Hearing Health Hour: Chronic Childhood Ear Infections and Related Hearing Loss
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Presenter: Regie Santos-Cortez, Ph.D., with moderator Anil Lalwani, M.D.

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DR. LALWANI - Hello, and welcome to our Hearing Health Hour webinar. We thank you for joining us for another research presentation from Hearing Health Foundation. Today's topic is one familiar to many parents of young children, chronic ear infections, and their effect on hearing. This event has a live captioner, and is being recorded. You can enable closed captions by clicking the CC button in the toolbar at the bottom of your screen. If you need any other assistance using Zoom, follow the link in the technical guide shared in the chat by Chris.

And by way of introduction, my name is Dr. Anil Lalwani, I'm a Professor and Vice Chairman for Research in the Department of Otolaryngology Head Neck Surgery, as well as the Associate Dean for Student Research at Columbia University Vagelos College of Physicians and Surgeons in New York. I'm a board member of Hearing Health Foundation, where I oversee the Emerging Research Grants program, also affectionately known as ERG. Now, ERG provides critical funds to researchers studying hearing and balance conditions. These grants supported many leaders in our field to become successful scientists, including our own illustrious speaker today.

And today, we will hear from Dr. Regie Santos-Cortez, who's an Associate Professor of Otolaryngology Head and Neck Surgery, or affectionately known as Ear, Nose, and Throat, at the University of Colorado School of Medicine. And we are so proud that we were able to support her very important work with an Emerging Research Grant in 2011, 2012. Now Dr. Santos-Cortez will address the varied roles genes, tissues in the ear, and bacteria, may play in chronic ear infections. Having done clinical and field work in the Philippines, she will also highlight the importance of combined clinical and population studies.

Now, Hearing Health Foundation's ERG program that provide the seed money to scientists doing cutting edge research is only possible through the generosity of supporters like you. If you'd like to support work on hearing loss, tinnitus, and related conditions, you can do so

today at hhf.org/donate. Now, we'll move to Dr. Santos-Cortez's presentation, Chronic Childhood Ear Infections and Related Hearing Loss. Please submit your questions that may come up through the Q and A box linked at the bottom of the screen, and we will address these at the end of our presentation during the Q and A session. Dr. Santos-Cortez.

DR. SANTOS-CORTEZ - Hello, everyone. I'm so pleased to be here to talk to you about our research when, well, let me see. I'm trying to share screen. All right. Okay. So when I was asked to give a talk here, I was so pleased and I said yes, right away. And it's because I am your atypical investigator in the US. I was trained in the Philippines clinically, and I had my PhD in Genetic Epidemiology in the Netherlands. Some of it I did at Suzanne Leal's lab at Baylor.

And so when I finished with my training, I went back to the Philippines, and practiced at my home institution in the University of the Philippines, Manila, at the Philippine General Hospital, and also at the Philippine Children's Medical Center. Then around the time when I started, the current Chair of the PGH Otolaryngology Department, Rina Reyes-Quintos, she invited me to go on a medical mission to this island where they have an indigenous population with a very high prevalence, around 50%, of chronic otitis media.

So we went there, and by the first night, we had this huge pedigree drawn up that connects almost everybody within that tribe of around 250 people. And so what we did was submit a grant to our home institution at the NIH there in the Philippines, and got seed money. However, something happened along the way, and I ended up going back to the United States. Thankfully, Suzanne took me back in her lab, working on my thesis project, which was Genetics of Hearing Loss.

At the same time, my colleagues, my wonderful colleagues from the Philippines, headed by then-Director of the National Ear Institute, Gene Abes. He continued with my other colleagues there to go back to the island, and work on medical missions. And so with the data and the samples that they got, we submitted a grant application to Hearing Health Foundation, and got funded as an ERG investigator. With that, we were able to get a few more grants from Action on Hearing Loss, from NOHR, and published the first gene that we found A2ML1, as a gene with variants conferring susceptibility to otitis media, not just in the indigenous population, but also with American children.

With that, we were able to get funding from NIDCD, with an R01 that tries to look for more genetic variants in various populations, as well as how these variants change the microbiome, or the microbial profiles in the middle ears of patients with otitis media. As we

went along, I was hired here at the University of Colorado with support from institutional funding, started my own lab, got some more funding from the Children's Hospital, and also some travel grant from the Philippines, from PCHRD.

