The Angel in the Marble: Antibiotic Durations in the NICU - Pediatric Grand Rounds-Meeting Recording 1-23-2026

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All right. Well, welcome to Pediatrics Grand Rounds. Today we're going to be hearing from Doctor Canty. He, I mean, I think all of us know him well. He's professor of Pediatrics here at San Antonio, but he completed undergraduate at University of Virginia, then went home to pursue his MD at Medical University of South Carolina. He then completed his pediatrics residency at Johns Hopkins in Baltimore, MD. And then, as we all also know very well, he completed two separate fellowships at UT Southwestern in Dallas, one in pediatric infectious disease and the other in neonatal perinatal medicine.

He is also heavily involved in clinical research and has published more than 70 manuscripts in peer-reviewed journals. Also, as I think you all of us know by now, he's one of the most personable, friendly individuals that you could possibly interact with. So I'm really looking forward to hearing what he has to say on this topic that involves both of his areas of.

expertise. Please welcome Dr. Canty.

Cantey, Joseph B 1:30

Thank you, Natasha. I I I will get your money immediately after the show. Appreciate it. Thank you for that introduction and thank you for everyone who's logging in so early as the cold weather descends on us. This talk is about antibiotic durations in the NICU, but I hope.

That you guys get the sense that some of these concepts apply equally well to all the other areas of pediatrics. So outpatient clinic management, pediatric wards, ICU care, subspecialty care, et cetera. I I I want this to be more of a framework talk than a neonatal specific talk.

But I'm doing the endology because that's what I know the best, so I have nothing to

disclose.
So a lot of antimicrobial management in the last few decades has centered around antimicrobial stewardship. And I think one of the most common misconceptions about stewardship is that we are the antibiotic police, that we are trying to do our best to drive antibiotic use.
To 0 or as close to 0 as we can achieve and and that is not true. Antimicrobial stewardship does not mean getting antibiotic use to 0. We could get to 0 use tomorrow if we just shut down all antimicrobials, but that would lead to cataclysmically bad patient outcomes. Nobody wants that.
So we try really hard to reframe stewardship as more about optimizing antimicrobial use. So not eliminating, but making sure that the right antibiotic, the right drug and the right dose for the right clinical condition for the right amount of time.
And Sarah Parker, who is a famous pediatric infectious disease doc in Colorado, refers to what she does as being an antibiotic sommelier. She's trying to pair the right wine with the right dinner. So we're trying that's that's what we are trying to do is optimize so.
One of the ways that we can do that is focus on duration of therapy. When we treat an infection, we really have three goals. One, we want to obviously eradicate the infection, whether that's sterilizing cultures or making the child clinically better or. Eliminating any radiographic signs or abnormal laboratory values, whatever that definition of treating the acute infection is, we obviously want to achieve that. We also want to make sure that as soon as we stop the antibiotics, the infection's not going to come roaring back. And so for things like osteomyelitis or.
Hardware infections or bloodstream infections where there's still an indwelling catheter. We want to treat it long enough to eradicate the infection, but we also don't want it to show back up on our doorstep five days later after the therapy is discontinued. And then finally, once those first two goals are achieved, we want to stop, right? So if we can achieve our goal with 10 days.
Therapy, we don't want to go 20 days because the longer we go with antimicrobials, the more we're going to invite in some of those adverse outcomes from long term or prolonged antibiotic exposure like resistance or future infections.
So I love to tell this story. I'm sure that any residents who are on the call right now would probably be rolling their eyes because they've heard this. But I trained in Dallas under Doctor George McCracken, who is one of the Mount Rushmore Peds ID people in the country. He just passed away last year.

And I remember the first time I was on service in my initial console note, I wrote will treat for 14 days. And he said, why are you telling them how long to treat? We're just meeting this kid. And I said because that was the question they asked me. They want to know how long to treat for.
And Doctor McCracken said we're going to treat this kid until he's better and we don't know yet when that's going to be. And even in my primordial peds infectious disease brain back then that that resonated. I was like, oh, that actually, that actually makes a lot of sense. So.
With that being said, how do we get there? So that's the theme of this talk. So Michelangelo said, I'm not even going to attempt the Italian. It's too early. I'll spare you. But Michelangelo has a famous, probably apocryphal quote. A lot of what Michelangelo said, like Mark Twain and Aristotle, he may or may not have said, but he certainly.
Express this theme in letters to contemporaries that have survived to this to this point. He said that we're sculpture. He sees what he wanted to carve and he chisels it out until all the superfluous stone is gone. I saw the Angel in the marble and I carved until it was free.
So how can we do that with antimicrobials? How can we take away every little bit of therapy that's unnecessary, too much, prolonged, and just leave the optimal duration to achieve those three goals that we talked about? How do we find what that is safely?
So we're going to talk about empiric therapy. We're going to talk about definitive therapy when we actually know what we're treating. And then I'm just going to spend a few minutes at the end talking about how we can design studies as a pediatric field that gets us closer to this optimal duration.
So for empiric therapy, obviously we're talking about antibiotics that are administered for to infants or to any children for the first day, day and a half, two days while we're waiting on all of our testing results to come back. So we don't yet know whether infection is present or not. We are treating empirically.
In neonatology, historically that was 48 to 72 hours. So if the baby was born and we drew cultures, we would start empiric ampicillin and gentamicin and we'd give it for, you know, 486072 hours. In the last decade or so that's the field has pulled back towards 36 hours and there are.
Few places who are currently looking at 24 hours, we are one of them. One of our senior fellows is doing a project right now to look at the safety and efficacy of 24

