Clinical Phenotypes of Sepsis

John Kellum

Speaker 1 (00:00):

Our last lecture for the session is by Dr, John Kellum. He 'll talk to us about clinical phenotypes of sepsis.

Speaker 1 (00:12):

Thank you very much. and thanks to the previous speaker for covering some of this already. So, it'll be, a little bit of a review. These are my disclosures. I think actually this may be the only talk I give in this session that doesn't have any, I'm going to show some biomarker data, but mostly it doesn't have anything to do with any of these, disclosures. So first of all, let's talk about an endophenotype is and why it's important. So actually, although this has come into our lexicon relatively recently, I would say the last five or six years, it's actually been around since the 1960s, and it's really thought to be sort of a way to differentiate between potential diagnoses that are present with a similar syndrome.

New Speaker (01:14):

I'll explain why that's important in a second. And it really came from genetic epidemiology. Believe it or not, it was first defined to identify various groups of grasshoppers that had a similar phenotype, but were genetically different. And they, essentially had different genes that we're producing in the aggregate, a very similar looking, phenotype. And so they had a different endophenotype mechanistically, but their phenotype looked similar. And then just the opposite occurred as well, where there were, grasshoppers that had a very different looking phenotypes despite the fact that their genes were the same. And of course you're familiar with, ways in which that can occur, epigenetics explains how we can have very different phenotypes with the same genotype, but endophenotype helps us understand how we can have a similar phenotype with different underlying genes.

Speaker 1 (02:17):

And i'll try to get through that. it then became invoked in psychiatric illnesses, And it's been, we think critical care and nephrology are kind of loose in terms of our syndrome, but psychiatry very loose, So over the years there've been all sorts of different categorizations of psychiatric illness, many of which do not map to any known genetic predisposition, but some of them do. And so there are some patients with schizophrenia who have a gene for schizophrenia, but the majority do not, and yet they have schizophrenia just the same. And so how do we understand all of that? So that's kind of where this comes from. This might be a better explanation than me rambling on with a complex slide. This is the idea that you could have a syndrome caused by different endotypes and then underneath that different, genetic, makeup and sepsis is a perfect candidate for this.

Speaker 1 (03:13):

Because we know that not all sepsis patients are the same. You can have a patient with sepsis who manifests a different form of organ failure than the next patient in the next bed, who has the

same organism, the same underlying, demographics and chronic illness. And yet this patient has acute kidney injury. This patient has acute lung injury and ERDs why are they different? They both have pneumococcal, sepsis, they're both 37 years old with no past mental history, . Why are they different? And so this concept endendophenotype describing sepsis, is important. And, Eric touched upon this moment ago and I'll just go into a few more details about how this was sort of done, the idea was could you take a large database of patients with sepsis? And this was handy that we have this database because we use this database, the SENECA database to develop the sepsis three, definition.

Speaker 1 (04:16):

So, sort of a convenient database to then mind to understand whether the patients who met that criteria would all be the same or whether we could by, machine learning process, identify clusters of patients that seem to be different. And then the question would be in those patients, even though they fit within the syndrome of sepsis, do they have different clinical phenotypes that then might translate into different endophenotypes that could translate into different mechanistic pathways that could be targeted differently. And that's the real key to all of this at the end of the day, are there different strategies that could apply? It's not just a academic exercise to see whether or not, this sepsis has brown hair and this sepsis has blonde hair. It's, really about figuring out whether there are different mechanistic pathways in play that could be targeted differently.

Speaker 1 (05:17):

And so what we did here basically we took this large database, minded the database said are there clusters of patients using a machine learning techniques? So, not an informative, non biased approach. And then taking those patients with the different clusters and looking for them in large clinical trials and see whether there's heterogeneity of treatment effect within those trials to see whether or not different strategies would work differently, potentially for these different endophenotypes? It's a little convoluted, but I'll try to bring it all back together at the end. So Eric showed you this, these are the two, of the four phenotypes, these two phenotypes, the delta and the gamma phenotype. Both had very high inflammation, both had high mortality, but the gamma phenotype didn't, exhibit the type of kidney injury, for example, that was seen, in the delta phenotype and the delta phenotype saw a lot less respiratory failure compared to, the gamma phenotype, for example.

