[APPLAUSE]

DR. DOMINIC DEKERATRY: Thank you. Well, good afternoon. It's nice to be back with you guys. I gave a Grand Rounds presentation a couple months ago on asthma. And I'm really happy to be able to speak about sepsis and septic shock. It's a topic that's very near and dear to my heart as an intensivist. And there's also a lot of hot topics regarding sepsis in our literature.

Just as a double check, can the folks in Georgetown and South Austin hear me OK? Are we getting a thumbs up over there? You're getting feedback, you said? OK. Let's see if we can increase it just a little bit. I'll try to keep my chin down.

All right. So the objectives for today's talk-- let me get our little advancing slide. Here we go. Thank you. You guys OK? To review the definitions of systemic inflammatory response syndrome and the spectrum of sepsis. This is a very sort of excited discussion that we have all the time with colleagues about what defines sepsis. And I think that sometimes folks tend to overstress the diagnosis or basically think that it's something that it's not.

It's a very simple term. There are some simple definitions. We're going to talk about those today. We'll certainly talk about the epidemiology of sepsis. And I want to review some key therapeutic elements pertaining to the resuscitation of patients with sepsis as they present to the emergency department, predominantly.

But if you all could walk away from this talk with one major pearl, and that is to really recognize the importance of utilizing a structured approach to managing these patients. Bundled guidelines are now pervasive in the literature pertaining to sepsis management. And these guidelines are evidence-based.

They are not intended to replace clinical judgment, but rather the contrary. They allow a team approach and allow constant feedback with the ability to reanalyze your data, reanalyze the patient's situation, but not just with one person, one provider involved, but the whole team involved. So there's lots of advantages.

So I want to give you a clinical vignette. I've got two. And one of them I think is really apparent. everybody in the rooms should recognize what's going on. The other one is a little more subtle. And it will sort of serve as a segue into these definitions I mentioned. These are real cases.

This is a 25-year-old young lady who presented to the emergency department one night with a complaint of abdominal pain. She had nausea and vomiting that had awoken her that morning, and she'd been sick all day to her stomach. Her past medical history was basically unremarkable. She has morbid obesity, but she was on no medicines and has a very good functional status.

Her physical exam when she came in was remarkable for a little bit of tachycardia, a relatively normal blood pressure. She was tachypneic and markedly febrile. The rest of her exam was remarkable for the fact that she had cotton mouth. She was just dry as a bone. Her lungs were clear. Her abdomen was soft. She had positive bowel sounds. And this was some of her lab work.

So her white count was elevated at 22,000. Her hemoglobin was 18.2, lipase was 7,800, and her lactic acid level was 5.5. So is she septic? Yes, she's septic? I got one. Got two. OK. So yeah, I think she's pretty septic. And so basically, she was admitted to the ward, was given some IV fluids. The next morning, we get a call, this sort of Dr. Leo or Dr. Blue, 9-1-1, at 0600 and walk into the room.

The patient's sitting up on the bed like this, 45 degrees, terrified, profusely diaphoretic, pale, rapid, shallow breathing, panting, 40 breaths a minute. [RAPID BREATHING] Humans are not meant to pant. Humans don't pant.

Try it. See what happens. Make sure you tell a friend before you pant what's going to happen. Don't do it in your closet. Do it on a bed so when you pass out after you pant, you'll be safe. But if you see a patient panting, there's a fundamental problem. They're trying to blow off acid, right?

So the heart is 180. And I say, what's the blood pressure? And they say, we can't get it. What do you mean, you can't get it? There's no blood pressure. So that's pretty sick. Abdomen was distended, tender. She had 22-gauge IV in her hand.

And you're like, oh, gosh. What's the diagnosis? Septic shock, severe sepsis, some extreme form of sepsis, right? And what are you going to do about it? What's that?

SPEAKER 1: After a line.

DR. DOMINIC DEKERATRY: After a line. Yeah, you bet. You bet. So here's your options. You can start dopamine. You could start norepinephrine. You can give a blood transfusion. You can give normal saline. You can give Hespan. Or you could give antibiotics. And more than one answer may be correct here, but just be thinking about what you might want to do. And remind me at the end what was being done and what I did, or what we did.

So this is the definitions of sepsis. Now, there are several definitions out there. This is one that's fairly old, but it's accepted by the American College of Chest Physicians. The Society of Critical Care Medicine has consensus guidelines. And I've got another slide in a moment that I'll show you some sort of updated diagnostic criteria, if you will. But fundamentally, we have a phenomenon of systemic inflammatory response syndrome.

It is the body's response to an insult, whether it be trauma or infection or whatever it is. And SIRS criteria are extremes of body temperature, either too cold or hot, relative tachycardia, tachypnea, or somebody's blowing down their CO2 to lower than, say, 32, and extremes of white blood cell count. So you can have any one of these criterion in a number of different scenarios.

But if you have SIRS and an infection, that is sepsis. It is nothing more than that. It is not a scary word. It is not a criticism. Oh my gosh, your patient's septic. Oh god, what did I do wrong? That's not the case. It is just a very clean, concise, simple definition that applies to all comers.