hours versus 36. So we've been able to chisel down a little bit this initial empiric therapy.
The main goal of empiric therapy is we've got to treat for long enough to make sure that those cultures are negative and are going to stay negative or sterile, to use the the term that I would ask the residents to use. We want to make sure those cultures are sterile and so we've got to cover the babies until that point.
The reason it matters is in the nursery setting, these rule out courses are the majority of treatment. So most of our antibiotic use are these 36 hour, 48 hour rule outs. And so if we make even small reductions in the duration of rule outs, it really drives the needle for overall use because so much.
Be in the NICU and nursery setting is that first rule out. There is going to be a lower limit of safety and so there's two factors that really have made us hesitant to go lower than 24 hours, the first of which is the aforementioned time to positivity of cultures. So for early onset infections.
In the first three days of life, as in the nursery and most of the NICU, the median time to positivity is 16 hours. 90% of cultures are going to be positive by 24 hours. 99% are going to be positive by 36 hours. The need to go 48 or 72 hours to wait on the blood culture really isn't there.
But if you go from 36 to 24, there is going to be the occasional baby that has a culture pop up in between there. If you go all the way down to 16 or 12, most of the babies are not going to have their cultures be sufficiently negative yet. And the last thing we want to do is discontinue therapy early just to have the culture pop up.
As positive a few hours later and that baby's no longer on antimicrobial therapy. It's obvious, but it needs to be stated up front. There is a limit to how short we can while we are dependent on blood cultures, and we still are in the NICU and nursery. There is no other biomarker that adequately predicts whether or.
Or not we need to send the blood culture and treat Cbcs, C-reactive protein, procalcitonin, IL-6 had its day in the sun. None of those non-culture-based blood tests are good enough for us to say CRP looks great. We don't have to send a blood culture or Oh my God, CBC is really abnormal. I.
He definitely has sepsis. We don't need to send a blood culture. We don't have that test yet. And until we do, we're reliant on therapy on blood cultures. The second one, and this is after sending emails back and forth. This is about as deep as I can go into this one, but there is some very, very, very new exploratory evidence.
That suggests that there might actually be a benefit to 3648 hours of antibiotics

among the more preterm infants, even if they don't have infection. We know from lots and lots and lots of observational data and now from some trial data that prolonged 5 days, seven days, 10 days.
Early antibiotics can be harmful to preterm babies. We drive up resistance, we drive up the pathogenic bacteria in their gut, and then they have worse outcomes down the road. And the assumption was that if we could get those babies shorter and maybe even avoid antibiotics entirely, that they would do better. But some recent trial data.
Suggests that very short courses compared to nothing may actually provide some benefit. And the theory is that that they may inherit abnormal bacteria from mothers if the mothers have been treated with antibiotics, or if the mothers have been exposed to inflammatory conditions like prolonged rupture.
Or preterm labor, which are very common reasons for preterm delivery in our NICU as in others. And if the babies are inheriting these bad bacteria from their moms, maybe a quick reset actually provides some benefit. Mothers who don't get exposed to antibiotics and don't have preterm labor or.
Lung rupture. There does not seem to be any benefit to treating those babies with antibiotics, but this is very, very new. The paper that this is citing hasn't even been published yet, so everyone keep it to themselves for a few more weeks. But this data is coming down the pipeline right now.
So that's empiric therapy and that is about the sum total of what we know, getting as short as possible where we're still making sure that we're treating long enough for cultures to to result and making sure that we're not going so short that we're accidentally causing harm compared to a slightly longer course.
Definitive therapy. There's more evidence. OK, definitive therapy is where we're talking about treatment aimed at either a positive culture or a diagnostically confirmed condition. And I'm going to use the term confirmed loosely here. So if we're treating necrotizing enterocolitis or if we're treating pneumonia where we don't necessarily have a positive culture in the baby.
But we all know what we're looking at. I'm lumping that into definitive therapy, obviously meningitis, bloodstream infections, urinary tract infections that are culture-based are going to go in this category as well. And you would think that when we talk about definitive therapy that we would have more rigid.
Objective data now that we have a positive culture, and that's not true. In neontology, as in a lot of Pediatrics, our treatment duration for these infections is

really more dogmatic than it is evidence-based. So everyone loves the multiples of seven, the multiples of five. You know, this is just the way we've always done it.
But head-to-head trials that actually compare duration of therapy are pretty scarce. And I'm going to prove it to you because I'm about to take you through all the trials in neonatology. It's not going to take that long. So again, just a reminder about our goals of treatment. We want to treat the infection, we want the infection not to immediately recur and then we want to keep.
The duration as short as possible to achieve those first two goals. So resolving infection when it's culture based is pretty straightforward. Sterilize the culture. Bloodstream infections in babies usually last about 24 hours of positive cultures from the start of impure of appropriate antimicrobial therapy.
So if the blood culture stays persistently positive, either there's a bone infection or a heart infection, or there's a plastic piece of plastic in the baby's body that's providing a source. There's an undrained abscess. There's some issue with source control if the bloodstream is persistently positive culture.
The one major exception to that, which a lot of people on this call have experienced, is Staph aureus. Staph aureus, for whatever reason, loves to stay positive for three days, five days, sometimes seven days, and we hunt and hunt and hunt for a source and we can't find one. That's that's just a a feature of that particular bacterium.
Urinary tract infections clear very quickly, again, unless there's a nephric abscess or some sort of indwelling Foley catheter that's providing a source. But a vanilla hematogenous UTI usually clears very quickly. We don't even routinely recheck in most cases.
Meningitis should sterilize really quickly within a day, certainly by two days. And when we repeat the lumbar puncture for babies with proven meningitis and that Organism is still there, that's a bad sign. And that may mean that they have complex purulence somewhere in their brain that's providing a source.
So culture is easy. Culture. The culture should sterilize. When it's not culture based, it's a little harder. Imaging takes longer to normalize than the baby does. So when we treat pneumonia, those X-rays may lag behind the baby's clinical improvement where they're on room air and they're feeding again and the X-ray still has some schmutz on it.
Necrotizing intercolitis. Same thing. Guiding neck duration by how the baby looks. Abdominal distension. Feeding tolerance is just as good, if not better, than relying on serial X-rays. Now we do both, but we know that the X-ray abnormalities can last

