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Carolyn Coyne: From UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics. I'm Carolyn Coyne. I'm a basic scientist in the Division of Pediatric Infectious Diseases.

Brian Martin: And I'm Brian Martin. I'm Vice President of Medical Affairs here at Children's.

Brian Martin: For today's episode, we welcome Alejandro Hoberman . Dr. Hoberman is the President of Children's Community Pediatrics and also the Chief of the Division of General Academic Pediatrics here at Children's. His studies focus on acute otitis media in young children, including a landmark trial published in the New England Journal of Medicine which demonstrated that the reduction of duration of antibiotics does more harm than good when treating ear infections in young children. Welcome, Dr. Hoberman.

Carolyn Coyne: Thanks for joining us, Alejandro.

Alejandro Hoberman: Thank you.

Carolyn Coyne: So let's talk about ears. I have a son at home with an ear infection as we speak and so I would like for you to tell us a little bit about your journey into how you chose the discipline that you work on and then also of course tell us a little bit about your research.

Alejandro Hoberman: So I was 26 I think and I was at Children's Hospital in Buenos Aires, Argentina and I was the only crazy person with a pneumatic otoscope trying to teach myself how to do a pneumatic otoscopy and remove the eardrums, which was described from the journals I was reading in those days. Jack Paradise here in Pittsburgh and Ellen Wald, then Charlie Bluestone was the one who most of the papers were from. I was excited about trying to learn how to do this, and I wrote to Jack and very interesting he sent me a telegram saying that some peoples coming to Children's Hospital in Buenos Aires and he would interview me there and invited me to interview with Allan Drash in Buenos Aires, who was the head of endocrinology here in that day.

Alejandro Hoberman: Then I came for fellowship and fellowship meant, I did know that when I was there, that I needed to do my own research studies. There you go, Jack Paradise and Ken Rogers made two mentors started pushing me like crazy, which is the project you're going to be working on over the next two years. I ended up working in multiple projects. I ended up doing work on urinary tract infections and otitis media and I have always had that problem in my life, I was a little unfocused. I was focused on two different areas, I continue that over the years.

Alejandro Hoberman: Sylvan Stool was another otolaryngologist here in those days and Sylvan, who was a pediatrician before being an otolaryngologist, had this huge cart with a big Sony TV, ones they have in the O.R, and Zeno light source and a otoendoscope and he said "You can do a lot more good with this than we can in otolaryngology, so why don't you take it and use it to teach the residents?" So we started gathering images, videos, and trying to use those in training pediatricians.

Alejandro Hoberman: Then, we opened up an ear check clinic to see children on follow-up after an ear infection. Then, we developed multimedia tools and then we got a grant from the CDC to teach pediatricians how to do a diagnosis of acute otitis media and distinguish it from otitis media with effusion and no effusion, then we got embarked on every single development on a new antibiotic that was coming in the market in the '90's and 2000's. Then, about 18 years ago, no more antibiotics had been approved for upper respiratory infections since then. I think 2003 or four was the last one that was approved. Everything else since has not been resulted in approval by FDA, so we got embarked on other studies instead.

Brian Martin: How has that change in the antibiotic development affected your pathway and the conversation in both your research life and also with your general pediatric colleagues?

Alejandro Hoberman: In my research life, I departed from being involved in a lot of, what I used to think of it as Colgate research, like toothpaste research, determining whether Colgate was better than Crest and so forth, and I got involved in trying to determine what or when do really need to use antibiotics. So we did a study which we looked at kids with bronchiolitis and we tried to determine okay, do they have an ear infection? If they have an ear infection are they viral or bacterial, and we tap the ears of those thirty-some kids, and we basically found that all had bacterial acute otitis media. So then we started thinking about we need to do a randomized placebo control study to try to determine the benefit antimicrobial treatment. In the mid-2000's, 2004 or five, we got funded by NIH to do a randomized placebo control study and that one we published in 2011 in the Journal of Medicine. We showed that by providing antimicrobial treatment not only resulted in substantial less treatment failures, but also there was improvement with regards to symptoms. In order to show both, that the abscess, the bulging ear drum, was likely to be gone if you received the proper antibiotic but also the child got better faster.