Now, sepsis plus organ system dysfunction, delirium, decreased urine output, systemic hypoperfusion, cold extremities, lactic acidosis, renal insufficiency, whatever it is, that's severe sepsis. And patients who have severe sepsis who get a fluid resuscitation but have refractory hypoperfusion, whether it be persistent lactic acidosis or persistent hypertension require vasoactive agents, those are the septic shock patients. So it's just a spectrum of disease.

Nowhere in the diagnosis of sepsis is bacteremia. Nowhere in the diagnosis of sepsis is hypotension. And I say this because we just need to get our nomenclature sort of on the same page. I have people that I love and work with every day, smart, passionate, experienced people, who say about once every 10 days, I say that patient's septic.

And people say, well, I don't think so, Dominic. They're not bacteremic. And I was like, well, that's not the definition of sepsis. It is systemic inflammatory response with a bladder infection. That's sepsis. Severe sepsis and septic shock are other categories of disease. This is a picture of the sort of overlapping concepts of systemic inflammatory response and sepsis.

And I want to just make sure that everybody's on board in terms of what else can cause SIRS. Acute pancreatitis is the prototype of the systemic inflammatory response syndrome that's not typically related to infection. Burns, trauma, huge cause of SIRS. And other things like drug reactions or blood transfusion reactions, that sort of thing.

Also, I want to clarify that bacteria are not the only thing that causes sepsis in terms of systemic inflammatory response and infection. There's a little thing called influenza that's killed millions of people worldwide. Malaria with parasitemia causes lots and lots of deaths worldwide because of systemic inflammatory response and sepsis.

So vignette number two. This is a 78-year-old woman who's the matriarch of her family. Previously very healthy, very functional, sort of a go-getter. She came in from home, was brought by her family for not acting right for the last 12 hours. Past medical history is remarkable for high blood pressure, but otherwise healthy. No surgeries, nothing. She's on some atenolol.

And here's her physical exam. Heart rate's 95. Blood pressure's 100 over 50. Respir rate's 28, and temp is 99.9. She's confused. And she has a little bit of abdominal discomfort. Is she septic? Yes, no, maybe? Possibly? Maybe. She's not bacteremic. We don't know if she's bacteremic, right?

She's breathing really fast, right? She's breathing 28 times a minute. And for a 78-year-old woman on atenolol, a heart rate of 95 is probably a little generous. So right there, you've got a couple of things that stand out. Plus the fact that she's confused. She has altered sensorium.

So what other information do you want in this scenario? Lactate. What else can I give you? Something simple. An elderly woman with confusion and possible infection. Get a UA. So let me give you this stuff. The white blood cell count was only 6.0. The hemoglobin was 13.2, creatinine was 1.1, and glucose was 142. Your analysis showed too numerous to count white blood cells.

All right. Let me walk through these. The hemoglobin is relatively normal. Creatinine is relatively normal. The glucose is 142, and she's not a known diabetic. So one of the pearls I'm tossing to you is that an indication of systemic inflammatory response is an elevated blood sugar in the setting of a non-diabetic patient.

Diabetics, they go crazy, right? Every diabetic that comes in the hospital, their blood sugar's 457. What do you want to do? But a non-diabetic can have an elevation in their glucose as well. So that's an indicator.

What about the white blood cell count as normal? Not very impressive. Any more information you want to get? What else would you like to get?

Differential? Is that what you said? Thank you. I'm sorry I didn't get the lactate. The lactate was normal. But here's the differential. 32% band forms.

So here is the treatment options for this patient. Same thing. Dopamine infusion, norepinephrine infusion, blood transfusion, normal saline, Hespan, or antibiotics. And again, you can pick more than one if you want to. Be thinking about that.

So this is a crazy chart. You can't see it from here to Georgetown, for sure, or South Austin. But this is just published in the *New England Journal of Medicine*, and conceptually it's the same thing as what we just talked about. This is the definition of sepsis. It is documented or suspected infection plus one or more of the following.

And this has got all the stuff we just talked about, plus a normal white blood cell count with more than 10% band forms. So pearl number two. I strongly encourage anybody who's involved with these patients to get a manual differential on the CBC. Because if you have a white blood cell count of six, it may be a bad deal. And in this case, the patient had 32% band forms, which is very suggestive of a rather aggressive inflammatory response.

For that matter, a low white blood cell count is probably more ominous than anything. If you have a white count of one, and that presentation, we're behind the eight ball. Not because we've done anything wrong. We're just not there yet. So normal white blood cell count with greater than 10% in mature forms, altered mental status, altered sensorium, hyperglycemia greater than 120 in a non-diabetic.

And also another thing is hypothermia. One of my colleagues and I was taking care of a patient together recently, a young person. Florid klebsiella pyelonephritis. Normal blood pressure. Normal heart rate. Temperature was 91 degrees Fahrenheit. And just cold. A little bit of altered sensorium, but cold. And so hypothermia is definitely in there in terms of this concept of SIRS, or lack thereof, if you will.