longer than the baby's.
Clinical course. So it's a little bit trickier when the infection is radiographically diagnosed than when it's culture diagnosed. So here's all the data for what we do about these definitive infections. So there are seven, excuse me, there are five studies for sepsis.
Kempley at all in the Journal of Hospital Infection looked at 90 infants, specifically with staff. It was an observational study, so they got treated from 5 days out to 8 weeks and they did not see an association between treatment duration and recurrence risk.
In press right now from Ohio State University and a couple of other centers is this cohort study of 76 late pre-term infants on average with gram-negative bloodstream infections. Again, observational 7 days out to 28 days, no association between duration of therapy and recurrence risk.
Now, both of these studies are observational. So I don't know why they treated this baby with five days and this baby with eight weeks. Clearly there was probably some differences between those babies. So take this with a large bucket of salt. But these are the two observational studies that have specifically looked at duration of therapy.
There are some trials. So Rohatke et al in pediatric child health in 2017 randomized 128 neonates with bloodstream infection to seven days versus 10 days. This was open label. They knew who was getting seven. They knew who was getting 10. They did not see a difference in outcomes.
For Sewell in Peds IDJ and just a few years ago, another open label trial of larger babies with gram-negative sepsis, 10 days versus 14 days. No difference in treatment duration and recurrence risk. They did. Obviously it wasn't a very big trial, but they did comment that they saw a few more line associated.
Complications in the group that had the 14 days, they they had a little bit of CLABSI, they had a little bit of line displacement, line removal. They had one episode of SVT from the line touching the right atrium and those those outcomes grouped were more common in the long group.
But 113 babies total. Chadari in Journal of Tropical Pediatrics 20 years ago randomized 69 infants to seven versus 14 days and again found no association between treatment duration and recurrence risk. Very, very small trial. You can make a solid argument that this was not really power.
To find those differences, they did have two recurrences in the short group. Both of those were line associated. They think they had one recurrence in the long group

that was not associated with the central venous catheter 69 babies 20 years ago. No difference in outcomes. And then more recently, just last year, Duta et al looked at 261 infants out who were larger than a kilo at birth and this one was blinded. So they took, they treated all these babies with for seven days.
And at seven days, if the babies looked good, if they had had clinically resolved infection, then they randomized to seven days of placebo versus seven more days of antibiotics. So this one was truly blinded, a little bit larger study. They did not see any difference.
Between the seven day group and the 14 day group in terms of outcomes, they did see again because many of these babies were term. They did see that the seven day group got out of the hospital a little sooner to take that with a grain of salt because they had to stay to finish out their placebo.
OK. And that's it for bloodstream infection. For a urinary tract infection, there's even less. So there's lots of data for neonates and young infants on how long we need to treat these babies IV before converting to oral therapy. And most of this research comes from the pediatric hospital medicine field. A lot of these babies were not physically in the NICU.
And these studies were being done. So Lawrence and Arctus Jill in 2022 looked at several 100 babies in the first three months of life with uncomplicated UTI. They randomized them. Sorry, they didn't randomize them. It's an observational study. They looked at the babies who went to oral therapy within 48 hours versus the babies who.
Stayed on IV therapy longer. The total treatment duration was the same for both groups. They they generally treated for about 14 days. They did not see an association between how long the IV treatment was and recurrence risk Desai Pediatrics. This is one of the early not not one of the earlier studies, but this one was in Pediatrics.
Same thing. They looked at 115 infants with bacteremic, no association between how long they were on therapy and their recurrence risk. But again, the total treatment duration was long, was two weeks. There is very, very little data on total treatment duration and outcomes, recurrent risk or treatment or.
Dedication Marsh in hospital Pediatrics in 2020 looked at 112 truly neonates. So these were all in the first month of life and they looked at different durations. So this was seven days out to 14 days was the interquartile range. The median was 10. They also in this observational study did not see.

Any association between treatment duration and outcome? It's a theme. They did have one infant with treatment failure who got a long treatment course. He got an immediate recurrence. No one really knew why. Again, one baby out of 112.
There are no randomized trials of total duration for UTI for neonates, which um. The first time I ever did a presentation on this topic, I was like, that can't possibly be true. And I went down the PubMed rabbit hole and then again last night as I was finalizing these slides, I'm like, is that still true? Nope. There are no randomized trials of total duration of therapy for neonatal UTI.
Meningitis. So there there's very little here as well as as you can imagine. Like if we haven't been brave enough to tackle UTI, we have not been brave enough to tackle meningitis. One of the largest studies for pediatric meningitis that gets cited a lot is Molinu from Lancet 15 years ago where they looked at over 1000.
2 month olds all the way out to 12 year olds, so preteens, but they excluded the neonatal period. If they had vanilla community acquired meningitis, usually meningococcus or pneumococcus, they gave them five days of therapy and if these kids were looking good at 5 days, then they ran.
Minimized to five more days of placebo or five more days of ceftriaxone and that study showed no difference in outcomes. And that was the study that really anchored shorter treatment durations specifically for meningococcal meningitis Pediatrics. And this has been shown in adults a lot too. You don't need a prolonged treatment course with pneumococcal or meningococcal.
Injitis that's otherwise uncomplicated.
These babies are obviously these kids are obviously not neonates. So here's the neonatal data. This one study from the Journal of Topical Pediatrics in 2015. It was in New Delhi, India. They randomized 70 babies with culture proven meningitis to 10 days versus 14 days and they looked at 28 day outcomes.
Treatment failure or recurrence of 28 days. They had five babies with treatment failure in the 14 day group. They had one baby with treatment failure in the 10 day group. They only had 70 kids, so that was not statistically significant. So there was no difference in outcomes between 10 and 14 days.
That is the sum total of our knowledge about duration for meningitis and neonatology. They were extremely brave to pull that study off. They did not find a difference.
OK, pneumonia. Pneumonia is even harder, OK, because neonatal pneumonia is very, very challenging for us to diagnose with certainty. Most of our infants, just like older

kids, most of our infants with pneumonia are going to have sterile blood cultures. And as everybody knows in the NICU, a lot of things look like pneumonia. So on the left there.

The top box is a picture of a baby with respiratory distress syndrome or surfactant deficiency, and the bottom picture is a kid with pneumonia. Maybe they look exactly the same, and even the radiologist will say, you know, granular opacifications consistent with surfactant deficiency cannot exclude pneumonia.

Yes, got it. We've very, very rarely ask for or or desire bronchoscopy. I I I think the risk of that procedure probably outweighs the benefit. And if we swab the upper airway, if we get into tracheal tube aspirates or or oropharyngeal suction, everything above the carina is not sterile. So we grow.

Microlab will tell us mixed respiratory flora and leave it to us to work it out. So pneumonia is hard, but ironically we probably have some of the best data for pneumonia. So Mather, yes, same Mather. Mather et al in 2018 looked at a randomized controlled trial of four days versus seven days for neonatal pneumonia. And they found that in these term babies, four days and seven days had complete success. That was plenty for both of them. Now again, some of those babies may not have had pneumonia in the first place. They may have had RDS or TTN where they're going to get better with or without antibiotics. But in these 70 babies who were labeled as pneumonia, they all got better with four days or seven.