We were able to continue with more visits to the island. And so this has been a project that's been going on for a little while, with the support of wonderful colleagues. They have all been staying with this project for more than 10 years now, Charlotte, Suzanne, Tasnee and Zubair. Unfortunately, we lost Debbie and Michele to cancers, but we will always remember their efforts for the study.

Along the way, I made some more wonderful friends here on campus, around 20 people are working as faculty in this project, as well as Lena from Finland, Allen from San Diego, and Mood, who's given us samples from his UK cohort. If I list everybody, that's around six slides. These people who have been wonderful, excellent investigators, helping out with the project, they keep me working every day.

So why study otitis media? Otitis media is inflammation of the middle ear, which is usually due to viral or bacterial infection. It can affect any person, any age, but in most cases, you see it in children under five years old. In the US, around 40% of children under age one will have at least one otitis media episode. In most cases it will resolve, however, in a certain proportion of children or adults, it can become recurrent, meaning repeated infections, or chronic, wherein you have a long-term infection.

To give you an idea how it looks like when you examine the ear using a handheld otoscope, the upper right would show you a normal ear, where you see a translucent eardrum, and there's no fluid behind it. And you also see some reflection of light called the cone of light, meaning that the eardrum is in the proper position.

On the other hand, if you have an acute suppurative otitis media, this is the classic appearance, wherein you have a bulging eardrum that's very inflamed or infected, and you have pus behind the eardrum, meaning that the ear cavity is full of infection. If this is not treated, let's say with antibiotics or surgery, what might happen is a spontaneous rupture of the eardrum, where you have a hole or perforation, and this might cause some relief to the patient who might be experiencing pain and resolve eventually.

On the other hand, it might also progress. That person might have persistent fluid in the middle of your cavity. And this might be how it will appear, wherein you have fluid behind the middle ear. There's no more pain, but there's still some fluid behind with some bubbles showing you that there's some air on top, but then there's some hearing loss without pain.

Some of this might resolve on its own and become recurrent, or it might become chronic like this, where you have a persistent perforation, or a hole, where there's draining fluid that's usually filled with mucus or pus. And then you have thickening of the middle ear lining or mucosa.

This is classic case of chronic suppurative otitis media. In some cases, this might also heal. The perforation might heal. We don't know though, unless we test this ear, whether there's some damage that's already inside like in the ears, in the middle ear bones, that connect the eardrum to the inner ear, or in the inner ear itself. When it heals, you might see this, where you have scarring, you have fibrous material deposited on the eardrum, or it might look normal, but there's some damage behind.

The worst case though is when you have a cholesteatoma. This is usually for chronically draining ears that are not treated or poorly treated, usually because patients might not have proper access to healthcare, or they're just predisposed to having some form of cholesteatoma. But this is really typical draining, not-treated cholesteatoma, wherein you have some keratin debris that you can see behind the eardrum. And there's a chronic perforation, and very inflamed mucosa. In this case, it looks like a granulation tissue, or polypoid, because of the severe inflammation.

What this shows you, there's a huge spectrum in terms of otitis media. All of this is otitis media, but they can appear differently. How an acute otitis media becomes chronic though, is still not well understood. So how does otitis media cause hearing loss? It depends on what type of structure in the middle ear is affected. If it's just the eardrum that's affected, you might have some small loss in hearing, usually in the low frequency.

But if you have the middle ear cavity filled with middle ear fluid, then you have a little bit more loss, and you can feel this as decrease in hearing. If there's some damage to the bones that connect the eardrum and the inner ear, here they're called the ossicles, then this can cost an even larger drop in hearing, around 40 to 50 dB of loss. And this might affect not just the low frequencies or low tones in your hearing, but also the middle and higher frequencies or tones. If the cochlea is affected, your sense of hearing organ, then there might be a severe to profound hearing loss, usually including the high frequencies. In the typical patient, you might have variability in how your hearing is affected, depending on when you have the infection, and whether it's affecting multiple structures in the middle ear.

This is an example of how we've studied the hearing loss in the indigenous population, in the island that we've visited. Over time, we've taken audiometric measurements that's

community-based. And so you can see that there are some patients with chronic suppurative otitis media, some have healed otitis media, or some still have normal ears, or those with otitis media with effusion. The normal ears are quite similar in hearing with otitis media with effusion. But once you have some healing, or scarring in the middle ear, you might have some patients with hearing loss already, even though it looks quite normal from the outside. And then obviously, for those with chronic suppurative otitis media, you can have permanent hearing loss already with severe to profound loss.