OK, so what is the definition of shock? We all have our definitions, but this is fundamentally a situation where the tissue oxygen needs and availability are mismatched. It can either be because oxygen is insufficient to match the needs like anoxia or severe anemia, or the tissue is unable to utilize available oxygen, which is a term called histotoxic anoxia. You have mitochondrial dysfunction, the oxidated phosphorylation process is broken, and even if you provide a whole bunch of oxygen, the cells are dead or they're dying or they're stressed, and they can't use the oxygen.

And so there's anaerobiosis going on. There's anaerobic metabolism. So shock with infection is septic shock. These are two of my favorite quotes. And I wish I had them hanging in my office. So we can talk about all the definitions in the world, but these fundamental concepts of shock and what happens and how much time you have, these have been thought of for a long time.

Samuel Gross said, "a rude unhinging of the machinery of life." and John Collins Warren said this is "a momentary pause in the act of death." And this makes me think. These guys were 150-year-old surgeons. Anybody know who Samuel Gross is? So he's a little American academic trauma surgeon who wrote a little textbook on anatomy, *Gross Anatomy.* Yeah. I know.

So John Collins Warren was another academic American surgeon who had another physician give his patient ether. And there forward, the anesthesiologist was invented. So he was also a co-founder of the *New England Journal of Medicine*, and the Massachusetts General Hospital. And he was the third president of the American Medical Association.

So these guys were thoughtful about shock 150 years ago. And there's literature going back many centuries about thinking about shock. What this prompts me to promote to you guys is to think about this golden hour. We have golden hours of trauma. We have golden hours of a lot of things.

And the idea is, the way I conceptualize it, is you've got a dam that is bursting, and you've got streams of fluid coming out. And you've got to put your fingers in the fluid and shore up the dam until it heals. And then you're good again.

We have stroke alerts for brain attacks. We have STEMI alerts for heart attacks. We have trauma alerts for motor vehicle attacks. We have not very many sepsis alerts or septic shock alerts. And that's one of the things that is, I think, a potential great help to institutions in terms of the approach to management of these patients.

All right, what's epidemiology? There's over a million cases of sepsis in the United States every year. About half of them are due to respiratory illness. About 25ish percent are due to urinary infections. And the rest are other. There's GI sources and cellulitities and whatnot.

The cost per episode ranges from $25,000 to $50,000 per case. And the mortality range is the sicker they are, obviously the higher the mortality. The mortality statistics actually jump around quite a bit. But conceptually, you can see that the sicker somebody is, the more likely they are to not survive this.

As far as the microbial epidemiology, there was a nice study published that looked at data from 1979 to 2000 that suggested not only an increase in sepsis, but also a change in the microbiology of sepsis, such that gram-positive cocci were actually more common than gram-negative rods. One of the original terms for sepsis was endotoxic shock, toxic shock syndrome, but from gram-negative toxic shock. And this data would suggest that gram positives were more likely.

But actually, there's even more data that says-- this is a study that was published in 2009 in *JAMA.* Over 14,000 ISU patients in 75 countries, and there were more gram negatives than gram positives. So probably in the United States, it's somewhere between 50-50, with what seems to be an increasing incidence of fungal infections and other microorganisms.

This is a disappointing statistic, and I mention this because sometimes our patients' families are at the bed side, and they're like, what are the cultures, what are the cultures, what are the cultures. You're sitting there and giving them a 25-minute spiel on, well, we're relatively stable, and the urine output is OK, and I think we're OK.

What do the chest X-rays show? What do the cultures show? Well, you know. So the cultures are positive in about one third of the cases. Some are between 20% and 50%, but on average, about one third. So it's a little disappointing.

This is a beautiful article that was literally, as I was preparing my talk, the *New England Journal* comes out with this sepsis article, of course. And I would refer you to this because it has some great art and talks about the immunopathology of sepsis. I want to comment on two concepts. One is that there is a proinflammatory response, which is basically the body's idea of aggressively pursuing the invading pathogen and eliminating the pathogen.

However, there's also a lot of collateral damage. There is local tissue damage, and there's also systemic damage. The systemic inflammatory response syndrome, right? You go into ARDS. You get pancreatitis. You get renal failure. Yadda, yadda, yadda. On the other hand, you have an anti-inflammatory response, which is basically the response that is intended to limit the collateral damage.

But by nature of limiting the collateral damage, you've suppressed the immune system. And there is a very well-developed concept of immunoparalysis that develops the longer the patient is sick, the longer they're in the ICU, the more likely they're going to have a compromised immune system, and they're susceptible to nosocomial infections. So the idea is, get them in, get them out. Get them better, and get them out.

This is a concept that I actually really didn't know much about, but it is a neuroinflammatory reflex. So sensory input comes through the vagus nerve, and then goes back out to the vagus nerve and goes to the splenic nerve, which then releases norepinephrine in the spleen, which causes some CD4 cells to elaborate acetylcholine, which then targets alpha seven cholinergic receptors on macrophages, which stimulate neutrophils. So that's the pro-inflammatory response.