In the United States, a similar study from Bill Engel up in Dallas, 73 babies. If they were term and they looked good at 48 hours, there was no difference in outcome between four days and seven days. But when that same group repeated the study a few years later and they looked at 2 days versus 4 days.

They actually did see treatment failure with two day therapy and they stopped that study early, which is why there's only 26 babies included. So seven days and four days seem to be the same, but four days versus two days, they started to see a difference. So this is a good example and we're going to talk about this more in a few minutes, a good example of very cautiously sort of finding your way to. Towards that optimal duration without risking patient safety any more than minimally.

Necrotizing enterocolitis. I will not bury the lead. There are no randomized control trials for duration of therapy for neck. There are three trials that look at what medicines we should use and generally those studies have shown that either no difference or if you include anaerobic therapy, which we all.

Do these days, so this these studies are never going to get repeated. But if you include clindamycin or zosyn and you include anaerobic therapy, you get a higher rate of survival, but you also get more strictures, which I've always interpreted as some of those babies who would have passed away are now surviving with strictures. But that's not necessarily what's happening, but that's at.
Three trials looking at drug selection, 0 trials looking at duration. Barring any trial data, what's everybody doing? So surveying neonatologists around the country paints this picture. So for a maybe that's neck, maybe it's not a neck rule out. Usually we'll go two days, three days and.
The blood cultures are sterile and the baby looks better. They have proven neck, meaning they have pneumatosis or other specific radiographic features of necrotizing enterocolitis. People are generally going somewhere between and if they're little bit more distended or maybe they have some blood in their stool, maybe we'll go.
Longer. If it's just pneumatosis, maybe we'll go shorter, but it's very hand-wavy and very vague. If it's surgical neck, meaning bowel perforation or impending bowel perforation, we'll go longer. Again, conceptually it makes sense, but not driven by a lot of trial data. Interestingly, there's not really any.
Evidence to support that within the same stage of neck that shorter or longer treatment differences seems to make a difference in terms of outcome or recurrence risk. This has actually been shown in the surgical data, but it's backed up by some of the observational neonatology studies as well. So does it really matter if we do 5 days versus 7 days for?
Sage 2 neck, maybe not. We don't. We really don't have a tremendous amount of evidence in this particular area. OK, so empiric therapy and definitive therapy, you guys are now fully up to speed with the entire neonatology division. You know every study that's out there. It took 15 minutes.
So how do we get to the optimal duration? So with with this graph, with benefit being on the Y axis and the length of therapy being on the X axis, we know for every infection and every baby, there's going to be a a duration that's too short. It's not going to be long enough to eradicate the germs. It's not going to be long enough to prevent recurrence.
But we also know that if we leave them on for months and months and months and months, we're going to no longer be reaping any benefit and we're going to be accumulating antimicrobial side effects, drug toxicity, resistance, cost, length of stay,

et cetera. Somewhere in there is a sweet spot where it's long enough to maximize benefit, but not so long that we start to.
Get on the down slope of diminishing returns. So how do we find that spot? So I. And cobbled this together from other smarter people who have written on this. But this is a proposal for framework of duration research. And again, this does not have to be neonatal specific. This applies just as well to all the other specialties in the hospital or and in the clinic.
So really, there's three pillars of this framework. One, non-inferiority of shorter durations is superiority, right? If we can get the same bang for our buck with slightly shorter courses, slightly shorter should be the default winner. Two, we have to be really, really careful of large generic one-size.
Fits all answers. Every clinical situation is different. Every kid is different. Every bug is different. And so these big sweeping statements, and I've made some of them in the last few minutes, but these big sweeping statements about, oh, we should treat meningitis this way we should be very skeptical of.
And 3rd, when we're doing these studies, the durations that we're looking at need to be different enough to be clinically meaningful. We're spending time and money and patient safety and IRB time. We've got to make sure we're looking at a meaningful difference, but we can't look at a difference that's so large that it's potentially dangerous to the patient. We have to do this.
Carefully. So let's take these one at a time. Noninferiority equals superiority. Can't escape one of my talks without seeing this slide. I apologize. So in animal models and in humans, as soon as you give a single dose of antibiotics, we see the number and diversity of bacteria in the gut.
In the skin in the lungs start to drop, and this happens over hours to a day or two. Even with only one dose, this new baseline of bacteria, this dysbiosis takes weeks to months to recover from, and in in neonates it may take over a year to recover from. We see this in all the microbiome, so one dose matters.
And we see this.
In all the microbiomes, this, this, this beautiful taxoma of all these different non-inflammatory bacteria that are that are preventing E coli and Klebsiella from moving in, that are preventing inflammatory cytokines from being generated that probably play a significant role in preventing autoimmune.
Immunity preventing asthma, eczema, inflammatory bowel disease, diabetes, one dose of antibiotics and we bleach all that out and you're left with this very low

Organism, very low diversity gut or lung or skin. I always use the I like to use the coral reef example because I think it's easy for people.
To think of, but it doesn't take a lot of antibiotics to go from the picture on the left to the picture on the right.
We also know from clinical studies in infants that each additional day of therapy beyond the normal rule out, so beyond 36 to 48 hours, each additional day of therapy has been associated with increased risk of these bad outcomes, late onset infection, necrotizing enterocolitis death.
And this has been shown over and over and over and over again in a lot of different clinical settings. And it matches up with what we know about the microbiome. So if we go 2 days of therapy for early onset sepsis versus 7 when the baby doesn't have a, you know, when there's no positive culture, those five extra days matter. They're increasing the risk of somebody.
These bad outcomes, and it's not just the preemies. We see this even in term kids, all of these things, yeast infections, drug resistance, atopic disease, these things are rare in term kids, but the relative risk is the same. So maybe we have to treat 100 babies to see it in a term kid as opposed to only.
10 babies and a preterm baby, but the data is very clear that each additional day matters. The primary risk for all the bad stuff on this slide is how long these babies were exposed. I'm beating a dead horse at this point, but we want to achieve our goals in the minimum amount of therapy resistance. Same thing. So this is this is a human.
Um study that was published in Nature a few years ago and you can see down on the X axis, those are days of antimicrobial therapy and on the Y axis is basically concentration of bacteria. These babies got four days of an aminoglycoside and you can see that everything plummets in the 1st 12 hours.
But then while the baby is still on aminoglycoside, either I think it was streptomycin or gentamicin in this particular study, the anaerobes are coming back and then the aerobes start to come back. I promise you, if they're coming back while the baby's still on therapy, they are now newly resistant to that aminoglycoside and it took less than 24 hours.
For them to start to recover with their new resistance genes. So duration matters. So if we can achieve the same outcome with a shorter course as we can with a longer course, the ties should always go to the shorter duration. Just like in Pro Football, ties go to the receiver, except in this case. Apologies to the Bills fans.