Here you can see that some of the losses are more severe at 4,000 Hertz, around 70-to-profound hearing loss. And so you might think like, well, if it's going to heal well, why do we care? Especially in the children, if you think that it will resolve on its own, then shouldn't we let it be? The problem is, especially in the children who are less than five years old, where this occurs more often, they do have sequelae, or outcomes that they carry through, or all through their childhood, or even in adulthood. It's known that children with repeated ear infections have worse developmental outcomes may it be in speech, language, or cognition, or even affecting their academic performance at school.

They might have worse reading ability, because they cannot connect the sounds that they hear with the words that they read. And sometimes, they might not have any sense of rhythm, or they might be out of tune when they hear music. Sometimes when you hear somebody sing out of tune, that might not necessarily be genetic, they might have had some ear infections when they were kids.

The other thing is because when one ear is more affected than the other, then they lose their sense of having hearing from both ears. And some of this affects the auditory pathways, the nerves that connect your inner ear to the brain. And this might occur even after the infection has resolved. In longitudinal studies, even after 30 years from the childhood ear infections, in adults, they might detect some permanent damage to the cochlea, especially at the high frequencies.

Some of these might not be easily noticeable, because they're at the very high frequencies beyond what you can measure with a regular audiometer. So in effect, we really have to treat the otitis media in younger children, because we do not want them to have hearing loss, it will affect their overall development. Aside from hearing loss, there are other complications from otitis media, it might affect their sense of balance, it might cause facial paralysis, it might cause collections of infection in the bone behind your ear called the mastoid, or it can extend even to soft tissues in the face, or in the neck.

The worst case scenarios would be when you have infection going to the brain. And these are obviously emergency cases. These are not that rare in places where there's less access to healthcare, but even in developed countries, we still occasionally see these complications. And so it's important that otitis media is treated effectively.

The global morbidity, or burden of disease due to otitis media in 2019, before the COVID pandemic, you can see it here measured across different countries. Most of the burden is borne in developing countries, worst hit being the Indian subcontinent, here, you can see it in red. But also countries in sub-Saharan Africa, Latin America, and Southeast Asia are disproportionately affected. If you want to look at the burden of disease over time, a lot of this has improved since the 1990s up to the present. But what I want you to notice here, the United States is somewhere around this, then it's flat-lined, which is good. It means that it's been pretty controlled over the decades.

But it has remained at the 40 DALY, which is a measure of morbidity or burden of disease over all this time. And if you compare that to hearing loss in the under five year old children, it's actually a bigger burden of disease for otitis media than hearing loss. Part of it is because of the lack of research in otitis media. If you track the publications for otitis media over the past 70 years, it's flat-lined, which is very different from how hearing loss has progressed immensely in terms of research over the past 70 years.

Diagnosis and treatment have remained the same. In terms of diagnosis, we use otoscopy or audiology in diagnosing. And if we want to look at the structures in the middle ear, if they're affected, then we use imaging. For treatment, it's still antibiotics and surgery. Antibiotics is usually systemic oral, or locally instilled ear drops. For the systemic oral, it's a concern because if it's used inappropriately, it can cause resistance to, bacterial resistance to antibiotics.

One thing that has really improved otitis media incidence, not just in the United States, but around the world, is the introduction of vaccines against Streptococcus pneumoniae, which is a top bug that causes acute otitis media. When it was introduced in the 1990s, there was a report that said, I quote, "There's been a hundred-fold decrease in acute otitis media incidence." The problem with that, people misinterpreted it as otitis media being solved by pneumococcal vaccines. And here you can see historically, it's only partially true. From 15 million cases per year in the children under five, the otitis media incidence has decreased to around 9 million. This is probably the wrong slide, sorry, around 9 million per year, which is a 40% drop, not a hundred percent.

This is because it's not just Streptococcus pneumoniae, that's causing acute otitis media. It's also Haemophilus influenzae, which is now the top bug in some countries, or in some communities, and Moraxella catarrhalis, for which we still don't have vaccines at this time. The other thing is there are viruses that cause acute otitis media, the top ones being the viruses that cause common colds, which is rhinovirus, and the older coronaviruses that have been around for centuries.