So you have these competing processes throughout the whole system, and you have quite a bit of ultimate damage the more critical the patient is. So this is the slide that just shows the tissue hyperperfusion and what happens. You have microvascular thrombosis, red cell deformability.

You have loss of barrier function, capillary leak syndromes, everything that we know clinically happens, and then ultimately organ failure. Just another picture out of another journal. This is the blue journal, recently published June, 2013, that looks at this inflammatory, both pro-inflammatory and anti-inflammatory cascade, that leads to this concept of immunoparalysis and death.

So what are the treatment goals here? The treatment goals are to understand what sepsis is, diagnose it early, and intervene it early, within hours, this sort of golden hour, if you will. That's probably not a good thing. [LAUGHTER] Gotta hurry. And this talk, I really want it to be focused on the patients that present to us in the emergency department or to the ICU from the OR or to the ICU from the ward. Not so much patients who are 96 hours into an ICU stay.

Early recognition, early intervention, is an entirely different approach to somebody who's already in multi-organ system failure with ARDS, on a vent, on a rotoprone, getting 10,000 different medicines, have the Christmas tree. Patients who are along their course in the ICU, it's a very different approach. They're not responsive to fluids. They develop critical illness polyneuropathies, and they have physical and neurocognitive decline. So the whole idea is to help try to prevent this in the first place.

So enter Manny Rivers. So Emanuel Rivers is a trauma surgeon, and he did the first randomized controlled trial of 263 patients with severe sepsis or septic shock presented to the emergency room, and the concept was this group of patients was managed with a goal-directed therapy, a quantitative resuscitation, and this group was usual care. And what he showed, or what they showed, was that there was a statistically significant mortality improvement with the goal-directed approach.

Since then-- this was in 2001-- since then, our literature has exploded with criticisms of this. So I'm going to take you through it. The surviving sepsis campaign-- for those of you that don't know, survivingsepsis.org is a great information website. They've got guidelines. They've got educational resources. It's really quite a nice website. And they've recently updated it.

The guidelines were first put out in 2002, and then 2004, and then they just put out 2012 guidelines. The agenda here is to build the awareness of sepsis, improve the diagnosis, increase the use of appropriate treatment, et cetera, develop guidelines. And I just kind of want to reiterate that the guidelines were not intended to replace clinical judgment. They're intended to facilitate the thought process and give this loop, this feedback loop, to the providers on sort of a constant audit, if you will, of the patient's situation.

So what are involved with these bundles? You'll see several different iterations, but the surviving sepsis guidelines suggest that within the first three hours of somebody presenting and being diagnosed with severe sepsis or septic shock, you should measure a lactate level. You should try to get blood cultures prior to the administration of antibiotics. Don't delay.

The sort of accepted published standard is no more than 45 minutes. If you're waiting, waiting, waiting, waiting, waiting, and it's an hour, it's an hour 15 minutes, you're waiting to get your cultures, just cut bait and get the antibiotics. I know it's a core measure. The core measures people are like, oh my god, don't do that. But I'll show you some mortality information in a moment that says if you wait too long, you're behind. You hurt the patient. So don't do that.

But try. Administer broad spectrum antibiotics. This is an interesting subject, and we're not going to hit on antibiotics too much. There's a lot of expertise involved in this room and the other institutions, but conceptually, antibiotics as soon as possible that are targeted towards the organ system that you think is the culprit. And then the administration of crystalloid fluid at a rate of 30 mLs per kilo for hypertension or if the lactate is elevated.

So that can be complete within the first three hours. And then to complete within the subsequent three hours, or a total of six hours, is to give vasopressor agents to those who have a persistent hypotension that's not responded to fluid resuscitation. Also, if the patient is still down and out, if you will, they're still in septic shock, they're still needing the vasopressors, then you really ought to consider placing a central venous line. Not a PIC. I'm going to get hit on that one.

And also consider measuring central venous oxygen saturations. And then at some point within the resuscitation parameter, recheck your initial lactate if it was elevated to try to assess the efficacy of your resuscitation. And the targets for these things are to try to keep a CDP greater than eight and a central venous oxygen saturation greater than 70 and to normalize your lactate. So we'll dive into these in a moment. Remember, this is the idea of goal-directed therapy, or I think the best buzzword is quantitative resuscitation.

Now, antibiotics. Lots and lots of information on antibiotics. And I just presented one slide on this. This was published in *Critical Care Medicine* 2006. This was 2,700 patients with septic shock. This chart shows what the odds ratio is between delay of administraton of antibiotics and hospital mortality.

And basically, the delay was associated with a 1.119 odds ratio increase per hour of delay, which translated into a 7.6% decrease in survival per hour delay for each of the first six hours. So the patients that were out here at six hours who didn't get antibiotics had a huge risk of death. The earlier, the better. I think most folks, most literature, most guidelines out there, would suggest getting them in within an hour.

