DEREK ANGUS: I'm going to do my best to try to set up the second half by touching on a number of clinical issues relating to sepsis. And then setting up some residual questions that hopefully will be logical for Bill to come in and answer.

So what I'm going to do a little bit then is start out clinically and talk a little bit about what we think sepsis is, current definitions for sepsis, how we think we're treating sepsis, and then some of these challenges.

So what is sepsis? Well, people have been looking at this for a while. This is not a hipster from Lawrenceville. This is Hippocrates, who a long time ago was already thinking that he thought he knew what sepsis was. He thought it was the process by which flesh rots, swamps generate foul airs at night, and wounds faster. It is rank, disease-producing, and evil.

That wasn't PubMed, but it began the first of many papers that would be published in sepsis over the next 2,000 years, going from Galen all the way through to Fracastoro in the 1400s, who was really the first to hint conceptually at the beginnings of germ theory the fact that there would be minute bodies going from one person to another.

And then of course it was Pasteur, and Semmelweis, and Lister and others, that really helped establish the principles experimentally that underlay germ theory. And that was a pretty excellent working model for centuries, and centuries, and centuries. And it really led up to Fleming, a good-looking Scotsman coming out with penicillin in the early part of the 20th century.

And it was really going along fine until the wheels came off a little bit with the birth of intensive care. And through the '70s, and '80s, and the realization that if you took someone with these syndromes these bad infections, and you gave them the appropriate antibiotics, they sometimes still died despite effective eradication of the organisms.

And so then Roger Bone and others began to say, wait a minute. It's not so much just about the germ. It's also about the host. And people began to think about this notion that sepsis is less about just about trying to fight the bug, but the fight itself. And the things that the organism, the host does, in trying to have this complicated dance with the organism.

And he began to conceptualize this idea that sepsis is a host response to an infection that has somehow gone awry. And these last two words are probably the most irritating in the field of sepsis right now-- defining what is "gone awry." And that's going to permeate throughout the rest of the hour.

So he got a bunch of people together after some failed RCTs in the 1980s where he was trying to modulate the host's response with steroids. And he said, we should sit down and come up with some standard definitions, and that led to the 1991 first international consensus on sepsis.

It's now gone through three versions, as pictorialized in this cute cartoon that came out in *JAMA.* When the third version was published almost about a year ago to the day in *JAMA,* it was a series of three papers. And for the first time used data to underpin updated consensus definitions.

And the nice thing for everyone in this room is that the data overwhelmingly actually came from UPMC, and analysis of 1.3 million hospitalizations that went through over a couple of years through 13 of the UPMC hospitals. And armed with these data, a bunch of erudite, aging, elderly, predominantly male sepsis experts-- way too male, and way too white-- ended up deciding that what sepsis today is is life-threatening organ dysfunction caused by a dis-regulated host response to infection.

Now the infections are pretty simple and straightforward in many, many series. About half of the time it's pneumonia but it can also be intra-abdominal or UTI. It's important to remember sepsis is not septicemia. The finding of positive blood cultures is only present in a third of cases of severe sepsis, and that is consistently the case from epidemiologic study to epidemiologic study, to RCT to RCT.

And it's a mixture of all kinds of organisms. And many people would argue, for example, that even the syndrome that develops of multisystem organ failure complicating, for example, H1N1, in many people's mind is sepsis.

How do you operationalize it? Well, this is a subject of great debate. But the current consensus task force said we had to have some sort of standardized way of measuring both the infection, which is basically following ICAAC and ATS rules on how to define infection, plus new onset organ dysfunction, which they declared was two new points of the so-called SOFA score as shown here. And I'm not going to bore you with the details of each of these organ systems.

A subset of sepsis is septic shock. And lots of people think septic shock is low blood pressure, but people also think that it's some sort of profound cellular dysfunction. And in the end, they decided that to have septic shock you really had to have not only hypertension-- either overt hypertension, or blood pressure that has to have vasopressors even after a fluid challenge to maintain blood pressure-- plus an elevated lactate as a systemic marker of essentially cellular stress.

So how many people have sepsis? This is a paper that we wrote about 16 years ago now, which I used to put this slide up and say there are 750,000 people who get sepsis in the united states. And the bad news for all these old people is it's predominantly a disease of the elderly.

And I don't have a pointer here, but I've noticed that I've been moving quite sweetly into the upticking part of the blue curve. In fact, I see several of my colleagues here, who-- I just want to point out to all of us that none of us are no longer dying on that flat isotope. We're all beginning to increase our annual risk of sepsis.