OK, secondly, we've got to be careful of these large, super generalizable studies because they may not be. They may not be as generalizable to us. The most famous duration study that exists right now is the balance study. This was published in the New England Journal of Medicine, not last year, two years ago.
In 2024, they looked at over 3600 adults in any ICU setting with any positive blood culture and they randomized them to seven days versus 14 days and they built it that way to be as generalizable as possible. So they took all comers, neuro ICU, medical ICU.
ICU, surgical ICU, CLABSI, bloodstream infection, bloodstream infection associated with kidney disease, right. They took them all and what they found was that there was no difference in 30 day outcomes between seven days of therapy and 14 days of therapy.
Which is great. That is a very big, very generalizable study, and it points in the same direction that a lot of the other data does. But especially in pediatrics, and especially especially in neonatology, these host factors matter a.
Teenager on the oncology ward is not going to be the same as an 11 year old in cystic fibrosis clinic is not going to be the same as a three-week old 24 weeker in the NICU. So I don't know. Trials are always going to try to maximize their generalizability, but I don't necessarily know that we our specialties need to air on.
On the side of generalizability, I don't know what the right answer is, but I'll ask you, those of you who are on the call right now, which would you rather have? Would you rather have a thousand baby trial of three versus seven days for UTI or would you take those thousand babies and break them up into four different trials, one for micro preemies, one for term gifts?
Kids one that just looks specifically at E coli and Klebsiella, and maybe one that looks specifically at kids who are in the NICU and have renal ultrasound or VCUG abnormalities.
Validity for that specific patient population versus generalizability is a tug of war and I don't know what the right answer is, but we have to think about it as pediatrics works towards finding these optimal durations. So oncology is excellent at that. Oncology is always my go to when it comes to clinical trials, but oncology is really good at this.
Very good at at zoning in on the particular disease they're trying to study and then making it as generalizable as possible within those confines. So that's probably what we need to think about is is making our target and then within that target being

generalizable across centers, across whatever.
OK, thirdly and and and well, not most importantly, but thirdly, durations have to be big enough to be meaningful, but not so different as to be dangerous. And just just to give you an example, obviously they have to be adequately powered. Some of those studies that have already happened that we whipped through when we were talking about bloodstream infections are interesting.
Interesting, but if you're only enrolling 60 kids and you're looking for these relatively rare outcomes like treatment failure or recurrence, no difference between groups is not really going to move the needle. So we've got to have trials that include enough kids where we feel comfortable about the safety results.
We also need the difference to be clinically meaningful, right? Two days, three days, four days. Like if you spend $10 million and work on a multicenter trial looking at 15 days for pneumonia versus 14 days for pneumonia.
That's a waste of money, right? No one is going to care about that study. So we've got to have enough difference where we can find something that's going to change practice. But it can't be reckless. Like no one is going to approve, I hope, a study that looks at, OK, we've been doing 21 days for peritonitis. What if we just did 3 like?
We have to tiptoe up to that Cliff edge and find how short is too short. We can't just go sprinting off of it like wild E coyote and plummet. So we we've we've got to be very careful about how we design this. And then finally we have to be very consistent and clear about how we define.
Treatment success, recurrence, failure. We need to make sure we're all using the same measuring sticks because these trials are going to need to be meta analyzed to carry a lot of weight. So if one person says treatment success is if the bacteria is gone at 7 days and someone else says no, treatment success is if the kid's doing well at 30 days and they haven't had a recurrence, we're not.
Going to be able to meta analyze this study. So we need to all get on board with what a good outcome is and obviously that's going to depend on the on the given clinical condition.
So just for an example, I did this one already, but within neonatology, A randomized control trial of 21 days for stage 3 neck versus 3 days for stage 3 neck is never going to happen. One, it's unethical. 2, it'll never make it through IRB 3, even if it did, no neonatologist. I wouldn't and don't think anyone else in my group would. No neonatologist and no.
Surgeon is going to agree to this. So we've got to be a little bit more judicious about

the time. So 21 to 14 to 10 to 7 to 5 to 3 is sort of asymptotic curve as we approach how short is too short is the way it's going to have to be because anything bigger than that is probably not fair to the clinicians and certainly.
Not fair to get. OK, again, neonatal pneumonia, they've done this already. They're a great example. So we know that seven days is the same as five days. We know seven days is the same as four days. We have a little bit of evidence to suggest that four days might be better than two days. So if you truly think they have pneumonia, they don't really need to stop at 36 to 48 hours because there is.
Some evidence to support a better outcome with longer therapy, but it's little. It's 26 kids at one center, so.
OK, finally, see, I lied. I said there was gonna be 3 legs to the stool, but it's a four-legged stool. The last one, just for consideration as I as I bring this talk in for a landing, is should we maybe abandon a priori durations of therapy altogether? And maybe we just treat them until they're better. We treat them until they're clinically improved, which is what Doctor McCracken.
Said to me 20 years ago, treat them until they're better. And the way that looks operationally is this. There's actually a study in neonatology right now that's going on in Denmark called the duration study, which is a great name. I'm always jealous of really good eponyms. The duration study is in process. I don't have any results for you.
But they're looking at 400. They're looking for 488 term or late pre-term babies with, pardon my eye roll. They're looking for suspected early onset sepsis, but sterile blood cultures. So they're looking for culture negative sepsis, which whatever, it's a distinct clinical picture. They're they're tackling it. I'm happy for them.
But instead of looking at specific durations, what they're going to do is they're randomizing these kids one to one versus standard of care, which I think for them is for 10 to 14 days. Or instead of a shorter duration, they're randomizing them to we're going to stop once they are clinically well and they've defined that as no longer tachypnic.
No hemodynamic instability. Their C-reactive protein is less than 3030 milligrams per liter, which is the same unit we use. I don't love cultronegative sepsis. I don't love CRP and neonatology, but I do very much love this 14 days no matter what versus we're going to treat them until we all agree.
He looks better cause he's on room air and he's comfortable and his blood pressure's fine and his heart rate's fine and his C-reactive protein is now undetectable. I can live