OK. Central venous lines. Now, there is-- you can use peripheral IVs. You can use PIC lines. You can use central venous lines in various locations. But there's data to support, not only from the early goal-directed therapy trial in 2001, but there's other data to suggest that central venous lines are helpful and not harmful.

This was a nationwide inpatient sample database, which is basically from the Agency for Healthcare Research and Quality. And this is a stratified probability sample. So these 203 patient hospitalizations with septic shock represents a million patients. And what they did was looked at the time frame from 1998 going to 2009, knowing that around 2001 was when the big trial was published.

And they looked at early, meaning the same day of admission, central venous catheter placement versus hospital mortality. And what they found is over the time frame that the insertion rate increased from 5.7% to 19.2% percent. So really only one out of five even at the end of 2009 were getting central venous lines. But that the age-adjusted hospital mortality declined significantly greater for patients with an early CVC versus no CVC. So this is the graph.

So this is the annual percentage rate change from 1998 to 2009 of patients who were severely septic, septic shock, who got a central venous catheter versus ones that didn't. Now, both lines-- this one's a did, and this one's a didn't-- got better. Everybody improved. But patients who had central venous lines, there's a suggestion here that central venous lines facilitate your ability to manage these patients.

This is also an interesting slide. Or, it is to me. I hope it is to you. Pre Emmanuel Rivers, pre randomized controlled trial on these patients, this is the odds ratio hospital mortality for patients with central lines. So there's a higher risk of dying if you've got a central line before we figured out how to use them, I think.

Yeesh. I've been around for a little while, and I think I was working around this time too. But for what it's worth, I think we got better. This is the Manny Rivers article. This is the Surviving Sepsis Campaign. And two things happened. One is that the mortality rate, the odds ratio of mortality, declined towards statistically significant, and also the confidence intervals narrowed.

So this suggests that using a central venous line is helpful. Now, what do you do with the line? So we'll talk about fluid resuscitation, pressor agents, central venous oxygen saturations, and also central venous pressures.

Enter controversy number 17. So crystalloid versus colloid. In 2004, in the*New England Journal of Medicine,* published what's called a SAFE trial. This was the Saline and Albumin Fluid Evaluation trial. And what these folks did was randomly assigned 7,000 ICU patients. About a fifth of them or a sixth of them, whatever that ends up being, it was 1,218 of them had septic shock or severe sepsis.

And they used 4% albumin versus normal saline as the primary resuscitative fluid. And their primary outcome was 28-day mortality, and there was no difference. There was a subset analysis that suggested that patients in the ICU with traumatic brain injury with increased intracranial pressure did worse with albumin. That's all I have to say about that. I'm not a trauma or neurosurgeon person, but it's out there. So you all know, even though that this trial suggested no difference in mortality, there was a subset analysis where it was not favored.

Now, the second one that I want to mention-- I'm mentioning this article. It's got some criticisms of it, but it's mentioned in the surviving sepsis campaign guidelines that were just published in 2012. So I think it merits a little bit of discussion. So these folks did a meta-analysis of 17 trials looking at albumin versus other solutions in patients with sepsis.

And they said that albumin in this study was associated with a reduced mortality, with an odds ratio of 0.82 favoring albumin. So in the surviving sepsis camping guidelines, it says recommend crystalloid, 30 mLs per kilo, but consider using albumin if the patient's requiring a lot of fluid. It doesn't replace decision making. The guidelines don't.

However, I do have some criticisms of this meta-analysis. You cannot do cause and effect with meta-analysis, number one. But two is that there were 1,977 in these 17 trials, including the 1,200 that were in the SAFE trial. So the other 16 studies, whatever that ends up being, 600 patients, there are not a lot of additional studies with large cohorts. They were 40s and 50s here and there. So that's number one.

Number two is that 12 of the 17 studies had hetastarch as the control fluid. And I'm going to talk about hetastarch in a minute. But you're talking about albumin versus hetastarch, and not crystalloid or Ringer's lactate or Ringer's acetate or normal saline. And then also, 3 of these 17 studies used gelofusine as a control fluid, which is something I've personally never used.

My understanding is that's used more commonly in the pediatric population. And for that matter, these 3 studies of the 17 were in children with malaria. So even though it's in the guidelines as a potential alternative, I don't think the data is there yet to say what truly is best in terms of a big control trial other than the SAFE trial.

All right. So let me tell you a little bit about hetastarch. This was published in the *New England Journal of Medicine* in 2012 . This is another randomized controlled trial. 7,000 patients. One to one randomization. 6% hetastarch versus normal saline for all fluid resuscitation while in the ICU. Primary endpoint is mortality difference, and there wasn't any.

The renal replacement therapy was higher, however, and that's a statistically significant number. A higher number of patients required renal replacement therapy if they received hetastarch versus saline. And also, the adverse events, which included bleeding risk, were higher in the hetastarch patients.

The next study was another one that was just published in the *New England Journal.* And this study was stopped prematurely because of evidence of intention-- not intention to harm, but harmful effects. This is a randomized controlled trial of 804 patients with hetastarch versus Ringer's acetate.