Alejandro Hoberman: We went on to how long do we have to treat? Do we need to treat the 10 days of treatment? The goal is to use the minimal amount that you need for any kind of condition, and we didn't know 10 days were needed. A lot of folks were reporting about using five days of treatment, and then we went back to the NIH and got funded to compare five versus 10 days on a blood agency analysis that took us many years to do. We randomized there 520 children, the goal was 600 but they stopped us early because they thought we answered the question, so they didn't want us to randomize anybody else. We showed that 10 days made

a difference compared to five days. Five days resulted in twice as many treatment failures, so the advice Carolyn to you and your son, is ten days complete the treatment because the likelihood of 5 A.M bulging ear drum's going to be a lot less.

Carolyn Coyne: I'm obviously into infectious diseases, so this is something I care a lot about and think a lot about and of course this idea of antimicrobial resistance and what a problem this is just globally in many, many aspects of healthcare. I'm wondering if you could talk a little bit about that, obviously a big concern is you're discussing what you mentioned before which is viral versus bacterial infections, how you distinguish those, and what the adverse outcomes can be if you prescribe antibiotics for obviously an unnecessary viral infection.

Alejandro Hoberman: You're absolutely correct. I think the key point is when do you prescribe the antibiotic? It's once you do have a bulging ear drum. The middle ear is the only place in the body where you can actually see the abscess. You cannot see in the larynx, you cannot see in the sinuses, you can see it with the otoscope in the middle ear. You can determine outcome by looking at the abscess and seeing if it’s gone or not. I would say we can do a lot more in decreasing the emergence of bacteria resistance by actually diagnosing the condition accurately. Making the effort to distinguish those who are just having little bit of fluid that doesn't need to be treated, that doesn't cause any harm, my mentor Jack Paradise showed that it doesn't make you less smarter to have fluid in the ear and it doesn't make you talk slower if you have fluid in the ear. We know that basically we don't do much about middle ear fluid, but if it's infected and it's an abscess and it's bulging, those children we must treat. Particularly, if they're young.

Alejandro Hoberman: The American Academy of Pediatrics had the guideline committee, I was part of that committee we had huge debates. If you focus on the children under age two, who are the ones that are most likely, that's where the peak incidents of otitis media is between six months and 24 months, those benefit from antimicrobial therapy. Then, using the right antimicrobial therapy is important to use amoxacillin the guidelines are very clear on that amoxicillin-clavulanate, when that fails, then cefuroxime, there is no room for azithromycin, there is no room for Ceftin, there's no room for those medications unless in the truly penicillin allergic patient who we know, but not that many. We label a lot of children as having penicillin allergies, but they not always have penicillin allergies.

Brian Martin: I'd like to come back to the sensitivity and diagnoses which you just spoke of, can you share with us some work which you're currently doing that's complimentary to your work in terms of assisting those who diagnose middle ear disease and improving the quality of our diagnosis which obviously feeds downstream to our therapy.

Alejandro Hoberman: Sure. I'm getting to the point after having done 20 years of developing multimedia tools, web base, CDs, write chapters, and participating guideline committees, and write about these things. Sometimes we get to a ceiling effect

of how good could we be at diagnosing otitis media. I would say when we're referred patients from practices or from a urgent care centers, emergency departments sometimes too, who are diagnosed with having an ear infection. Many times they don't have an ear infection, they just have fluid in the middle ear. The variability in the diagnose for otitis media, of acute otitis media, is high.

Alejandro Hoberman: We'd like to try to assist and develop diagnostic aids and over the last few years, I've been working with folks that were coming out of university. My colleague, Jelena Kovacevic, was the head of Electrical and Computer Engineering at CMU and now actually she just departed and she's now the dean of Computer Engineering at NYU. She and I are still collaborating and she is the queen of classification algorithms, she taught me that we can teach computers how to do the same things that we do in our minds when we diagnose otitis media. Later, she and I, and others and Jack Paradise have worked on developing algorithmic thinking on how we think when we go look at an ear drum. The key point is is there a bulge or no, if there is bulging we're done, we don't need more things. If there's no bulging, if there is opacity of the ear drum, it could be middle ear effusion, those are the things that we consider in general. If not, it's a normal ear drum.