The chronic otitis media types, they're caused by multiple bacteria, the most common being Pseudomonas and Staphylococcus aureus. And so if we're just targeting strep for prevention or vaccination, then naturally, there are other bacteria or viruses that come into play. And it doesn't really solve the high incidence of acute otitis media around the world. Now, the effects of COVID-19 is another event that has affected otitis media research. You can see here that after the lockdowns in the US, there's been a precipitous drop in cases of otitis media recorded across clinics, as well as decrease in surgeries and complications. This is partly because of social distancing, better hygiene, which is great, but then this is probably temporary.

As you can see here, if you track the blue line, you'll already see that there's an increase beginning from May 2021. And if I hear my colleagues here right, right now they're about 90 to 100 percent already, as the same as pre-pandemic levels in terms of otitis media cases. So these are temporary effects on the otitis media incidence. In the end, what we think is for otitis media research, it will continue to be important in the next decades. And we will still have to look at disease mechanisms, try to understand how they happen, so we can create more effective management strategies, including prevention of hearing loss.

There are many known risk factors for otitis media, many that we've known for decades, and we try to prevent. For example, we know that it's very prevalent in young children, so we try to monitor their ear health. If you see a child that's tugging their ears, they're probably in pain, and we have to take a look at that. If there are upper respiratory infections, we try to manage them along with other co-morbidities like allergies, or immune conditions, to minimize the effects. If a child is attending daycare, we try to practice hygiene, and also minimize crowding in the home, or at school. We promote breastfeeding, no smoking, or less exposure to tobacco smoke would be good, and optimize the nutrition of children, keep their ears clean, especially if they're swimming, try to not put dirty water in their outer ears. And all these we've been trying to do.

But in some cases, even if you try to optimize conditions for children, there are still some who might have family history, or inherited factors that cause them to have a higher risk of otitis media. And this is what we've been targeting with our studies, so that eventually we

can have targeted management for those who have family history of otitis media. And just to show you, there's a few more topics that are not as well teased out. This includes laryngopharyngeal reflux, air pollution, chemical exposures, and other adult-onset diseases that are associated with otitis media.

Since we got our funding from NIDCD, we've tried to identify genes and variants that confer susceptibility to otitis media, and how these variants change the microbial profiles in the middle ears. And this includes both good and bad bacteria that are detected in the middle ear. Our motivation for this is because for otitis media genetics, it remains understudied. Most of the studies that are done in thousands, or hundreds of thousands of individuals are in adults rather than in children.

On the other hand, we have access to DNA samples, and clinical data from families that we know have high heritability for otitis media. We hope that the variants that we find will be useful for screening, surveillance, and for counseling these families. At the same time, if we know what bugs are prevalent, depending on what variants they have, or what kind of microbes are in the specific middle ear tissues, then this might be used to guide antibiotic treatment, or the need for surgery.

Our study rationale, if you look at these cartoons, if somebody has a change in their DNA sequence, then we expect that this might change how the coding is transferred or transmitted to the cell, which makes the proteins that are expressed on the mucosal cell surface. So if we change the expression of proteins, or the levels of proteins on the surface of the cell, this might also change how the good and bad bacteria are on the surface of the cell. Which we might say is the microbiome, or the collection of different bacteria on top of the mucosal lining, or the lining of the middle ear.

So far, what we found, this kind of holds up. For some of the genes that we found, we know that specific microbes bind to the middle ear lining depending on what variants are present. So for example, for FUT2 and ABO, the variants that we've detected, they determine the levels of A antigen. Like the A antigen is what you detect when you have your blood typed, right? So if you're type A, you have A antigen, and you express it also in the epithelium or the lining of your middle ear. So based on whether you have A antigen or not, the types of bacteria that bind to the mucosa or the lining would differ.

We found that type A for example, was associated with an increased risk for chronic otitis media with effusion. While those that have a type O, they're protected against recurrent acute otitis media. This is also similar to what we see with a CDHR3 variant, which changes how a person might have rhinoviral infections. And as we've said earlier, the

more you are at risk for rhinovirus, and rhinoviral infections, the more at risk you are for otitis media. The other thing we've found is depending on your genetic variant for FUT2, then you might also have differences in how your genes are expressed in the middle ear. And what we found for those who carry this specific variant that's found in around 50% of many populations around the world, it changes how mucins are expressed in the middle ear, and not just the epithelium is changing in terms of expression, but also how their immune system, or the defense system in their mucosal lining might also change in how they express themselves. Altogether, this changes a person's risk for otitis media.