And these patients had severe sepsis. And basically, there was a mortality difference. More patients died with hetastarch, 51% versus 43%, and more patients required renal replacement therapy. And there was a trend towards more frequent episodes of bleeding in this group.

So based on these two studies, the FDA now has a black box warning against hetastarch. And in fact, what they're saying, and also what's published in our literature and our pulmonary critical care literature, is that these solutions should no longer be used in the treatment of patients who are critically ill adults and with sepsis or, for that matter, anybody who's admitted to the ICU. And you also shouldn't use them in post-op coronary bypass graft patients because they do have an increased risk of bleeding. And my understanding is that it's already been taken off the order sets for post CABG patients, which is wonderful.

So the bottom line is, with crystalloid versus colloid, is that there's unclear benefit of albumin versus crystalloid. I did a little pseudo subset with the assistance of one of my clinical pharmacists that I work with and looked at the St. David's costs of what would be the cost of the albumin solution in the SAFE trial versus the normal saline. And it was $322.30 versus $5.40. So I mean, we give $1,000 treatments every hour, right?

But that's a pretty big difference, and multiply that times a million and see what you get. So my sense is that there's no clear benefit for albumin over normal saline, and normal saline is pennies on the dollar compared to albumin. There are currently three randomized control trials looking at this, and we may have some more information over the next year or so. Hetastarch is out of the running in terms of resuscitatve fluid for NICU.

So pressors. Gosh, there's a lot of dopamine on the carts, right? Everybody's got dopamine in the bags, pre-mixed bags, and forever and ever, we use dopamine. You want dopamine? You want dopamine? No. You can use dopamine, but just be careful because there is a randomized control trial published in the *New England Journal* that looked at 1,679 patients with shock.

Most of them had septic shock. Some of them had hypovolemic shock and required pressors, and some of them had cardiogenic shock. And it turns out that their primary outcome was 28-day mortality, and there was no difference in one or the other. However, the patients who had cardiogenic shock had higher mortality. They did break out these subsets a priori in the study, so I think this is a valid statistic to comment on.

Evidence-based medicine suggests that dopamine has a little higher mortality risk in a cardiogenic shock patient. Why? Probably because of their malignant arrhythmias. There is a greater number of supraventricular and ventricular arrhythmias in dopamine versus norepinephrine, and that's a very highly statistically significant number.

This is a page out of the surviving sepsis campaign. I actually couldn't find this chart published in a peer-reviewed article. But what it shows is a compilation of the studies that have been done in dopamine versus norepinephrine, and basically comments on three main things. This is the relative risk of norepinephrine in terms of risk of adverse events compared to dopamine.

And here's six studies with 2,000 patients, and these studies had 1,900 patients. So pretty good number of folks. And what it showed was that the relative risk of norepinephrine in terms of mortality was 0.91 compared to dopamine. The relative risk of serious supraventricular arrhythmias was 0.47, obviously favoring norepinephrine. And the ventricular arrhythmias, the relative risk for norepinephrine was 0.35.

So the potential benefits of norepinephrine of dopamine are pretty well-validated at this point, and it's recommended to the pressor of choice. Now, how do you infuse the pressors? Enter the central line again. Norepinephrine vasopressin, epinephrine, phenylephrine, are all caustic to the vasculature and the extravascular spaces.

Generally, the central venous catheter, for that matter, pick line, anything centrally placed is better to administer these medications than a peripheral IV. So there are times when you are in the middle of resuscitating somebody, and you've got two 18s in the antecube, and you're throwing in the fluids, and they've still got a blood pressure 50 over 30.

Give me some norepinephrine. Fine. Do it. Run it. But as soon as you can, get a central venous access because the risk of extravasation in ischemic necrosis, [INAUDIBLE] necrosis, is fairly high if these medications extravasate. With dopamine and dobutamine, there's a theoretically reduced risk of ischemic necrosis.

High doses of dopamine is just as bad as anything else. So low levels probably OK. You've got more time to sort it out. I feel like I'm going pretty fast. Anybody have any questions so far? OK, just butt in. Raise your hand. Give me a buzz. If you have any questions, I'll stop.

Central venous saturations. All right. So the goal of a central venous saturation, according to our guidelines, is to keep it greater than 70. So a central venous catheter that is placed in the superior vena cava, and you draw the blood out of it, and you send it to the lab, and you get a saturation, that is a central venous saturation. It is not a mixed venous saturation, which we get, sadly not as commonly as we used to, from the distal port of a PA catheter.

A mixed venous sample is mixed because it bypasses the atrial mixing, the valvular mixing, the ventricular mixing, the patent ductus arteriosus mixing. It goes way out in the pre-capillary vessels, right before the blood in the lung picks up oxygen. That's a mixed venous saturation.

We tend to use the central venous catheters because they're easier and probably associated with improved outcome, and pulmonary catheters are potentially associated with worsened outcome. So we use our central venous as a surrogate for a mixed venous saturation. Femoral venous saturation, femoral line central venous saturation, is not a surrogate. And there is a nice study recently published in the *Critical Care Medicine* journal, that looked at healthy patients undergoing a cath, a diagnostic cath, versus OR patients versus a small cohort, I think about 30 patients, of critically ill patients.

