonia-related sepsis than a big group of undifferentiated sepsis patients. By reducing the near-prohibitive costs of clinical drug trials, such slim studies might find a sepsis-specific drug at last.

Sepsis, like cancer, is legion. Perhaps it's only natural that our approach to it is constantly changing, our very definitions reshuffling. Gunnerson, for one, expects to see surprises as he studies and treats patients in the EC3.

"The more we learn," says Gunnerson, "the more we'll find out that maybe we weren't even asking the right questions 10 years ago." [M]