Sarah Alger: Welcome to Proto, a podcast that explores the frontiers of medicine. I'm Sarah Alger.

Dr. Michael Phi...: And I'm Dr. Michael Philbin. Sepsis is the deadliest disease that most people have never heard of. It kills as many as 300,000 Americans every year, and the condition is all the more dangerous because it flies under the radar of even trained medical staff.

Sarah Alger: We'll look into new efforts to spot and treat sepsis, including one approach that uses cutting edge gene sequencing technologies.

Dr. Kai Sohn: We are trying to identify the offender by the traces he's leaving at the crime scene.

Dr. Michael Phi...: And we'll hear about many other tools that hospitals are trying out to head off this major killer.

Sarah Alger: A battle plan for sepsis, coming up on this episode of the Proto Podcast, brought to you by Massachusetts General Hospital. Descriptions of sepsis date back to the Ancient Egyptians, and the first recorded use of the term belongs to Homer, who used it in The Iliad to describe the wounds of the warrior Hector. To the Greeks, sepsis was the process of rotting or decay. And for most of recorded history, that is how healers thought about sepsis.

It's a process that began with an injury, progressed through a serious often pungent infection, and ended in a painful death. It wasn't until the 1960s with a more fine-tuned understanding of microbiology that the real story was revealed. Sepsis is now understood as a life-threatening condition that arises when the body's response to an infection, that is to say the immune system, injures its own tissues and organs. Yet, despite this better understanding, deaths from sepsis are still desperately widespread.

Here to talk about the problem is Dr. Michael Philbin. He is a physician in the MGH Department of Emergency Medicine and a leader of the hospital's sepsis initiatives, Dr. Philbin, welcome.

Dr. Michael Phi...: Thank you for having me.

Sarah Alger: Fewer than half of Americans have even heard of sepsis, but the disease is the leading cause of death in hospitals. It kills more people every year than AIDS, breast cancer, and prostate cancer combined. How does a killer like this fly under the radar?

Dr. Michael Phi...: I think sepsis flies under the radar because it's elusive. It can be elusive even to healthcare professionals. It's often difficult to detect initially or ever establish that a patient definitely had it in the end. I think for that reason, it's difficult to educate the public about and compared to easier to grasp medical emergencies, such as trauma, heart attack, or stroke.

Sarah Alger: Can you explain exactly what sepsis is?

Dr. Michael Phi...: Well, sepsis is a syndrome. I.e., it's not really a single identifiable process, and there are two key ingredients to sepsis. The first is infection, so any kind of infection, pneumonia, urinary tract infection, skin infection, or even a virus. The second ingredient is an abnormal or over-exaggerated physiologic response to that infection that leads to organ dysfunction, such as low blood pressure, kidney dysfunction, brain dysfunction or altered mental status, and, unfortunately, often death.

Sarah Alger: I gather that there's still no gold standard for diagnosing sepsis. There are a couple of competing systems with names like SIRS, SOFA, and qSOFA. Can you explain why?

Dr. Michael Phi...: Yeah. Well, this alphabet soup of risk and illness severity scores, they're intended to help us classify patients into risk groups. They don't really define sepsis. They're simply a collection of vital signs or lab results that either point us to the possibility of infection or that there are signs of organ dysfunction. Again, the two ingredients of sepsis. Fact is though that none of these crude tools even comes close to being perfect in defining the condition of sepsis.

Sarah Alger: Are there any biomarkers that might work as a test?

Dr. Michael Phi...: Well, the search for a reliable biomarker or set of biomarkers to detect sepsis is really like the search for the holy grail. There is not yet been a promising kind of silver bullet diagnostic for sepsis and really actually nothing even close. The search for biomarkers in sepsis aims to find a common link between the inciting infection and the subsequent pathologic immune response to sepsis or that we call sepsis. This is really the rub.

Because just as sepsis can result from any number of different bacteria in various sites in the body, cause organ dysfunction to any or all organs, the body's response to infection or the host immune response likely also manifests in many different ways. There may be a way though to characterize several classes of immune response through biomarkers that would allow us to target specific therapies depending on the type of immune response present in any particular patient.