And look at femoral venous saturations versus central venous saturations. And what they found was that the central venous saturations ran about 4% higher at p equals zero, time one, whenever you first go in and make the assessment. But more than 50% of the values diverged more than 5% in absolute value over time. At hour six, they were very close together, the total numbers, but you didn't know which one was going up and which one was going down.

The values came closer together, but there was so much divergence, you can't use them as a surrogate marker. So just avoid that. If you're going to place the femoral line because you've got to get it in, it's emergent, patient's got a coagulopathy, and you need something you can hold pressure on, that's fine. But don't rely too heavily on the central venous saturations at that point.

A low central venous saturation in septic shock suggests an imbalance between oxygen consumption and oxygen delivery. So if you have a low sat, you have a high extraction ratio. And that can be because the consumption is higher or the delivery is lower.

Very often, as patients come in and they're getting resuscitated, if they're getting worse and worse, and they've developed multi-organ system failure, and they've developed a cardiomyopathy of sepsis, with all the bad chemokines and interleukin 6, 8, 10, tumor necrosis factor, whatever it is or whatever they are that are causing the global cardiomyopathy of sepsis, you have reduced oxygen delivery. And in that setting, an inotropic agent like dobutamine can be helpful. So norepinephrine is a primary vasopressor agent, and dobutamine as a primary inotropic agent can be helpful and complementary in terms of resuscitating the patient.

I put this in here just to kind of remind everybody that there's a little bit of a difference between early and late treatment and assessment, but also that the central venous saturations don't necessarily differentiate between fluid responders and non-responders. Also, a normal central venous saturation without lactate clearance is not necessarily a good thing. Because you can have anaerobiosis going on, slow lactate production, there's underperfusion, and your central venous sat comes up.

What this means is it's not being utilized. So make sure that you don't use anything exclusively. Another take home point, if I may. None of these parameters are exclusive. None of them should put all your eggs in one basket. You never did that anyway, right? In life, or certainly in dealing with sepsis. Take it all in. Understand that a high lactate and a normal central venous saturation, that's a bad thing.

If everything's good, urine output's great, patient's [INAUDIBLE], skin is not mottled anymore, we're making progress. Lactate clearance is another hot topic. Really not so much that it's valuable in terms of clinical parameter, but what's better, lactate clearance or central venous saturations. And this was a study that was published in *CHEST* just recently, a couple months ago. And it was a preplanned analysis of an ongoing randomized control study in sepsis resuscitation.

We've known since 1962, '63, that a lactate that's above four is associated with increased mortality. Lactate above eight, oh my gosh, 80&% mortality, something like that. And a variety of different studies have looked at lactate clearance. What's the best predictors of outcome? This study showed that 93% of the patients in this study who had an abnormal lactate that went normal survived. So the odds ratio compared to the other survivors was 5.2.

So really, if you have a lactic acid of seven on hour one, and you've got a lactic acid of 1.2 on hour six, almost always you win. If you have a lactic acid that drops by about 50%, it's still a pretty good indicator of improved survival. And odds ratio here is about for 90% of the patients in this study survived if they had at least 50%, or around there, clearance of lactate.

Interestingly, in this study, the patients who had a 10% clearance, it couldn't be identified in this study as an independent predictor of mortality. Yet, it was a predictor of survival or mortality, depending on which way you look at it, in the early goal-directed therapy for sepsis trial. Also, sadly, only 50% of patients with septic shock have an elevated lactate in the first place, for what it's worth.

OK, central venous pressures. There's lots of controversy on whether or not a central venous pressure is helpful. And I want to sort of tease out this literature as well. Basically, the question is, if somebody has a CVP of nine, does it suggest that they'll benefit from a fluid bolus versus a CVP of 17 in Lasix, or whatever it is. And a meta-analysis published in *Critical Care Medicine* July, 2013, two months ago, 43 studies, 1,800 patients, looking at fluid responsiveness.

They defined fluid responsiveness as an increase in cardiac output or stroke volume with a pre-load challenge. Either fluid bolus, sometimes albumin, sometimes hetastarch, sometimes saline, and sometimes with a passive leg raise. And they found that there was no significant predictable fluid responsiveness in these patients. And so they said there's no data to support the widespread practice of using CVP to guide fluid therapy.

Problem number one is that the mean baseline CVP in these patients in this group that were responders had a normal CVP of 8.2. And the ones that were non-responders had 9.5. They didn't break it out whether that was statistically significant or not. But they all had normal CVPs.

Problem number two is that 22 of the 43 studies were in the ICU, 20 were in the operating room, and one was a volunteer study. None of them were patients in emergency department presenting with septic shock. The early goal-directed therapy for sepsis trial that was published in 2001, those folks had a mean central venous pressure of five.