The other class of genes that we've seen, are those that the first that we found, A2ML1, and SPINK5, these are genes that encode serine protease inhibitors. So what do these do? When the proteins are encoded, what they do is they try to catch the enzymes that might cause damage to the mucosa, and clear them out of the middle ear. So if these genes are defective, then it might lead to undue damage to the middle ear. And true enough, what we see in the middle ears of the mice that we have so far, for further study, we see some persistent eardrum perforations. This might explain why we see atypical bacteria in the middle ears of patients with variants in these genes. Our hope in the future, if we are successful with this mouse model, would be to find a way to introduce protein into the eardrum, so that it can heal properly.

So what do we do now, if there are multiple variants? This is not your typical Mendelian gene for hearing loss, where one gene causes the disease. What we see in otitis media, there are multiple variants that might change somebody's risk for middle ear infections. So using the indigenous population as an example, we've seen three different genes with variants in this population, and we've counseled them depending on what variants are in each individual. So here, the easy thing is we haven't seen any significance in terms of the other environmental risk factors, except for gingivitis and the genetic variants that contribute to otitis media or middle ear infections.

Because we've been going to the community several times for the past how many years, we've provided services to them. One is to do follow-up or surveillance of their middle ears using audiologic screening and examinations, giving them the proper medical treatment. We brought in genetic counselors and also dentists to help educate them on how to mitigate or decrease the risk for disease. We've taught them how to clean their ears, promoted pneumococcal vaccination, and used the microbial data that we have to guide antibiotic selection. Unfortunately, because of the access to health care, we have not done any surgical intervention.

For us, this is an opportunity also to figure out if we did tympanoplasty, for example, if we tried to fix the eardrum, would they heal properly, or would persistent perforations occur because of their genetic defect? And we'd like to know more about that using the mouse model.

In summary, how does our research help management of otitis media? In the future, we want to know if a genotype or combination of genotypes will help predict our risk for otitis media, whether it's recurrent or chronic, if it's predicting risk for hearing loss and other complications, including occurrence of cholesteatoma, whether they are associated with a specific microbial profile that might guide our use of antibiotics and surgery, and eventually novel treatments for specific genetic variants.

We're nearing the end. I'm going to the non-genetic component of our study. What we did, we took samples from the middle ears of individuals undergoing surgery at the Philippine General Hospital. So you can see here from the left panel, a picture of cholesteatoma, that's the keratin debris that you see on the upper left. And then you also have granulation tissue, or inflamed middle ear lining that was sampled. So what we found in these samples, if you compare the cholesteatoma itself versus the mucosa or the granulation tissue, there's lower biodiversity, or there are less bacteria that are detected in the cholesteatoma, and the pus or middle ear discharge compared to the middle ear lining.

And the types of bacteria that we found, it would be helpful, because these are not your typical bacteria. We see Porphyromonas, Fusobacterium, for example, that's more in the cholesteatoma than in the mucosal tissue. Similarly, if you grouped by cholesteatoma diagnosis, whether a person has cholesteatoma or not, we see differences in the other types of tissues.

Overall, what this leads us to think is depending on the bacterial studies that are done intraoperatively, and then submitting those samples for antibiotic sensitivity tests, then it will be helpful to guide how to give postoperative antibiotics. And this is important because in many cases, what we've been using may be studies from 20 years back. And so what's happening is we keep pushing the microbial profile of the patient towards more and more infection with bacteria that are not being treated well. So what you might see is recurrence of cholesteatoma, and otitis media.

All right. Last few slides, for the future directions of our research, we'd like to look more into viruses, how our immune system responds to the different otopathogens with their genetic background that we see, application of new analysis techniques, and also sequencing, the latest sequencing techniques that we have. And eventually, what we want

to see are comprehensive profiles that will allow us to predict risk for children so that we can identify them early if they're going to have recurrent or chronic otitis media. And so we can implement some preventive measures. Lastly, this is a slide that somehow outlines all the otitis media research excitingly going around the world. And so for Hearing Health Foundation, I hope that you continue to support early stage investigators that are working on otitis media, so they can also contribute in decreasing the burden of hearing loss. Thank you.

