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John Williams: Once again, from UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics. I'm one of your hosts, John Williams.

Steph Dewar: And I'm Steph Dewar. I'm vice-chair of clinical affairs and the co-director of the Pediatric Residency Training Program.

John Williams: And I'm the division chief of Pediatric Infectious Diseases.

Steph Dewar: Today, we're thrilled to have with us, Dr. Andrew Nowalk, who, in addition to being a medical doctor is also a PhD. He's Associate Professor of Pediatrics at University of Pittsburgh School of Medicine and he's a member of The Division of Infectious Diseases.

Steph Dewar: Dr. Nowalk, welcome. We're so happy to have you here with us.

Andrew Nowalk: Thank you for the invitation this morning. I appreciate the opportunity.

Steph Dewar: So, you, Andy, have a lot of varied interests and I'm just wondering if you could maybe let us in on what's the latest with the infectious disease recommendations nationwide, or things that you're seeing here at Children's that folks might be interested.

Andrew Nowalk: Yes, Steph. I wear many different hats here. In my clinical interests, one of the things I've had a long interest in since my fellowship days is Lyme disease. I am in the interesting position of having started doing basic science research in Lyme. I have a PhD in microbiology. Then, while I was doing that basic science research, we have had an epidemic in Western Pennsylvania of Lyme disease. So, we, in our group, and me as a clinical and laboratory researcher, have had the opportunity to watch an epidemic happen, which has been fascinating from a scientific point-of-view, and we've been able to describe a lot of very interesting things that happen to children with Lyme disease. We published some papers this year in Clinical Infectious Disease and some other journals about our experience and I think we're learning important lessons here in Western PA.

Andrew Nowalk: I would say that what's new and innovative is more so what the Red Book has done this year. So, for those of you who are listening who are engaged in primary care pediatrics, or see patients in the emergency room setting, or are in parts of the country where children get hospitalized for Lyme disease, if you open up your 2018 Red Book, what you'll find are some significant changes in the Red Book recommendations for the treatment of Lyme disease that actually

have gone ahead of the Infectious Disease Society of America recommendations.

Andrew Nowalk: So, the IDSA, which is what John and I belong to as a professional association, has a longstanding set of recommendations from 2007 for the treatment of Lyme disease and those have been pretty much mirrored by the Red Book for the last ten years or so. Red Book in 2018 came out and changed some significant recommendations and probably the one that will be the most surprising to folks, is a universal recommendation for the use of Doxycycline under the age of eight in children with Lyme disease-associated facial nerve palsy. This is a big change for our traditional teaching because both of you probably remember from medical school, anything that ends in "-cycline" stains your teeth, so you should never use that in a child under the age of eight unless they're in dire circumstances. One of the good examples John and I would know would be Rocky Mountain spotted fever, it could kill the patient. So, patient first, teeth second, in that situation.

Andrew Nowalk: Well, the Red Book this year went ahead, based on some data from European studies primarily, but also some US data, and made a recommendation that for facial nerve palsy specifically, any child at any age can be treated with Doxycycline. So, that's a pretty surprising recommendation. It is based on a lot of data in the last ten years that have started to destroy the connection between Doxycycline, specifically, and tooth staining. The data on Tetracycline is old and good. Tetracycline definitely can stain your teeth. Doxycycline, even in the early days of appreciating the link between Tetracycline and dental staining, was not thought to have the same capacity. In some studies that have been done in Israel in 2007, and more recently, some US studies looking at kids who've received multiple courses of Doxycycline for the treatment of presumed Rocky Mountain spotted fever, have found no increased incidents of dental staining.

Andrew Nowalk: We are becoming more and more comfortable with the fact that it can be used for short courses in children under the age of eight and see no appreciable dental staining. There's a little bit of pushback. Gary Wormser, who's a very prominent Lyme disease expert in the adult field has just published a paper recently saying that maybe this a little bit too quick to make that recommendation, but it's part of the Red Book now. So, when we see a Red Book change like that, it's typically based on some pretty good data for pediatricians to consider. Our group has used Doxycycline for prophylaxis in children as well as under the age of eight for the treatment of Lyme disease, not just facial nerve palsy, on a fairly regular basis based on European and other data, and we've had no problems with tooth staining. I think that's probably the biggest change when you think about the changes in the recommendation.