with that. And they have defined their primary outcome as treatment failure, meaning death, recurrence of sepsis or readmission within 30 days. They've got a well-defined.
Find primary outcome and then their secondary outcome, which is really the focus is how long are we treating these kids and how long are they stuck in the hospital. So again, I don't have results yet, but this is a study that is they're not doing 14 versus 7 or 14 versus 5, they're doing 14 until or until better and we'll see if this one.
Shorter and has it just as good, if not better outcomes. Really like them. OK, conclusions. So one we will we want to treat infection until it's resolved and not a moment longer. If we can, if we can pull that off. No trial in neonatology has shown superiority of a longer treatment compared with a shorter treatment.
But there is a theoretical lower limit that is too short. And we again, we've kind of seen this with pneumonia. We will eventually find this with other infections. We'll find it with bloodstream infection. We'll find it with meningitis once we put on our big boy pants and get brave enough.
So we have to tiptoe up to that point. We we we can't go crashing into the duration that's too short. That's not fair. We got to do careful step wise clinical trials to find that lower limit that is too short and then individualized therapy that ends when patient specific goals are reached.
Is probably better than one-size-fits-all durations for these given conditions. To pull that off, we have to be very meticulous with our study design. We have to be very clear about what's better, what's a bad outcome, what's failure. We have to all be on the same page, but if we can pull that off, tailoring therapy to the individual.
Is probably our winner. And once again, I'm going to cite oncology. How long is chemotherapy going to be for my child with leukemia? We don't know yet. We're going to see how they, how they, how they go through this and we're going to end when we've achieved specific goals for your kiddo.
Thank you guys so much. I appreciate your listening. I tried to leave us about 10 or 15 minutes before faculty meeting for questions. I appreciate you guys being here. Everybody stay warm and safe this weekend.

Varughese, Natasha A 42:57

Thank you so much, Doctor Canty. That was a fascinating talk and it's really impressive how how you summarize the entire field in such a short talk. Doctor Pearlman had a good question in the chat. He asks, could a negative rapid bacterial

PCR panel be used while cultures are pending to stop antibiotics before 24 hours? hours.

Cantey, Joseph B 43:18

Jeremy, it's a good question. I I think the molecular era that we're entering and and I say we, I think hospital medicine is spearheading this one as much as anybody. It has its blessings and its curses. The advantage is, yes, it would be, it would be super fast. They're very, very sensitive as as as we know.

So if you if we could develop a rapid Multiplex bloodstream PCR that says, Yep, there's definitely none of all these bacteria that you were worried about, then that might be something that would forego the need for culture. So a negative molecular test.

Is would be handy once we have it right now the molecular test that the micro lab runs, they're only running on positive cultures. So we get the once the blood culture is positive for gram negative rods or whatever, we get what it is and are there any resistance genes really quickly, but they have to still wait for the culture to grow. But I think Jeremy's question is.

Once we can run that on direct patient samples, yes, that'll be super fast. The downside is those molecular tests pick up DNA, so it'll pick up dead bacteria just as easily as it will live bacteria. So in neonatology or in newborn medicine.

If mom has choreo, mom gets amp and gent, delivers the baby. The baby's blood culture is sterile, but there was some GBS or E coli in the baby's blood that was killed by mom's antibiotics. The molecular test is going to go GBS detected and we're like little lumbar puncture, 10 days of therapy, right? And in the culture days, that kid would have had a sterile.

Culture we go home at, you know, 48 hours. So we have to when molecular testing gets here, we just have to remember how sensitive it is and build that into our workflow. Just like when we swab a kid with RVP, a respiratory viral panel and they've got Rhino intro and we look back in the chart, Rhino intro 3 months ago, it looks like it's still there because they're so.

Oh, sensitive. We have to be. We'll have to be careful. But yes, I do think molecular is going to help us shorten duration safely when they're negative.

Varughese, Natasha A 45:16

Daniel V on the topic of antibiotic duration use, can you give your opinion on data on acute otitis media 5-7 versus 10 days?

Cantey, Joseph B 45:27

So Full disclosure, it's been a while since I've since I've personally done otitis and I think this, it's a good example. Obviously it's super common. It would be very studyable. This is an example of how we've already started to move towards patient centered outcomes, so.

If that particular kid is old enough and healthy enough, we'll even do watchful wait. I say we, I don't do it anymore, but but watchful waiting is an option. So zero days of therapy can result in the same outcome. If they got infection that the provider feels like needs to be treated, there's very limited data on how long we need to treat those kids.

I think a study of, you know, amoxicillin for seven days or 10 days versus amoxicillin until the ear pain is resolved for 48 hours would be very doable and very interesting and and and with with otitis, you know, pretty clear failure is if within the next month they have otitis in that same.

Year or heaven forbid, any separative complications of otitis, like if they get mastoiditis or or epidural abscess, obviously that's going to be very much a treatment failure. So I think those studies are doable, but to my knowledge that they have not happened yet.

Varughese, Natasha A 46:43

OK, um, Doctor Meyer asks, has procalcitonin come to neonatology?

Cantey, Joseph B 46:47

Um.

I plead the 5th. It is not come to our division, the one that's probably the best.

Not saying that's accepted. The ones that is most used in neontology. Obviously CBC with differential has been around forever and it gives us a lot of information on other cell lines, so that's never going away. C-reactive protein is probably the one people reach for the most. It's sensitivity and specificity in preemies is about 6570%.