Sarah Alger: Oh boy! Okay. Artificial intelligence is being applied to a lot of problems in medicine now, and I gather it is also being applied to the problem with sepsis.

Dr. Michael Phi...: Well, certainly. AI has rapidly entered the realm of clinical medicine with the advent of the electronic health record and the oodles of data that we have available to put into machine learning models to help us predict clinical outcomes, such as sepsis. In MGH, we're working with data scientists at MIT to develop machine learning models that might help us detect sepsis earlier, or maybe to recommend when to start an antibiotic, to give additional fluids, or to start vasopressor medications.

Yet, there's a lot of technical and administrative hurdles to introducing these predictive models to the bedside into clinical practice. In the end, we just don't really know if they're going to make a difference in outcomes, but I suspect they will if they're thoughtfully implemented.

Sarah Alger: It sounds like other current tests have been problematic. Teams at Duke are looking to do a sepsis alarm system based on AI. But in an early version, they were getting as many as a hundred false positives a day on a single patient. And at the other end of the spectrum, an AI system at the University of Pennsylvania wasn't really identifying any new candidates. How do you tune an AI so that it's actually helpful?

Dr. Michael Phi...: That's the key. I think the value of AI, as I alluded to, is to assist the clinician in making their own decisions. I think one way to do this is to present them with a risk assessment say in the form of a score that tells them, "Hey, based off of millions of patients in my database, your patient with their constellation of symptoms, vital signs, labs, et cetera, has a say 75% chance of having sepsis that will need ICU level care, or your patient has a 90% chance of benefiting from an additional liter of IV fluid or vasopressor medication."

The machine will never be perfect, but it can help the clinician stay in the right lane by making sure they're not veering off in the wrong direction, because clinicians do have a lot of things competing for their attention.

Sarah Alger: To get back to interventions for a moment, you've talked about some of the treatments that you typically use for sepsis. Part of the issue was trying to knock out the infection. But in most cases, you don't know what's causing the infection. How do you decide on a treatment when you're not sure what's going to work?

Dr. Michael Phi...: Well, we only have so many tools at our disposal. When a patient is really sick and we're thinking it could be an infection, we grab for the big gun antibiotics to cover everything, so to speak, until we can be certain about exactly what's causing the infection. And still, we often never know what caused it. We resuscitate to maintain perfusion to vital organs. We take pictures, chest x-rays, CT scans to look for hidden sources of infection if the patient is not getting better with our basic interventions.

Sarah Alger: Are there dangerous to over-treating a suspected sepsis case?

Dr. Michael Phi...: Well, there might not be a danger in the moment of over-treating a particular patient, at least when it comes to the big gun antibiotics. However, treating every patient with a possible infection with a big gun antibiotic breeds antibiotic resistance resulting in harm for others down the road. And unnecessary antibiotics can breed an invasive GI pathogen called clostridium difficile in patients you are treating. So whether and when to give the big gun antibiotic is often a gray zone in clinical practice.

Since, as you say, we're often flying in the dark, the question is who to treat immediately and whom it's safe to wait for more definitive diagnostics. There are general guidelines. Yet a disease that can present in vague and elusive ways, the decision can be a difficult one.

Sarah Alger: Thank you so much, Dr. Philbin.

Dr. Michael Phi...: Thank you.

Sarah Alger: Can genetic sequencing technologies help in this fight? We'll speak with a researcher behind a new multicenter trial in Europe trying to answer that question.

Dr. Michael Phi...: Coming up next on the Proto Podcast, brought to you by Massachusetts General Hospital.

Sarah Alger: Sepsis requires a quick response, but physicians can't be 100% certain about the best treatment without first knowing what caused the infection. One item on a sepsis wishlist would be a kind of a test that could tell you quickly and effectively just which microorganisms have set the immune system in motion. A new technology may fit the bill. Next generation genetic sequencing is a way to sift through a sample, such as a blood sample from a sepsis patient, and identify all the organisms that are present there. It does this by looking at their genetic signatures.