Andrew Nowalk: You'll also see a much better set of recommendations for duration of therapy. I've joked with my group for years that if you want the worst duration of therapy table in the history of mankind, look up duration for Lyme disease. One

of the IDSA recs, says 10-28 days, with is the definition of a non-useful duration of therapy. Now, the Red Book is getting a lot more regimented, and so it's a more universal recommendation for 14 days of therapy for many of the early and the disseminated manifestations. Then, 28 days remains for arthritis, for which we have very good controlled data on. They also have said for Erythema-Migrans you can go as short as ten days with Doxycycline specifically. That will be another big change for folks, but I think the data behind it is fairly good. So, in terms of hot ID topics, that's a big set of changes for folks to appreciate in terms of the drugs and the durations.

John Williams: Let me ask you a question on that, Andy. We're so lucky to have somebody who has both a scientific interest in Lyme as you do and experience with research, and you've been here the whole time during the epidemic. This is anecdotal, and we should always base our care on evidence, but as you know, I spent many years in Tennessee where we did not have Lyme, but we had many, many, many cases of Ehrlichiosis and Rocky Mountain spotty fever and I, personally, treated hundreds of kids with Doxycycline and I've seen one child who had dental discoloration that his dentist thought might have been due to it. So, I think the safety data, it sounds like, are really there. What's the advantage? Is there an advantage of using Doxycycline for facial nerve palsy or for other central nervous system disease?

Andrew Nowalk: That's a great question. I think that what we have seen here is that Doxy and Amoxicillin seem to have very similar efficacy. I've always liked Doxycycline a bit better because it's penetration into the central nervous system is at a might higher level. We know that Amoxicillin is like all Penicillins. There's a big step down when you move from the gut to the bloodstream and then, there's a similarly big step down, like all Penicillins, when you move from the bloodstream across the blood-brain barrier. Doxycycline is a much more lipophilic medicine, and so it moves much more readily into the gut. So, the absorption of a dose is probably five to ten times better than the absorption of an Amoxicillin dose and the penetration into spinal fluid is excellent. So, when I'm treating a central nervous system infection and syndrome, I'd like to have more drug in there. That's a theoretic advantage. I will tell you, there are no studies to suggest that that theoretic advantage is reproducible in clinical studies.

Andrew Nowalk: I think the explanation for that is a basic science explanation. So, when we see facial nerve palsy in Lyme disease, what we're observing is much more of an immunologic phenomenon than a direct infection. Lyme meningitis is a great model for this. Lyme meningitis is a bacterial meningitis, which makes us all stand up and want to run out of the room, and do a spinal tap, and get Ceftriaxone on board. But, when you look at the CFS parameters and when you look at the symptoms ... And this is well described by Steve Eppes, the early parts of the 2000s, in a great paper he published from his work at duPont ... Lyme meningitis looks like an aseptic meningitis, very, very similarly and in fact, there are a few distinguishing features in terms of the longer duration of

symptoms at presentation, presence of facial nerve palsies, but really, it's a great imitator of an aseptic meningitis.

Andrew Nowalk: So, a lot of the clinical manifestations we see from Lyme are due to the fact that you have few bacteria but a lot of immune response. So, that may explain why Amox does just as well in most studies as Doxycycline. I still like Doxycycline when I'm dealing with the central nervous system, but I think that the recommendation to use Amoxicillin was never a bad one for the treatment of this infection.

John Williams: Well, that's very interesting. In terms of just following that brief point you made about the meningitis, one of the papers you published in fact looked at a lot of the cases we had seen and found that presumably for the reason you just stated, that oral Doxycycline was safe and effective compared to IV Ceftriaxone for a long period of time.

Andrew Nowalk: Thank you for that shout out. That's a paper from my group. Brian Campfield and Santiago Lopez, who's now at the University of South Dakota. It's a paper that stands on the shoulders of the European work. Again, we were doing nothing more than imitating some lovely studies from Europe that showed, in comparative studies of Ceftriaxone and Doxycycline, that the outcomes were similar.

Andrew Nowalk: We know that Doxycycline is effective from the European studies. The other thing we know, are PICC lines are mischief-makers when we send people home with them. So, you can pick lots of different rates. Your former colleague, Buddy Creech, published a real nice study a few years back on the frequency of complications from PICC lines being in the 20-30% range.

John Williams: Those might have been Buddy's own PICC lines.

Andrew Nowalk: They may have been in fact.