Alejandro Hoberman: The American Academy pushed to even make on the latest guidelines from 2013, that the right ear drum does not constitute sufficient to diagnose acute otitis media. So acute otitis media could give you a right ear drum, unilateral, doesn't have to be bilateral, and we don't treat those patients. If we were strict to treating those who are truly having a bulging ear drum, we could do a lot of good and decrease the likelihood of resistance.

Alejandro Hoberman: Going back to Jelena, the engineers are the ones that designed this systems that classify blood cells or tumor cells, or whatever it is. She applied the vocabulary and the grammar that we think once we look at ear drums to the way they interpret images. We created system that actually creates a automatic segmentation of the ear drum, removing the ear canal, and uses eight additional features that actually classifies them into three categories: normal, middle ear effusion otitis media with effusion, or acute otitis media. The system is close to 90% accurate. We compare that with what we get with pediatricians and unusual variabilities at about 80% the best. The system works very well. We're now doing video captures, we developed an application for the iPhone and we are actually using an endoscope coupled with an iPhone to capture video images. With the video images, we get hundreds of images, not just one image. If there is a little wax occluding on one area, we can view the next images it will allow us to do that. Reapplying all those features to those video segments that we're collecting now, and hope to incorporate it into a grant we're submitting to DCD, Deafness and Communication Disorders Institute, looking at clinical decisions supporting the emergency department and the pediatrician office to actually look at can we aid in the diagnosis of acute otitis media by providing the answer.

Carolyn Coyne: How does this sort of misdiagnosis occur? Is it sort of a lack of understanding of the diagnosis, of the definition, how does that come about?

Alejandro Hoberman: I think it has to do with the misdiagnosis is generally in babies. It's not in a five year old complaining of ear pain, those are easy. If you can see the ear drum and the wax is out of the way and you can visualize the ear drum, the five year old is simple. The baby is a moving target, so you have cerumen in small ear canals, cerumen that partially obstructs the ear canal. Then you are relying on really subtle visual findings that are occur in a brief observation of the ear drum. I think that's the catch, that sometimes in the most experienced eyes, a brief observation may be all that you need. Not everybody is at that level and it's very hard to get to be really sure that you saw enough of an ear drum to make a judgment there.

Carolyn Coyne: Especially in a crying infant.

Alejandro Hoberman: Correct. Where sometimes you don't have the best holder, the parents want to hold their child in their arms and you really know to do a good exam you got to hold them on the examining table and get somebody to get a grip of the head and a grip of the arms. [crosstalk 00:13:52] that you're using the right otoscopes, they have the right bulbs with the right amount of light. Once we get old we start needing reading glasses so we need to switch to otoscopes that have double dioctors so you can-

Brian Martin: With all these things it makes 80% accuracy sound like-

Alejandro Hoberman: Correct.

Carolyn Coyne: Pretty good, pretty darn good.

Brian Martin: Pretty good. Do you see Alejandro, do you see any role with the emerging technology focus here on the diagnostic side for this to also aid in shared decision making and communication with patients and their families in regard to the situation? The reason I ask is because if we think about the retail medicine trend and consumerism in medicine, for example, in my clinical world sometimes people show up with a Google diagnosis in their head that they've done at home and they have made the decision that they want X, they want an antibiotic, or they want a particular prescription. Any thoughts on how this could also assist in talking or do you ever find we have to talk parents out of antibiotic therapy, if it's an otitis media with effusion where we don't have an indication for antimicrobial.

Alejandro Hoberman: Absolutely, yes, and I think it has to do with purpose too. It's on the parent side and the trainee side as well, so you get tool that makes it easier on the parents and the children because you can go in with a device like this with the application on the endoscope, you can capture a segment of video and then nobody has to go in to look at the child again, you have the video to discuss with

the trainees what to consult with somebody else or to use it in telemedicine application if you need help.

Alejandro Hoberman: We're deploying actually in three offices: one at South Hills in the South Hills of Pittsburgh, another one in Pennsylvania at a rural qualified health center, and then one in the north in Cranberry, Pennsylvania, and we have it at the primary care center with us as well. We're deploying these and we're using them for training purposes and we're using it for parent's purposes too, where the parent can see what the ear drum looks like and we can justify here is why we need to use antibiotics. This is an abnormal ear drum, this is the bulginess, and this is what we want to try to make better. In contrast when it's completely normal and the parent wants antibiotics, we can say this is why we don't want to use antibiotics because when it becomes infected like this one, let me show you a picture of what represents a video of an ear infection, when it looks like this then I want the antibiotics to work. The parents are very responsive to that approach.