Speaker 1 (06:30):

So there were, already sort of differences in this clustering, such that the distribution of organ failure in sepsis was different across the different phenotypes, it didn't seem to matter what organism they were infected with. I don't have a slide on that, but just take my word for it. And it didn't seem to matter, what site of infection, whether it had pneumonia or urosepsis, abdominal sepsis, these Igloo plots are a little challenging to read, but here's the phenotypes and here's the site. And you could see that lung is predominant in all of these, maybe a little bit less here in the delta form, but that's just because the overall and is lower, abdominal sepsis is the next and GU follows that and another is the last, so the site of infection didn't really inform these phenotypes nearly as much as the distribution of organ failure. Inflammation.

Speaker 1 (07:26):

As I mentioned a moment ago, these are the different trials that, the data looked at. They're not necessarily trials, GenIMS study for example, was an observational study. but the different data sets, whether it was ProCESS or PROWESS or ACCESS, or GENOMS, you can see that the high inflammation was generally seen in these two gamma-delta, phenotypes compared to much lower inflammation, in the alpha and beta. And this is just looking at it by IL-6. You can also look at host of other, inflammatory biomarkers. And by in large, the data were similar, and the mortality was, significantly different in these different studies. So this on the left. This is, the original PROWESS Trial, and on the right is the ProCESS Trial, they are goal directed trials that we did.

Speaker 1 (08:23):

and you can see that this delta phenotype has, the highest mortality than these two phenotypes in the middle, the beta and the gamma phenotype, despite the fact that are very different, had sort of middle of the road, mortality and this, alpha phenotype had the best, survival. In fact, in ProCESS mortality was extremely, low in this particular phenotype, but that's not the real question. The real question is when I alluded to a moment ago, which is that if you then say, I've got a therapy, would it work differently across these phenotypes? And does that matter? So that's actually why we did this. This slide shows what that looks like with simulation.

Speaker 1 (09:24):

So a little bit complicated, I'll walk you through it. On the left, we have, a simulation where we vary the frequency of the alpha phenotype. This is the phenotype that had the least amount of organ injury and have lowest inflammation, lowest, mortality. And we go from having no alpha to the maximum of alpha in the upper bound of the simulation, which happened to be a hundred percent for alpha, very common, phenotype in general. And it could be as high as a hundred percent just by random chance. And you could see that the PROWESS, study or drotrecogin alfa would work best if we eliminated the alpha group entirely, and it would work progressively less.well, the further we go toward having alpha dominate in the population. So if you randomized a cohort of patients that were predominantly alpha, they had sepsis, they meet sepsis three criteria, but they're predominantly alpha sepsis even PROWESS, which was a positive trial is going to be negative.

Speaker 1 (10:39):

Whereas the ProCESS study of early goal directed therapy actually shows benefit when you get into the alpha group, but it shows harm if you take all the alpha group away. Similarly, if you take the delta group, which is the group that had the most, kidney injury, had the most inflammation, had the highest mortality, you could see, that a similar pattern is seen that, you get increasing benefit from early goal directed therapy, probably from drotrecogin alfa in the PROWESS trial, as you enrich for this phenotype, you can only get up to 44% because it's a relatively rare phenotype and the simulation only gets us enriched to 44%, but you can see this group has the highest benefit. And yet it actually has the highest harm from early goal directed therapy. And this of course matches what's been shown in subsequent post hoc analyses of the ProCESS trial, showing that patients with a more severe illness actually had less benefit from early goal directed therapy and just the opposite if they were less sick.

Speaker 1 (11:51):

Now, there's another way to look at this though, begins the process of saying, can we discover subtypes of sepsis by mining large databases, and then do those differences map to differences in outcome. But there's another way of looking at this. This is, the ProCESS, trial and the way we looked at this in the ProCESS trial, was that we asked the question, are there phenotypes that are masquerading in the context of sepsis? So for example, in pediatrics, we talk about macrophage activation syndrome. We tend to talk about it as much in adults. probably because it's linked to certain genetic diseases, which are often fatal, prior to reaching adulthood, but do heterozygotes for those genetic diseases do they carry enough of a trait that when they get really sick from sepsis, they develop a macrophage activation like syndrome that just looks like bad.