A champion of this approach is Dr. Kai Sohn, a biologist who leads the functional genomics group at the Fraunhofer IGB, the largest organization for applied research in Europe. In 2016, Dr. Sohn and his colleagues published an article in genome medicine about the logistics of using next generation sequencing to identify bloodstream infections. Now, Dr. Sohn is involved in a multicenter study, Next GeneSiS, which we'll look at the clinical realities of using such a test.

Proto's editor Jason Anthony spoke to Dr. Sohn about the challenges his work hopes to address

Dr. Kai Sohn: From our studies and others, we know that more than half of sepsis patients are treated not in the most appropriate manner, as the exact pathogenic is not known. The sooner you know the infectious pathogen, the sooner you can clear the tricker. Knowing the exact bacterial species will provide the best chance to intervene with the most adequate antimicrobial.

Jason Anthony: With the current technology, how do physicians decide what pathogens are present in a case of sepsis?

Dr. Kai Sohn: The standard of care is a blood culture, taking a blood work from the patient and culture it. But in most cases, this blood culture will remain negative. Sensitivity is clearly limited and leaving the physician in a situation not knowing how to treat adequately.

Jason Anthony: How long does a blood culture take when a physician does this process?

Dr. Kai Sohn: This is not an effective process. That is also one of the basic motivation of doing an alternative test. Normally if at all blood culture is positive, it takes two to five days.

Jason Anthony: And by that point, the patient I would imagine is in some jeopardy of having their condition worsened from the sepsis.

Dr. Kai Sohn: Yes, definitely.

Jason Anthony: You are working on a new type of test, which uses something called next generation sequencing. These tests look at all of the genetic material in a sample. That's not just human DNA, but also the DNA of anything else that might be in the blood. Is that right? Whether it's a fungus or bacteria or a virus.

Dr. Kai Sohn: That's exactly how the technology works. You take the DNA from a given sample. And with next generation sequencing, which is an open and unbiased technology, everything is getting sequenced. And afterwards, you can assign the DNA sequencing to the respective species, what is coming from the host and what is coming from bacteria or fungi or viruses or parasites.

Jason Anthony: How would a next generation sequencing test help identify what's happening in the case of sepsis?

Dr. Kai Sohn: It's like a forensic diagnostic test. We are trying to identify the offender by the traces he's leaving at the crime scene. If we take the pathogen of the offender, this pathogen also releases cell-free DNA as a trace in the blood plasma. We take this DNA out of the plasma. We do the next generation sequence. And afterwards, we identify those fragments, which can be assigned to a specific pathogen. That's how we identify the pathogens. The advantage of that approach is that this kind of trace or diagnostics is much more sensitive than classical approaches.

Jason Anthony: I understand that you're exploring the use of these tests in a multicenter trial. Can you tell us a little about that?

Dr. Kai Sohn: Yes. It's called Next GeneSiS. We are going for about 500 patients. It will allow us to figure out how robust is the task in different settings, what is the performance of the task if the primary infection is differing, for example, from the pneumonia or genital infections or abdominal infections. These are really important benchmarks, and we can learn what it needs to also implement such a test into the clinical routine.

Jason Anthony: You're using next generation sequencing tests during these multicenter trials to determine what the infectious agent is, which means that you're using these tests after the diagnosis of sepsis has already occurred. If these tests prove robust and prove reliable, is there any possibility that you could use a next generation sequencing test to diagnose sepsis the first place?

Dr. Kai Sohn: That would be great and I hope that in the future that will be the case. Because if we pick out those patients which will have a higher probability to develop sepsis and we will get these patients earlier for appropriate antibiosis, we will prevent these patients due to go to the intensive care unit.

Jason Anthony: Dr. Sohn, thank you so much for being with us today.

Dr. Kai Sohn: Thank you for having me.

Sarah Alger: Dr. Sohn is a biologist who leads the functional genomics group at the Fraunhofer IGB. He spoke with Proto editor, Jason Anthony. My co-host again is Dr. Michael Philbin, a physician in the MGH Department of Emergency Medicine. He is a leader of the hospital's sepsis initiatives. Dr. Philbin, is anyone pursuing next generation sequencing here in the US?