So it's slightly better than a coin toss. I don't love it. I don't think we use a lot of it in our group. We do reach for it sometimes when we know we have an infection that's a cult, like a neonatal osteo or a neonatal septic arthritis, and maybe we want to trend

something. But from a diagnostic standpoint, I'm not a fan.
And no, procalcitonin not really around yet. Now that being said, for any, for any of the, I can't see the walls on the call. If there's any residents or fellows on the call for term babies, those inflammatory markers become better. They're not perfect, but they're better and certainly for the babies who are presenting to the Uh.
234510 weeks with neonatal fever, procalcitonin and and CRP and CBC is a big part of the of the neonatal fever stratification risk. So I'm not poo-pooing it on older term kids, especially term kids coming in from the community, but in the NICU it's utility. Is limited.

Varughese, Natasha A 48:16
Doctor Perlman, Dr. Perlman had a second question about he was wondering if you could address other specific cases. He was wondering about sinusitis, osteomyelitis. You kind of already addressed otitis media.

Cantey, Joseph B 48:26
Yeah, Osteo is a is a great story. You know these these infections that are generally both either radiographic and or clinically proven. You know a lot of times with Osteo we have the MRI and we have bone culture, blood culture. So there's not, you know, there's not a lot of debate for those.
This is a good example of we just need to be rigid about what treatment success is, because it'll take longer for the MRI to normalize than it will for all of the bacteria in the bone to be dead. So in Doctor Perlman and I's career, we've seen it trickle down from.
You know, you get do not pass go, do not collect $200. You're coming into the hospital, you're getting a PIC line, you're getting six weeks of parenteral therapy because we know that's what it takes to to treat this. And then it became, well, maybe we could go to oral and finish out six weeks. And then it became, well, maybe we can do oral for four weeks. And so we're seeing that inching towards.
It's shorter and shorter durations, but there obviously is going to be a duration that's too short and going to lead to recurrence of osteo, which is which is a horrible outcome for the kid. So I think at the moment the uncomplicated hematogenous osteo and an otherwise healthy kid, we're kind of down to the 3-4 week range, I think 4 weeks.
Probably the medium. If anyone's going to go shorter than that, it should only be in

the setting of good surgical drainage and then well-defined clinical trials with a sharp line about what's failure. You know, how do we know that two weeks did or didn't work?
And again, they said I'm sitting here doing multiples of seven instinctually. It doesn't have to be two weeks. It can be we're going to treat you until your pain is gone, your CRP is, you know, normal and you've had at least X number of days of therapy and whatever day that is, we'll stop, right? It doesn't have to be a a multiple of seven or a multiple of five.

Kamat, Deepak M 50:17
Brooks has question.

Cantey, Joseph B 50:18
My favorite, my favorite infection is, is, I'm sorry, is neurocysticercosis.
Neurocysticercosis in its parasitic form before it calcifies, we treat for eight days. I always wondered where the eight came from. It's the only one that has this weird even number in the in the red book. Eight days for neurocysticercosis.

Kamat, Deepak M 50:39
Doctor Brooks has a question. I think he has raised his hand.

Cantey, Joseph B 50:42
Hey, boss.
Or maybe he's just saying hi. Hi.

Kamat, Deepak M 50:53
Doctor Gong, you have a question you can ask.

Gong, Alice K 50:56
I do. Thank you, JB. That was excellent. Now I just want to challenge the infectious disease person that not all illness is infection. So if you use Wellness as a import, you may not be dealing with an infection, but some other.
Cost and I was a challenge to necrotizing enterocolitis is always infection because we know is a lot of can be inflammation and other things. So if you're looking for an

important of Wellness, you may not.
Find your cause of illness.

Cantey, Joseph B 51:37
Yeah, I 100% agree. And I think that's why pneumonia.
Had so much, why it was so simple, let me not use the word simple. I think that's why pneumonia was able to peel down the duration of therapy and studies back in the in the early 2000s. For that reason, I think a lot of what we treat as pneumonia, me included, is probably not actually bacterial pneumonia. It's TTN, it's meconium maspiration, it's.
RDS. It's a little bit of everything and the contribution of bacteria is minimal, if not zero in some cases.

Kamat, Deepak M 52:12
Dr. Saidner, you have a question.

Seidner, Steven R 52:16
Wonderful presentation as always JB question if there with your new data, if there may be some benefit of 24 to 48 hours of antibiotics to some babies, how would we ethically find out if there was a benefit to some we weren't suspecting sepsis?
Some preemies we weren't suspecting sepsis.

Cantey, Joseph B 52:37
When, when we, excuse me, when we weren't suspecting at all, like would we? That's a great question. So again, the study that that is coming from is still embargoed and I I don't want to overstate our findings because I want everyone to read it themselves and decide, but the babies who were included in that study were all babies that were suspected.

Seidner, Steven R 52:50
Great.

Brooks, Edward G 52:52
OK.

Cantey, Joseph B 52:57

Of being at some moderate risk for sepsis, the babies that were excluded from the study were babies that were too healthy or too sick. So you're saying how do we look at that healthy group and ethically expose them to anthem? I'm not sure.

Brooks, Edward G 53:03

Yeah.

Cantey, Joseph B 53:13

I'm not sure I.

If there was sufficient data to support that, that there might be some.

I can answer this, but I can't do it without talking about any bongo data. I I I think that we're going to very soon have microbiome data to suggest whether or not we're barking up the right tree if we are correct. And it's this dysbiosis that mom has had forced upon her by obstetrical antibiotics.

Or or inflammatory pregnancy conditions. Then the flip side of that coin would be maybe these other moms have normal bacteria and those babies don't need treatment. That's what that's the preliminary data. But we'll know for sure with the we'll know better with the microbiome data.

If we're right about that, I I have a hard time seeing us randomizing like a 29 weeker who was born by a C-section for pre-e and comes out. It looks great. I think it's going to be really hard to give them antibiotic exposure unless we're certain they're they have a chance of benefiting from it. That's gonna be tough. That's a good question.

Seidner, Steven R 54:07

Good.

I guess, I guess the broader question would be, do you think we might hit an era where we're not only using antibiotics to treat potential or real infection, but we're also using antibiotics to change the microbiome?

Cantey, Joseph B 54:28

I do. And I think it's going to have to be, it's going to be a reversal for us. You know, we infectious disease, we don't even like it when people use erythromycin for gut

motility or use azithromycin for its anti-inflammatory. We're like, no, those are for one thing and one thing only. And then we're going to change and be like, actually, you know what, we can tailor the microbiome and maybe we enter.

Seidner, Steven R 54:39
Mhm.
Mhm.