Andrew Nowalk: So, we know that PICC lines give us no advantage here. So, when we made this move, that paper came from a look at the European data and, to a certain extent, taking a little bit of a chance because we were swimming upstream a bit. What we found over the 40-some patients in that study is that there was absolutely no difference between children treated all IV and children treated either all PO or mostly PO. Again, Doxycycline gets in so well it's like an IV medicine given by mouth, and so we were very comfortable with it. I think when you see further recommendations from the IDSA, you'll see a lot more reflection of the fact that there's a strong role, at least for downgrading children who are leaving the hospital, from an IV medicine to an oral medicine.

Steph Dewar: So, I'm curious, Andy. Why are we experiencing this epidemic? And, what happened with the vaccine?

Andrew Nowalk: So, those are two very interesting questions that are quite separate from each other. I'll take the second one about the vaccine first. The vaccine worked. It required some boosting and it could be not 100% efficacious, but a very high degree of efficacy. The vaccine went off-market primarily because of lack of demand. It's not that it didn't work but there was a lot of legal action around the vaccine and the company was not selling very many doses by the time it went off-market in 2002. It is an effective vaccine. Reformulated for pets, it still works. I will joke sometimes that if you want to get a Lyme disease vaccine in Pittsburgh, it's easy. Leap in front of your dog at the last moment and your veterinarian will deliver a dose to you.

Andrew Nowalk: It's a commentary on the fact that vaccine manufacturers, there are not that many of them anymore because there's a lot risk associated. There's a lot of internet mythology about vaccines, as we all know. To get a new vaccine to market, you really need people to weight the balance of delivering a lot of doses, and buying those doses, and not suing you very often. It's a commentary on how complex vaccine development is in the United States today.

Andrew Nowalk: The first part of your question, why do we have this epidemic, is just fascinating. ID doctors are nerdy by nature, I think, so to be able to sit here and watch the dynamics of a development of an epidemic in this period of time has been amazing. I think there are contributions of climate, clearly, because ticks like to circulate in warm weather and with the warming of the climate, even in Pennsylvania, that gives ticks more time to circulate. There's contributions of actually manmade ecosystems. So, the Lyme disease epidemic, if you look at the CDC map, has a barrier along the Appalachian Mountain Chain, which makes a lot of sense.

Andrew Nowalk: There's not a lot of animal passage over that mountain chain. It's passed over the Appalachians in one saddle area, which is the north-central part of Pennsylvania. There is a large highway that runs through there, so there's a huge amount of clearing along that saddle region of the Appalachian Mountains, and there's much more traffic of deer, ticks, and white-footed mice through that area. So, we think that a lot of this movement has been the movement of infected ticks across that saddle area, probably hanging on to many small mammals, and then getting into our area and taking over as a larger part of the infected tick population.

Andrew Nowalk: Some great work done by collaborators of mine at Indiana University of Pennsylvania, Jamie Hutchinson and Tom Simmons' group, showed that in the 90s, the western half of Pennsylvania had almost no Lyme disease in it at all. Then, in 2015, Tom, in particular, published a paper in an entomology journal showing that every single county in Pennsylvania had at least 20, 30, or 40% of their ticks infected. So, the western half of Pennsylvania had really caught fire with respect to infected ticks.

Andrew Nowalk: One of the harder to answer questions that's probably all about ecology is, it's not just that we have infected ticks, we have a lot more ticks and what contributions the bird population plays, the warming of the climate, and the predators in that area, we don't know but there seem to be a lot more ticks out there. So, more ticks, which are more likely to be infected and lots of people building their nice houses out in the woods, is a good explanation for an epidemic in our area.

John Williams: Well, it's just really fascinating. I mean, for those of us who either have been here for a while or who were here many years ago, it really is very different. As you see, to both see it happening and to be able to get the clinical expertise and be able to do the research that you and your colleagues have done to help understand and manage that, it's really remarkable.

Andrew Nowalk: I would give a shout-out to UPMC Children's, is absolutely the epicenter of the study here. I would give a shout-out to my colleagues in the community. Community pediatricians were the proverbial canaries in the coal mine here, and particularly community practices in the northern half of our western side of the state, were the ones who fired up the first flares and really contacted us to say, "Boy, we're seeing a lot of kids with facial nerve palsies with Lyme arthritis." So, the collaboration we've had with the very tight-knit network of pediatricians in this half of the state, and our hospital, and our division, has been a really wonderful one. I want to pay a lot of tribute to them for being great partners in this.