In red is the number of cases, and you'll notice it flattens out to the right. Because sepsis becomes so prevalent that once you get to about 90% or 95%, if you didn't get it last year you'll almost certainly get it this year. And indeed, John Marshall used to quip-- what's the old name for sepsis? Natural causes.

Amber Bernardo from here did some very nice follow-up work to some of this original overall epidemiology work, showing that not only is sepsis very common, but it's particularly common in those who least need to get it-- in minority populations and in the poor. And indeed, when you look worldwide there are easily about 30 million cases per year. And about 80% of the cases are occurring far from modern intensive care, in low and middle-income countries.

And obviously it's associated with lots of mortality. Even in a high income country such as the United States, sepsis has now gotten to the point-- as we showed in the paper analyzing Kaiser data from about a year or so ago, that it's now the number one cause of hospital deaths in the United States.

And in Pennsylvania, thanks to Billy Davis who's in the audience, we can say looking at PHC4 data that at least from 2013 there were 163,000 cases in Pennsylvania, and almost 30,000 deaths. And notably, you'll see the same reflection. Very sick people get sepsis far from the modern ICUs of Presby. So for example, 40% of the cases in Pennsylvania were cared for in very small hospitals.

All right. So let's segue into-- this is a superficial skim across a number of issues. Let's move into treating sepsis. So the modern management of severe sepsis, of course, has to think about both the infection, and then the shock, and the organ dysfunction.

So for the infection, there's nothing like giving prompt antibiotics. And since they may present in shock you want to give some resuscitation fluids. Thereafter, you quite quickly move to really doing the institution prevention and monitoring of organ dysfunction with all sorts of organ support, mechanical ventilation, dialysis, and so forth.

All of this gets wrapped up into something called the Surviving Sepsis Campaign treatment guidelines, a bit like the AHA guidelines for CPR. AHA got a head start with CPR.

But Surviving Sepsis Campaign guidelines, which is very similar-- there's about 60 or 70 experts. There's extensive systematic reviews supported by Cochran and others that all gets graded. And they come out with what's up to about now 65 statements on the right way to care for a sepsis patient.

We're now about to have later this month the 2016 version, which is the fourth version. These guidelines have been a great resource for summarizing all of the current evidence. And in fact, they've been cited over 15,000 times the first three issues.

Notably though, there's very few "Grade A" recommendations. Now I could also give a talk to cardiologists, and point out that most of the AHA guidelines for CPR aren't based on Grade A recommendations, either. But it's sobering, that despite our ability to make 65 separate statements about how to care for a sepsis patient, very few of these statements are supported by at least two high-quality RCTs.

So we were involved in evaluating treatment bundles as advocated by the Surviving Sepsis Campaign, that essentially teach these hospitals and providers how to do a whole set of things-- to take care of the patient when they're in septic shock. Both in the first six hours and then over the first 24 to 48 hours.

And it's not a paper I'm particularly proud of. And the more it gets cited the worse I feel about it, because methodologically it's pretty woozy. But this basically is a sort of time series analysis of as hospitals around the world picked up these guidelines and started adopting them. Then from the month that they picked it up, how did their mortality change.

And as they picked up the guidelines they adopted them more and more over time. And as they adopted them more and more over time the mortality dropped. And so many advocates would say, these guidelines are fantastic. Increasing awareness about sepsis and promoting these guidelines will save lives.

And I'm not here to dispute that, in part because they'd be very upset with me. But it is notable, as I already mentioned, that the evidence under the guidelines, the actual individual interventions, often couldn't themselves be demonstrated to make a difference.

For example, early goal-directed therapy-- one of the most notable, done by Manny Rivers, a former fellow from here-- that itself it was probably a single center RCT, published in 2001 in the *New England Journal of Medicine.* That individual paper has about 7,000 citations. It was absolutely the shock heard around the world. Everyone jumped to do early goal-directed therapy.

We led the process study from here, but there were actually three studies all published in the *New England*-- one from here, one from Australia, and one from the UK. And as best as we can tell, early goal-directed therapy did squat. The pooled odds ratio was 1.01. Not inspiring as a pillar of treatment principle in the Surviving Sepsis Campaign.

And everything I've said about treatment had nothing to do with this notion about this host's response that's gone awry. Everything I've talked about is just about individual organ dysfunction and individual infection. What about getting to the heart of the problem? Trying to directly modulate the host's immune response during sepsis.

Well, it's not for lack of trying. We have been taking every single potentially deleterious pathway, developing a monoclonal antibody, trying to block it, commercializing it, and testing it in RCTs for 30 or 40 years. We've got well over 50 failed phase three trials, let alone all the failed phase two trials, and it's been an absolutely rocky, depressing road.