Dr. Michael Phi...: There's been a race to find a genetic-based diagnostic for rapid pathogen detection that's useful in the clinical setting, and it's been done. I think the major hurdle is incorporating this technology into a diagnostic platform that could be practically used in hospitals. Like all things in medicine, these things take time. There is a diagnostic platform developed locally by a company called T2 Biosystems that rapidly detects the five most common bloodborne pathogens that was just FDA approved.

And recent large studies showed that it's quite reliable in identifying those five pathogens compared to the traditional blood cultures.

Sarah Alger: But are there limits to a test like this? I gather that not all sepsis patients have bacteria in the bloodstream. Would that limit the effectiveness of a next generation sequencing approach?

Dr. Michael Phi...: You're correct, that less than half of patients that we call sepsis end up growing bacteria in their blood. So yes, this test cannot entirely rule out sepsis, and we'll still need to treat the sick and possibly infected patient with broad spectrum antibiotics, regardless. However, it's really good to know if your patient has bacteria in their bloodstream and what type of bacteria, as Dr. Sohn was saying, so we can target our own therapies. And in reality, this test will be much more sensitive than the traditional blood cultures.

Sarah Alger: What other promising programs are there for detection or treatment?

Dr. Michael Phi...: Well, the approach to sepsis will always be multimodal, starting with education, good clinical care, and quality systems in place that provide feedback to clinicians on their performance. However, from a scientific standpoint, all the things we've talked about lend to the concept of sepsis phenotyping or classifying sepsis by clinical types or immune response type or by inciting pathogen type. Different sepsis phenotypes likely respond best to different types of therapies or personalized therapies.

Future clinical trials in sepsis will be based on these phenotypes with randomization to specific therapies based on underlying patient phenotype. This is the basis of precision medicine, which is widespread in cancer therapies, and it's on the horizon for sepsis.

Sarah Alger: Last July, the US government published a resource about sepsis treatment and how various hospitals fared in combating it. And shockingly, the national average for early and appropriate treatment for sepsis was at about 50%. What does it take to move those numbers higher?

Dr. Michael Phi...: Well, first off, these government measures are controversial. The requirements that they lay out for treatment are very specific. And as I said, sepsis is a disease with many faces, and one specific treatment strategy is maybe not the best for everyone with sepsis. And for a sepsis case to pass the government standards, there are many different actions that are required. And if you fail just one little piece of the measure, you fail the whole thing.

Failing by these government standards does not necessarily mean bad care, and the statistics that you quote are difficult to interpret. However, these standards are meant to keep everyone in the right lane, so to speak, to alert hospitals or individual clinicians that their care might be outside of the norm.

So moving the numbers higher, education, quality initiatives, like I said, with performance feedback, electronic health record tools to aid an early detection, decision support tools based on machine learning, big data analytics, novel biomarkers, early pathogen detection technologies. Again, no single silver bullet. Sorry. No easy answer.

Sarah Alger: Now, if all of these silver bullets get deployed, how many lives could be saved?

Dr. Michael Phi...: Well, if you do the math, 300,000 cases annually, about 25% mortality rate, that's about 75,000 deaths per year. I think reducing mortality to 15% maybe possible, which translates to 30,000 lives saved annually. But it's really not all about just the lives saved, but the quality of life. Sepsis leads to long-term disability, kidney problems, cognitive issues. In the end, sepsis is a disease that's well worth fighting.

Sarah Alger: Dr. Philbin, thank you again for joining us today.

Dr. Michael Phi...: Thank you.

Sarah Alger: Dr. Michael Philbin is a physician in the MGH Department of Emergency Medicine. And listeners, thank you for tuning in to the Proto Podcast.

Dr. Michael Phi...: Today's podcast was produced by Emily Silber, Bradley Klein, and Jason Anthony.

Sarah Alger: Thanks also to our technical directors Adam Keller and Chelsea Andes. Subscribe to the Proto Podcast on iTunes and Stitcher and follow us on Facebook, Twitter, and Instagram. See you next time.