So the take home from my perspective is that CVP is not the greatest surrogate in the world. It's not measuring LVEDP. There's a lot of variables along the way. There's the valves, and there's ventricular and atrial compliance, and there's pulmonary vascular resistance. There's a lot of things that can impair the reading from the central venous pressure all the way down through the system.

However, just as in anything, you never put your eggs in one basket. Extremes. If somebody comes in with septic shock, and you drop a line, and their CVP is zero, probably they're going to benefit from fluids. If their CVP is 32, you're gonna go, gosh. Man, I missed the boat on that one. Let's give them some Lasix, or let's give them dobutamine or whatever it is. Between 5 and 15, probably not all that helpful. But that's OK.

Now, this is some up and coming things in terms of addressing the controversy of whether or not CVP is valuable. Other measures of systemic profusion or tissue profusion. This is laser doppler flowmetry. This is MR spectroscopy, near infrared resonance spectroscopy, side stream dark field.

There's a lot of things you look at the blood profusion at the microvascular level, and the hypothenar eminence, and it's supposed to predict your fluid responsiveness. There's no randomized comparative trials on outcomes in this stuff yet, but it's forthcoming. It does not exclude the concept of a guideline approach to this. For that matter, there's other ways of assessing fluid responsiveness.

There's dynamic ultrasound at the bedside, looking at IVC excursion and whatnot. Problem is that most institutions don't have that capability to do it on an ongoing basis. So right now, what we have is these things. Early restriction of antibiotics, and resuscitative fluid is the goal. Consider isotonic crystalloids first. Consider norepinephrine over dopamine.

Consider central venous catheters for patients with severe sepsis and septic shock. I'm not advocating that everybody that comes in from the nursing home with a UTI gets a central venous line, just so we're all on the same page here. Unless they have band forms are 32, but-- and no single clinical parameter should be used to guide your rescusitative efforts. Convinced or not convinced about the global approach here? Let me finish with just a couple more slides.

This was just published in the blue journal. This is a multi-center implementation of a severe sepsis and septic shock treatment bundle, Intermountain Health in Salt Lake City. These folks looked at a whole bunch of patients and looked at mortality based on compliance with the bundle. And they actually had 11 things in the bundle, which I'll show you in a minute.

It's a little busy. But it had all of the stuff we've already talked about, plus a couple of other things, like reasonable [INAUDIBLE] in the RDS patients and that sort of thing, DBT prophylaxis. And what happened was they had 18 ICUs, 11 hospitals, 4,300 adult patients admitted to the ICU from either the ED or the OR.

And from January, 2004 to December, 2010, mortality decreased from 21% to 8.7%, and their bundle compliance increased from 4.9% to 73.4%. That's a relative decrease in mortality of 59%, with a highly statistically significant number here. Interestingly, the patients that weren't included in the bundle that dropped out because they weren't compliant with the bundle, they also did better.

Of the 11 things in their bundle, in 2004, they fell out because on average they missed four of the things of the 11. They had a 21% mortality then. But they also dropped to about 9.7%. At the end, they were missing one out of the 11. So the idea is participation in this bundled approach is associated with improved mortality.

This is their bundle, lactic acid, blood cultures-- don't wait-- fluid therapy, vasoactive agents and monitoring, et cetera. This is the chart. This is compliance with the bundle. This is mortality.

Conclusion. Timely, aggressive, and efficient recognition and management of patients with severe septic shock is of paramount importance. This doctor, Dr. Peter Safar, said that-- I'm going to put myself out of business here-- "the most sophisticated intensive care becomes unnecessarily expensive terminal care once the pre-ICU system fails."

This gentleman was a pioneer in CPR, EMT training. He had the first ICU in the United States and had the first ICU training program in the United States. He's been there, done that, recognizing that you have this goal in the ER before the patients get to the ICU to recognize and intervene as early and as aggressively as possible. The key is early detection.

You have to have a team approach. EMS needs to be involved. The emergency department needs to be involved. The ICU needs to be involved. For that matter, in a lot of institutions, a lot of patients that come to the ICU with sepsis are from the floor. So you need to have your floor teams, your med surg units involved.

Paramedics, physicians, nurses, respiratory therapists, pharmacists, everybody. Remember the concise consensus definitions. It's not a bad word, sepsis. It's not a criticism. It is a very simple SIRS plus sepsis, and sepsis plus organ system dysfunction is severe sepsis, and those refractory patients with refractory hypertension systemic hypoperfusion, despite fluid resuscitation, there's the shock patients.

This is a quote from Machiavellian 1513. "Hectic fever, at its inception, is difficult to recognize but easy to treat. Left unattended, it becomes easy to recognize and difficult to treat." I think that says it all. Early recognition is not easy. There's nothing easy about trying to triage somebody who comes in with a little bit of altered sensorium, a little bit cool to the touch. Blood pressure's OK. Stats are fine. Heart rate's 90. They're OK, but they're a little bit septic.

So I leave you with this. This is my email, my cell phone. If I can help with any of you with organizing your bundles or any clinical approach to these patients, I'd be very happy to do so. It's my pleasure to visit with you, and I'd be happy to take any questions.

[APPLAUSE]