And so much so that *Nature Medicine* ran this little story a couple of years ago, where after highlighting the drotrecogin alfa trial-- this was the repeat of the Eli Lilly drug which had actually come onto the market. But then when they revalidated it, it didn't work. They took it off the market.

And on the right was a test of anti-TLR4, which came out in the same year as the Nobel Prize which was handed out in part for discovery of toll receptors. And Eritoran [INAUDIBLE] is a beautiful blocker of TLR4. You'll hear more about that pathway in Bill's talk. This thing, everyone thought should have worked. It, too, resulted in a humblingly negative RCT.

And so the commentary in *Nature* was "Trial failure prompts soul-searching for critical care specialists," and we need to overhaul our RCTs. Lots of people thought that this was a depressing comment. I do think it's inspiring that *Nature Medicine* did think that critical-care specialists had a soul. They just lost it.

All right. So let me move for the final few minutes to a segue to set up Bill. Why is this so difficult? Well, a couple of things.

First of all, it's very pernicious. This is an article from 2002 about someone who was completely well, turns up in the ED, looks quite benign, the ED docs miss the case, they send the case home, and he dies of septic shock at home. More recently, Rory Staunton is the most famous example-- the 12-year-old kid who had the same fate, that actually led to changes in the law in New York to start mandating that hospitals have efforts to screen for and treat sepsis.

The part of the reason why you get into this trouble in trying to diagnose it is the signs and symptoms clinically are not very discreet. If it was ideal, you would have a clinical marker that was never present in well people, and always present in sick people. And so you would have this very nice separation between normal and disease, and there would be a valley in the middle, a zone of rarity. No one would ever show up with an indeterminate value.

And so you would say, blood cultures. It's very hard to have partially positive blood cultures. They're either positive or they're not. Although, as we've already said, not everyone with sepsis has blood cultures. Intubation would be good cause it's hard to be partially intubated, so maybe intubation could be the same for respiratory failure.

But not everyone with sepsis has respiratory failure. And in fact, what we have in sepsis for all the potential measures of sepsis it gets very murky. So the so-called surface phenomenon, the clinical measures, have no zone of rarity in the middle.

There's no such thing as a dearth of people with a white count of 10 and a half. It's not like you either have a perfectly normal white count or a white count of 30. It's not like no one has a creatinine of two. There's lots of people in the border zone.

And indeed, sepsis is on two axes. Organ dysfunction and sepsis. Sorry, organ dysfunction and infection. So what we really want is this near bump with blue, blue water, and all the islands completely discrete from each other in-between. But instead, everything is completely amorphous so you have these smooshy border zones.

All right. So clinically-- clinical criteria are having a hard job parsing out clearly sepsis patients from clearly not. Let's go back to what's driving all of this. Remember we talked about this host response gone awry.

So the original studies began back in-- these studies published in from the '80s and '90s took healthy volunteers, so-called healthy volunteers. They were largely NIH critical care fellows, folks like predecessors to Mark. And there may have been some conflict of interest rules, because they apparently volunteered to have their attendings give them an IV bolus of endotoxin. And then they waited to see what happened.

And they couldn't wait until they got organ dysfunction, so you couldn't wait until they got sepsis. But you could wait until they really felt like shit. And when they felt like shit, what immediately happened was TNF shot up in about 20 minutes, then IL-6 came up a little bit later. And this began this notion of this cascade, of this cytokine-driven, innate immune response cascade in response to infection.

And that actually even drove the study designs for the therapies to try to fix sepsis, people forgetting that sepsis isn't a critical-care medicine fellow at the NIH who just got a bolus of IV endotoxin. And indeed, it was still from the NIH when Steve Calvano, who showed-- once we started to have the early days of microarray studies-- if you gave endotoxin to these same human volunteers thousands of genes came on. Just even in circulating white cells. In fact, precious little does more to the host than endotoxin. It makes you completely light up.

And indeed, when you think about it, we now know through really an explosion of understanding about the host and innate response to injury, is that there's actually all sorts of pathways with both negative and positive feedback loops, generating both of turning on an inflammatory response. And as fast as you're turning it on, you're also then turning on all sorts of things that try to dampen it down and go, whoa boy.

And the issue is in the midst of all of this mess, when is it a helpful response to gram-negative challenge? And when is it as a response that's gone awry? So when we look to pneumonia patients, not critical care fellows at the NIH, they didn't have that same cytokine expression.

By the time they arrived within one hour of arriving in the ED, they were already on the downswing of that initial inflammatory burst. Not on the upswing. That upswing is taking place at home when you feel like crap. By the time you come to hospital you're already in the decay or the tail.