Speaker 1 (13:03):

Sepsis, but is it, something else that's driving this hyper inflammatory response? So what we did in this study was we said, we're not going to do an unbiased data mining approach. We're going to do the opposite. We're going to start from a supposition that rare causes of this hyper inflammation could be detected if we just looked for these patients carefully within the data set. So this is looking at all 1300 patients. And we asked the question, if you found the patients with the highest ferritin levels and ferritin is a marker of inflammation, but it's also an indicator of macrophage activation syndrome. And you can say, take the six top patients. Because that's all we had the money for when we did this part of the trial. We have more money now. So we're doing more of this work, but when we started it, we said, let's just look at the top six and see whether they have any genetic markers for conditions known to be driving macrophage activation syndrome.

Speaker 1 (14:09):

And then could those diseases be masquerading essentially as garden variety, sepsis, and the reason that's important as I'll show you in a second is we have therapies for these particular conditions. So basically what we did is we took these six patients. And as you can see, they run the gamut. These are all from the 1,341 patients randomized in the ProCESS trial took the six that had the highest ferritin levels. And you can see that their ferritin levels are extremely high. they were all above 5,000, there's one, that's 55,000. I've never seen one that high before. and we genotyped them looking specifically for genetic polymorphisms that were associated with conditions that were associated with macrophage activation syndrome. You wouldn't think to find these in adults. I mean, you know, the range of ages here, there are two 70 year olds, a 64 year old.

Speaker 1 (15:06):

You wouldn't expect to see this, but the question is, do these patients carry, genetic risk for these kinds of rare subtypes that can look like sepsis? So this is what we found basically six out of six had, at least one and a couple of them had more than one, a genetic marker for conditions that are known to be associated with with macrophage activation syndrome, such as atypical HUS. HLH , I can't remember what CAPS stands for, familiar Mediterranean fever. and so you can see that these, diseases, these patients been asymptomatic, for their entire life. Maybe one patient has had an interesting note in the chart about having a childhood illness, which was maybe and just survived it. and but most of these patients didn't appear to have any underlying, knowledge that they could have been carrying. one of these, traits and the minor linear frequency is shown on the far right. And you can see, these are extremely rare, we shouldn't have found any, or maybe just

one of these patients in the entire data set. And here we found six out of six, So even if we found all six, like these are the only patients, none of the other, 1,335 patients had, any genetic traits associated with these diseases. Even if these were the only six, this is still statistically way out of proportion to what you would have expected to find by how rare these conditions are supposed to be. So what I'm trying to say there is that it seems likely that in a population of adult sepsis, we do have these patients masquerading as a potential, sepsis.

Speaker 1 (17:06):

And we wouldn't know because we see them and we say, well, they just have bad sepsis. interestingly 50% of these patients had at least one polymorphism that, was associated with atypical HUS. And if we look more at those patients, we find that many of these patients in the data set, were found to have thrombocytopenia and, we of course know that thrombocytopenia is very common in sepsis and we tend to call it DIC. And in fact, you can't make the diagnosis of atypical HUS unless you stretch the diagnostic criteria because you read the diagnostic criteria in it. The very first line says that can't have sepsis, or cancer and here I'm telling you, we've got a cohort of patients with sepsis thrombocytopenia, acute kidney injury, and a genetic marker for an atypical HUS

New Speaker (18:10):

and so I would submit to you that some of those patients probably had atypical HUS, and we just didn't know it. we screen these patients for, looking at the entire dataset This is, looking at all 1,341 patients. And you can see that, DIC doesn't explain the thrombocytopenia, particularly patients with platelet counts between 50 and 99. And even the patients with severe thrombocytopenia, less than 50,000, only a third of the patients had DIC. TTP was rare, as it should be. although even probably a little bit more common than you would have guessed, actually these are confirmed cases with ADAMTS-13 levels below, 10%. and then you could see the 90 day mortality rates. They're staggering. If you have Nadir platelet count in sepsis is less than 50%, even if you don't have DIC as the explanation your mortality goes up considerably.

Speaker 1 (19:06):

Now, remember the pathogenesis of DIC is very different, and patients should be able to be screened out because of development of probably coagulopathy and bleeding, et cetera, that you don't see, with, atypical HUS. Atypical HUS has multiple genetic links, including the ones that I showed you on our, genotyping paper. but there are a number of other as shown by these, red markers, a number of other places, in the compliment cascade where there can be a genetic, defect that, manifests as, atypical HUS,. These is list of all the known genetic defects associated with, atypical HUS. The reason this is important of course, is we have treatments.