DR. LALWANI - Well, that was an amazing talk, just really amazing. It's kind of interesting that in the past, we would have never thought about genetics, or genes, playing a role in otitis media. We just thought it was bacteria. And now, you're showing us that it's not only the genetics, but the population of bacteria as well. We no longer think about a single bacterium being important as much as the population of the microbiome of the bacteria. So that's really fascinating.

One of the questions we have from Sharon Jenkins, she asked, as she's been a teacher of the deaf and hard of hearing for about 28 years in Chicago, and over the last few years, she's seen fewer students with conductive hearing loss, and then it may, I'm sorry, then the recent uptake in the last five years. So have you found a reason why ear infections may increase or decrease over time? Is it a population-specific thing? So maybe if you could broadly comment about what leads to prevalence just going up and down of conductive hearing loss, that'd be great.

DR. SANTOS-CORTEZ - All right. So it also depends on the characteristics of the population you're looking at. So for example, if you're talking about very young children, if they have less of the risk factors, which is great, that might be better breastfeeding, less smoking, less daycare, also early catching of the infections as they come, so they get treated, or they're surveilled, or watched more often. So these contributed to a decreasing of acute otitis media incidents. And what we're saying here is there's still a segment of the population that even if you tried to give them all the benefits of what's around us, including vaccination, they might still have some of the recurrence or chronicity.

Following them over time, that might also give us an idea of what's going on in that population. What we also see is there are differences in the genetics of different populations. So for example, the FUT2 variant, it's not significant in the Finnish population, but the ABO variants are. So depending on what the genetic background of your population is, that might also change how they manifest otitis media.

DR. LALWANI - We have a question from Jane, what are possible complications from chronic childhood ear infections for adults aside from hearing loss, and are there ways to prevent or treat these possible long-term consequences? And what do you recommend?

DR. SANTOS-CORTEZ - So the good thing is around the world, it has improved quite a bit. Many of these complications that you find in textbooks, they're quite rare now, but they still exist. You can still see them. So there was a slide that I presented where you can see it can affect the cranial nerves or the facial nerve, for example, where you can have facial paralysis, you can have the infections extend to the soft tissues close to the middle ear, where you can see it here, or down here, or even to the neck.

For these types of infections, the important thing is to try to treat the middle ear infection, drain if there's any pus that's in there, and in the affected structures, for those that have problems in the middle ear, bones that connect your eardrum to the inner ear, that's fixed by the otologist by reconstructing those middle ear bones, so that you can hear again, and a few try to repair the eardrum also that contributes to better hearing.

For other severe infections where you have brain abscesses, that's an emergency situation. Usually it's the problem in the neurology, or in maybe in your balance, or in how they move their limbs that would manifest first, or in sensorium, or in how, whether they're awake or not. These are the ones that manifest first that's primarily a neurosurgical problem that has to be treated, and then we can go to the middle ear and treat the source.

DR. LALWANI - So you know, you showed several the genetic predispositions to otitis media, and I think you're possibly saying that they lead to more susceptibility in certain bacterial infection over others. Or more viral, could you talk about that some more? Larry wants to know, did you say that depending on one's genetic profile, that they may be more prone to infection to certain microbes than others?

DR. SANTOS-CORTEZ - Yes. So that's what we're seeing. It seems like depending on what variant you have, you might have a different profile in your middle ear, even in the back of your nose, your nasal pharynx, what types of bacteria might be more prevalent. And in this case, we're talking about not just the bad bacteria, the pathogens that cause the infection, but also the commensals, or the good bacteria that are normally in the back of the nose. It might make it to your middle ear when you have an infection.

It's important because the balance of the good bacteria and the bad bacteria in your nasopharynx, they predict your risk for otitis media also. And they also contribute to your immune response or to the response of your defense system against infection. What we

want would be a good balance between these bacteria, rather than eradication of all bacteria. That will not be good. We want to have more of the good bacteria in our nasopharynx, or in the back of her nose, so that our middle ears also stay healthy.