Carolyn Coyne: Yes, as a parent I would love that. I'm probably a pain in my pediatrician's because I always want an answer to why, what virus is it, what is it? As you were talking about before about the bulging ear drum, is that I mentioned my son is sitting at home with an ear infection. I've never seen what that looks like and so for me that would actually help me understand a lot of the symptoms and the causes and perhaps because I tend to be a little more scientific and thinking, that would be a wonderful asset and tool to have. Talking about the parents, compliance, this idea of again antibiotic resistance emerging because as you said before you should very nicely that you needed a 10 day course of antibiotics to sort of get maximum effect. What do you tell people who aren't compliant to that, after two or three days fever comes down, symptoms go away, the parent may say to themselves "oh I don't need to keep dosing, why do I need to keep giving an antibiotic clearly the symptoms have gone away." What do you see as ways to address that or the potential problems that that causes?

Alejandro Hoberman: We generally share the fact that we do have the data of the 10 day improvement over five days of treatment. We even did another study recently in which we are looking reduced concentration of capulin and we actually looked at kids at seven days to see if can we get in between, can we get between five and 10 and still accomplish it. We got two observers, myself and Mary [inaudible 00:17:50], our best nurse practitioner who trains all the residents by the way and is outstanding at examining ears, to commit ourselves would we stop treatment at seven days, even though we're not stopping for the study. Do we have enough improvement that we can stop treatment? The answer was no. In most children we would continue treatment, 60 some percent we would continue treatment. We even gave up on the seven days, which is something the Finnish have used in their studies in older children they have used seven days of treatment. I was thinking of five, no, maybe seven maybe eight, but you know, I would just stick to the 10 days.

Carolyn Coyne: Ten days is best.

Alejandro Hoberman: One more thing that is important too, is in the context of the studies that we've done, we also showed that there was no impact on resistance. In the five versus 10 day study we looked at them over a one year period. Every time they got an ear infection we treat them with five or 10 days, there was no increase resistance in the 10 day group.

Alejandro Hoberman: Nasopharyngeal colonization with pneumococcal resistance to penicillin. That was shocking, I thought they would be more resistant than they were.

Brian Martin: Do we see any resolution to this 18 year drought of new antibiotics? We sometimes see in popular media are getting concerned about antibiotic resistance and the bacteria are out stripping our ability to innovate and to develop new antimicrobials, is there anything on the horizon in regards to antimicrobial therapy that might be able to strike a middle ground in terms of duration of therapy? Some parents and children as we know are more difficult to get medication into than others, is there anything on your radar screen that might allow us to be shortened or modified in the future?

Alejandro Hoberman: We are working on a redevelopment of a antimicrobial amoxicillin-clavulanate, not with the goal of inventing a new antibiotic, we're trying to decrease that adverse event profile. The most effective antibiotic, amoxicillin-clavulanate, causes a high proportion of children having diarrhea, high proportion of children having... babies having diaper dermatitis, parents discontinue treatment in many instances. They stop for a few days and then restart, which is the worst thing we can do, but they're having adverse events so we shouldn't blame them for that.

Alejandro Hoberman: What we did was we reduced the clavulanate to less than half of what's in the current clavulanate and we were able to accomplish from the pharmacokinetic standpoint to get levels of the area under the curve, the amount of antibiotic the baby is exposed to, that are only 5% less. Even though we decrease 55% the amount of clavulanate, we only got a 5% reduction in the area under the curve. With about a third of the reduction of the diarrhea, reduction of diaper dermatitis, and a 90% reduction in discontinuation of steady medication. We had a meeting with the Food and Drug Administration, they're really interesting in using the minimal amount of drug that is needed to accomplish the goal. The efficacy was even a little bit better on the open label study that we did. We're going to do a four month trial for a approval of that drug and labeling with FDA. We hope to have to have at least one new antibiotic in the years to come on this.

Brian Martin: Fantastic. That sounds like a win-win. Well, I want to say thank you very much for joining us today, we had a delightful conversation.

Carolyn Coyne: Thank you for joining us.

Alejandro Hoberman: Thank you.

Brian Martin: Thank you.