John Williams: Well said. I would resent your remark about ID docs being nerdy except, sadly, I have to confess that it's true. I want to ask about something else you do. You mentioned you wear a lot of hats. You're a clinically practicing ID doc, you do clinical research on Lyme disease and on antibiotic resistance. You're the clinical director of the ID service. You do a lot of teaching and you're a co-director of the residency. But, I wanted to hear about trying to recruit new doctors who are interested in a career like yours, who are interested in a research career, in short, future nerds, and what are you doing in that area.

Andrew Nowalk: Future cool kids, let's call them.

Andrew Nowalk: One of the reasons that I was interested in taking on the role of the residency program director was a long passion I've had for training but also an interest in training future pediatric scientists. I think that we've all identified for a long time that all you need to do is Google or type into PubMed "pediatric scientist workforce" and you will find a lot of opinion papers that state clearly we don't have enough and, in fact, in many places, we can see the supply is declining. So, this is a big problem for us. I think department chairs have identified it, and national leaders have identified it and it's a thorny problem. There are lots of economic forces that make this challenging. The ups and downs of funding from not just NIH, but lots of other places, make this challenging. So, how do we do

that? How do we keep people who are passionate about discovery work involved in discovery work?

Andrew Nowalk: So, one of the things that is apparent to everyone who's involved in this is that the pipeline is so long that we lose a lot of people just through exhaustion. So, the average age of an R01 funded researcher, with an R01 being the biggest and basic currency of research grant, is moved into the almost mid-40s, and so when it takes that long for people to reach that first milepost, which is so important for promotion and career success, that's a big problem.

Andrew Nowalk: So, when we came together, when Steph and I became program directors, one of the first things we wanted to do was to create a space in the program where those people could thrive. Our theory behind it, and it's a theory that we're going to continue to test and compare with other institutions, is that the key way to do it is to keep them here, to be completely honest. So, what we're doing that's different is that we upfront very clearly state, "We would like you for six years, or seven years, or six-plus.", because we think if we have you through the whole residency to fellowship transition, we can create new curricula during that period of time to train you. Whether it's a non-standard pathway of the American Board that shortens or changes up how you schedule your training, or more leadership development, which is part of our program, or just the close attention of the chair and other leaders within the department who are really looking over the mentoring and the career development of these residents and fellows very closely.

Andrew Nowalk: We think lots of things will be needed to have a higher success rate than we have now. So, we started this program almost as soon as I took over as a program director, and then formalized it and put it under a moniker called the Pediatric Scientist Development Program about two-and-a-half years ago with Terry Dermody took over as our chair. We now have eight residents and fellows in our pathway. We're hoping to have somewhere around 12 to 15 or 16 at any given time once we're completely staffed up. What we've seen is some wonderful things. Our folks are very dedicated, and very interested in research, and don't flag from that interest, which is good, so we're sustaining interest. Number two, we're getting them into interesting pathways that our fellowship programs are very appreciative of. Then, finally, something that makes me very happy is that when we look at the clinical performance of these folks, what we have found are a cadre of folks who have a good scientific community and are also fantastic clinicians. So, we're accomplishing several things at once. We're training great clinicians, but we're keeping them interested in research as well.

Andrew Nowalk: Then, in five to ten years, when I do this podcast again, I'll tell you how those folks are doing when they make it to the important next steps, which is competing for funding and whether they're able to compete for independent funding and move out as scientists. This is a great, interesting question for us to answer. It's critically important. There are lots of tides that are pushing against people who are interested in doing discovery work in pediatrics. I think only

with big commitments organizationally are we going to be able to fight against those tides.

John Williams: Well, I'm really grateful, Andy, that we have people like you and Jackie working on that. I mean, we're in Pittsburgh, where Jonas Salk discovered and invented the polio vaccine that has saved millions of lives around the world. So, that's the kind of discovery that we need in pediatrics going forward.

Andrew Nowalk: Yeah. Our department chair does say, "We're bringing hope to kids who don't have hope now.", and I think that's not a cliché, that's real. Jackie Ho, thank you for bringing up Jackie. Jackie Ho is one of the nephrologists here at our hospital, is my co-director for this program and I will say that our team here for the Pediatric Scientist Development Program is a great woman. Jackie is a great co-director and we're hoping to kind of bring a number of these places together in the near future so we can talk about common ways to help pediatric residents find careers in discovery.

Steph Dewar: Well, Andy, I'm so glad that you were able to join us today on the podcast. I certainly enjoy working with you every day. We have a very unique relationship, much like my relationship with my co-host on this podcast, but I think it's one that benefits both of us and brings a lot of joy. So, thanks for joining us.

Andrew Nowalk: Thanks for the invite, guys.

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