Cantey, Joseph B 54:48
World where we get microbiome testing on a baby or on a child. We get it back quickly and we say, OK, based on this fingerprint, you need a day of aminoglycoside, you need one dose of Bactrim, and you need this probiotic for four days. And that's going to reset you to what we think the healthy microbiome. I think we might get this very.

Seidner, Steven R 54:59
Yeah.

Cantey, Joseph B 55:08
Very precision, tailored medicine 5/10/2030 years from now as we follow this path down as we learn more and more about the microbiome and how we can modify it.

Seidner, Steven R 55:19
Thanks.

Cantey, Joseph B 55:20
In the meantime, before Doctor Gong tackles me. In the meantime, avoiding antibiotics that we don't think we need skin to skin care, breastfeeding, kangaroo care, mom's microbiome, family's microbiome, transferring back and forth with the baby is still the best evidence we have at the moment.
Yeah, there's this thing, Doctor Gong. I didn't want you to come come head on me later.
Oh, gosh.

Brooks, Edward G 55:47

JB, this is Ed. I my mic was muted previously. I apologize. So I I like your comment about Doctor McCracken's comment that when the baby gets better and I'm wondering if people have approached it from that standpoint. In other words, what are the?

Cantey, Joseph B 55:49

Oh, hey, that works.

Brooks, Edward G 56:03

Clinical parameters at getting better means is hard to quantify specifically. And of course, a lot of these studies include expert opinion, and often the physician's opinion that the baby looks better has been unquantifiable. But you know, from an expert clinician that that's one of the most important things. Doctor Maria gave a nice lecture.

On accumulating all the laboratory data and these other clinical parameters and outcomes research and using machine learning, et cetera. And I'm wondering if these studies, whether they go 14 days for track those parameters and say, OK, this is correlates with success.

Whatever those parameters might be.

Cantey, Joseph B 56:47

Yeah, the the ones. So the the ones that have looked at those have been more focused on.

Risk factors leading up to the neck or coming out of the neck. They haven't really focused on duration, but you're right, we.

Certainly computers or or Doctor Blanco, she's got the database. Can we tie in more objective parameters to how long we need to treat, you know, machine learning for X-rays, trending CBCS, trending abdominal circumferences, things like that. Right now it's all very, very subjective. So anything.

Brooks, Edward G 57:09

OK.

Cantey, Joseph B 57:26

We can anchor to objectively may help us if it turns out to be predictive.

Creation allowed.
Like that. Um, it's sorry in the in the bot.

Kamat, Deepak M 57:38
There's a question on CME and Vance, Val and Galsan Kluvir in the chat box.

Cantey, Joseph B 57:43
Yeah.
That. Oh boy. Um.
That's a that's kind of a whole different talk. The question is valganciclovir for congenital CMV, especially if symptoms are detected, if the CMV is detected later. Long, long answer and and to be respective of time, I will just say the hardest thing for us, for me and the other CMV.
Docs around the country is if you have congenital CMV, you should be shedding virus in your urine at delivery and for a few, you know, for a long time after that. If you acquire CMV through breast milk, even on the first feed, you know when you're born and you go skin to skin and latch for the first time and you acquire CMV, it'll take about.
Three to four weeks for that CMV to show up in your urine. So testing before 3 weeks, we know it's congenital. If the baby's tested at a month or later, it can be very hard to know for sure if it's congenital or postnatal. And those have very different implications. So in the NICU now we universally screen for CMV, which is great. Some states are trickling towards universal screening for everybody. Minnesota and Massachusetts are both doing it. It's hard to know whether we should treat with Valgan when the kid's diagnosed at two months and we're like, I don't know if this is congenital or not. We don't usually treat postnatal disease or we don't for very long anyway.
I hope that answers. And then Thomas Tran, MS3. Hi, Thomas. Has there been evidence for early warning systems based on vital signs? Yes, this is also a whole different talk. But just like in obstetrics, when they use fetal heart monitoring to look at the the the autonomic happiness of the baby, there is evidence that.
We can do that with babies in the NICU, looking at heart rate, looking at accelerations, looking at bradycardio episodes. University of Virginia has a proprietary one called the HERO system, which takes a lot of getting used to. But

basically it's like a traffic light. It's green, yellow, and then it goes to red as the sepsis risk goes up and it's.

Brooks, Edward G 59:44
Yeah.

Cantey, Joseph B 59:48
Based on things that we would be familiar with from obstetric care and we watch them in pediatrics neonatology informally, we say, oh, you know, this baby had five apnea, 6 bradycardia episodes overnight. That's new. We need to look at infection. This is just a way to formally quantify that up on the monitor where people can see it. It works better at UVA than it does when they've outsourced it to other people. I think it just takes a lot of getting used to, but it is one more tool to be like, oh, maybe we should think about that baby in bed 7 because he just went to yellow because of his heart rate parameters.
Oh, and sorry, I don't know if we have time. Rachel Pearson. Hi, Rachel. Parents worry about dysbiosis and long-term allergies. Some refuse antibiotics even when they are clinically indicated. Yeah, it's the goal. I would phrase it.
As the Goldilocks, there is definitely durations that are too long and we want to minimize that dysbiosis, but there's also durations that are too short. And so you know, just like vaccine hesitancy, which is, you know, parents generally are just trying to do what's best for their kid and.
In the context of your busy clinical days, it's finding the minutes to sit down and be like, look, I understand where you're coming from. But what's best for your child is that we get this infection treated. And I promise you, as soon as it's treated and it's safe to stop, we're going to stop because I'm with you on the dysbiosis. We don't want that to happen.
But it's been a long, again, it's been a long time since I've had to sit down in the clinic setting and try to convince anyone of anything. So I I have full respect for the people who fight that fight every day because it's it's no longer me.

Kamat, Deepak M 1:01:37
Thank you, Doctor Canty, for that wonderful presentation. I think Doctor Vargis is off. I don't see her. Thank you all for attending this on in grand round. We have a faculty

meeting in a few minutes. See you all there. Thank you. Have a wonderful weekend. Thank you.

Brooks, Edward G 1:01:41

OK.

OK.

Cantey, Joseph B 1:01:52

Thank you, everybody. Thank you for having me. Thank you to Doctor Vasquez for covering me. I'm on my way.

Calderon, Delia stopped transcription