And then it's also true that there's not that much of a difference between the people who are mounting a good response to pneumonia, versus people whose pneumonia is being complicated by organ dysfunction. And lots of people didn't have the decency to even have inflammation. There was lots of heterogeneity.

And so that led to folks like Richard Hotchkiss doing this cartoon in the*New England* when he said, I know what the solution is. There's just people on different courses. There's like old, immunosuppressed people who can't mount an immune response, versus young people who mount a very brisk one.

But that's a simplistic way of embracing heterogeneity. In fact, it's assuming that I just need to know the patient's age and I can tell you what's going on underneath the surface. I'll skip by that.

In fact, what's probably going on in everyone is a much more complex dance as very cutely alluded to by Medzhitov in this paper a couple of years ago in *Science.* It's notable that the host is a mouse and not a human. That's science for you.

But you can see here that there is a very complex interplay. The host shows up at the top, has a dance with the pathogen. The pathogen challenges the host which could be bad. The host tries to mount a response. In mounting the response, the host can have a variable ability to sustain collateral damage from its own response, as well as sustaining direct damage from the pathogen and so on. And you can imagine in any individual patient all of these things are in play.

Indeed, if you go back to that same set of seminal studies that led to the Nobel Prize for immunity about four years ago, the two classic studies for Jules Hoffman and Bruce Beutler. Jules Hoffman's lab discovered that if you didn't have the toll receptor, and you were a fruit fly, then you died of fungus. So not sensing the infection killed you.

Bruce Beutler noticed that if you didn't have TLR4 or you had an under expression of TLR-4, you were resistant to endotoxin. In other words, he was finding that you did well if you didn't sense the infection. So the two seminal studies were actually highlighting the yin and yang of knowing that you're infected.

And indeed, that plays out in things like this PNAS paper from a few years ago, still on TLR4, where well-conserved polymorphisms relate to evolutionary pressure from constant infections. If you live in a high malaria area, then you tend to be well-conserved for polymorphism to protect you against malaria, but increase your susceptibility to gram-negative septicemia. And the reverse is true for European descent.

So this all adds up to if you run this into say trials of Enbrel, which, for the medical residents here actually began in sepsis and didn't work, and now we made it into rheumatology, when you go and re-simulate those trials as Gilles Clermont from here did-- I won't explain all of this other than to say that across very plausible quartile variation in things we don't measure-- pathogen virulence, pathogen load, TNF responses, and not age, not simple things-- the number of people who are white helped by the therapy, the number of people who were black killed by the therapy changes dramatically, completely changing the results of the RCTs.

So in other words, you can see two sepsis patients that look similar, and they are completely different under the surface. This has led to all sorts of work trying to do more complex genomic signatures, such as this very nice work from Julian Knight's group that was published last year, showing that there were complex, essentially molecular signatures expressed by circulating white cells.

That when they simply looked at agreement and clustered on them they clustered into these two groups. And then when they look at what happened subsequently there were big differences in prognosis. And they said, see, there's like phenotype one versus phenotype two, and they were clinically indistinguishable.

The problem with this, as we outlined in a nice paper from Hailey Prescott a few months ago, is that this is trying to sort by prognostic phenotype, which still doesn't get us what we want. What we want is predictive phenotype for drug response.

I don't want to know the genes that turn on that will almost certainly kill the person regardless of what I do. I want to know the pathway that tells me this is the pathway that would drive the person to get drug X versus drug B.

OK. So I'm going to come to a sort of interim conclusion to then hand over to Bill. So what I've tried to say to you here is that-- hopefully you agree. Sepsis is a life-threatening condition. I think the consensus panel got that right. And we think it's when the body's response to an infection injures its own organs. It leads to shock, multiple organ failure and death, especially if not recognized early and treated promptly, which has driven a lot of these national and regional initiatives for increased awareness.

It's the primary cause of death from infection despite all the benefits of this later half of the last century, including vaccines, antibiotics, intensive care. And millions of people die of sepsis every year worldwide-- number one cause of death in US hospitals. Number one cause of disability, adjusted life, years lost worldwide.

Sepsis is not explained by germ theory. Hopefully I made that clear. Rather, it's a complicated dance between the host and the germ. The current definitions operate in a space where there's no gold standard. We have these overlapping clinical criteria that are somewhat difficult, and so we have engaged in these early steps to use subclinical phenotypes.

Current treatment. We often struggle to find definitive RCTs, but attention to basics is associated with improved outcome. And novel treatment will rely on further progress towards identifying injurious pathways, and progress towards selecting the right patients.