Speaker 1 (19:59):

We have plasma exchange, which by the way, it's interesting. I don't have a slide on this. I was going to put it in,, but I didn't think I'd have time. if you look at places in the World where plasmic change has been used effectively in both adults and children with, sepsis, you find that it tends to be in places where there was a bit more with atypical HUS. So, there's a big data set from Turkey. for example, showing that, plasma exchange, is effective, the data from, Taiwan,

and these places have, traditionally been reporting higher rates of atypical HUS than in the rest of the world. A Kulsum App is another therapy.

Speaker 1 (20:54):

Of course, a Kulsum App has an immunosuppressive effect, which you'd be reluctant to give to patients with sepsis at least acutely, but maybe after you've controlled their infection and the renal dysfunction. If you knew you had a patient with a atypical HUS and you cleared their infection and everything else is getting better, but they continue to have renal failure. You might consider using a Kulsum App in those patients. In addition, there's a whole pipeline of drugs that are being developed for this indication that have less or no immunosuppressive properties. So there may be in the future ways of treating this and the phenotype of sepsis, or maybe it's adjacencies the more liberal you are with definition, the more patients will fit into this bucket. And so will some of those patients benefit from these treatments.

Speaker 1 (21:52):

this is just another, tantalizing piece of data. this is looking at a very large set of patients in the CTSA databases. This is from 14.6 million patient encounters, both inpatient and outpatient. And all I've done here is just ask the question, how many patients are out there with, sepsis and AKI with platelet counts less than 50%. And how many of those have an obvious explanation? Like, how many of those have been coded in the record as having aHUS or TTP? And the point to be made here is that this is a very common syndrome that having sepsis, having AKI and having a low platelet count very low platelet count can occur in as many as 25% of patients, from multiple different institutions and yet, having a diagnosis of HUS or TTP is extremely low.

Speaker 1 (22:56):

What I'm suggesting to you is that we're missing a lot of cases that probably do have this condition, which could be treatable by plasma exchange and or Kulsum App. interestingly in the couple of, institutions that reported a mortality rate, it was exactly the same as what we found in our sepsis, study mortality rates between 67, very tight, data showing 67 to 68% mortality. there's a slide that was missing. I guess I gave you the wrong update version. I just want to come back to this, because I think this group would be interested in this, this isn't published yet, but when we looked at the alpha beta delta gamma phenotypes, there were two groups that had renal dysfunction, beta and delta. And so we wanted to ask the question is AKI different. If you have beta sepsis than it is delta sepsis.

Speaker 1 (23:55):

And the answer is, it is, most of the acute on chronic is in the beta group. Whereas most, of the AKI that occurs, without background of CKD occurred in the delta group and the severity was worse than the delta group and the likelihood of recovery was considerably lower in the delta group, suggesting that not only are these syndromes, these sub phenotypes, these endophenotypes of sepsis, perhaps important for sepsis research and developing strategies for sepsis, but the AKI that emerges in those populations appear to be different as well. So sepsis is not a single disease, intra infection variation, meaning two patients that have the same organism in the same site of infection can be more different than two patients that have the different, organism and different site of infection. And that's interesting and curious to us, there is, the

organism in fact seems to play a relatively small role suggesting that these things like the grasshoppers, are related to different sets of genetic, causes that are, not being driven by the environmental factors.

Speaker 1 (25:08):

Machine learning identifies 4 sepsis subtypes with different distributions of organ failure, different survival, and most importantly, perhaps different responses to trial interventions. And it's not subtle. you saw you could have a positive trial or a negative trial depending on the distribution of these phenotypes within your study. So for those of you out there, and I know there are a few of you who think we'll never make progress in critical care, by doing randomized clinical trials, you're dead wrong. We will make progress, but we have to do smarter clinical trials. And we have to stop calling sepsis, sepsis and AKI, AKI because within those groups, there are different, endophenotypes, which need to be treated differently. And this a tantalizing link that genetic defects known to be causing, a macrophage activation syndrome, for example, in our study were found in six out of six in the, in the cohort of 1,341 patients. And half of these, had a condition that was specific for activation atypical HUS a condition, which we have therapies for which we don't tend to apply to patients with sepsis. So with that, I thank you for your attention

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