DR. LALWANI - There's been a lot of work on changing the bacterial composition that we have in our body, and like, you know, eating stool for the GI tract, or blowing bacteria, or taking probiotics. Do you envision a future where, you know, the balance of bacteria could be restored in a nasopharynx, which may be a source for otitis media? Do you think something like that may be a part of what we do down the road?

DR. SANTOS-CORTEZ - That's an active area of investigation that's very interesting. People have tried that, even done clinical trials, wherein they sprayed in nose with bacteria that are known to be good, for example, Corynebacteria, this is known as a good commensal. And so there are some active studies doing just that, trying to make probiotics for middle ear health.

DR. LALWANI - There is a question that you may or may not have the answer to for one of our listeners. What is the combined sensitivity of otoscopy and tympanometry findings in otitis media with effusion? It's a very specific question, not really about your presentation, but if you have an answer, that'd be great.

DR. SANTOS-CORTEZ - So for that, it really depends on what type of otitis media you're looking at, it will vary. So if you have a perforation already or middle ear hole, right in the eardrum, then tympanometry will not help, because you already know that's going to be a type B, whatever you do. So it will vary. We have a manuscript written up based on that slide, where we have the hearing losses, and we have the sensitivity, sense specificity profiles. What we see is it really depends on what's the current condition of the patient when you're doing the tests.

DR. LALWANI - Got it. Susan asks what should be taken under consideration when using PE tubes as a treatment for otitis media?

DR. SANTOS-CORTEZ - Oh, that's a full article.

DR. LALWANI - I know.

DR. SANTOS-CORTEZ - Maybe we can just give you the article for that. There's the one that recently came out from Rich Rosenfeld, we'll just provide that.

DR. LALWANI - Biofilms and otitis media. What is the current understanding of their roles in recurrent ear infections, are they not being effectively treated with antibiotics?

DR. SANTOS-CORTEZ - So this is really exciting, because there are a lot of new data coming out in terms of biofilms, how both the host defense system contributes to the formation of biofilms, and obviously the types of bacteria that contribute to it. And there's some exciting research coming out of Lauren Bakaletz's group for example, wherein they do some kind of, how they target the scaffolding that you find in the biofilm so to get rid of it. So I think is a very active area of investigation that you should look out for in terms of treatment.

DR. LALWANI - Are there any earlier markers that show whether otitis media-related hearing loss will result in permanent conductive hearing loss?

DR. SANTOS-CORTEZ - There are studies on audiometry. This has gone on for several years now, where they say you see something in the audiometry result, if there's a specific air-bone gap, and then you couple that with what you see in the otoscopy or the imaging, then you can predict that there's a circular discontinuity, meaning that the connection between your middle ear bones are broken. And that will give an idea to the otologist that they have to repair those bones. So that's one. There are also new techniques for imaging that are coming up aside from the usual imaging MRI, CT, that also tries to detect biofilms, and how to associate that with specific bacteria. So I put that in the last slide. Those are probably coming up in clinical trials in the years to come.

DR. LALWANI - Some clarification, you had mentioned that you can develop high frequency hearing loss from chronic ear infections. Is this for children, or adults, or both?

DR. SANTOS-CORTEZ - All ages. It can happen to anyone. I think that's what I wanted to make clear. People think that you can only have hearing loss if you have a chronic infection that's been going on for many years. Unfortunately, that's not true. Studies show that you can have residual hearing loss, even from just one about, or multiple bouts of acute infections when you were a kid.

DR. LALWANI - You know, one of the risk factors you mentioned was smoking. And I think that's a really interesting one, in that it not only affects, of course, the microbiome, it affects the vasculature. There's a lot of literature about causing sensorineural hearing loss. What's your advice for families that have smokers and stuff? What do you normally, would tell those parents?

DR. SANTOS-CORTEZ - Of course we'd want them to quit, right? But that might be difficult. So try to smoke outside, away from your children, of course. Because we already know when there's more exposure to different components of tobacco, of the cigarette, it's not just the nicotine, but other things in there. Also the particulate matter when there's a lot of pollution, wind, or when they're using firewood inside the house, all of these, they contribute to otitis media. So exposures to these kinds of smoking, smoke inhalation, it really is bad for your respiratory health. So we just try to reduce exposure as much as we can.

DR. LALWANI - Audrey wants to know what can be done about frequent ear infections due to eustachian tube dysfunction? And if you could also talk about, is there a familial, eustachian tube disfunction can run in families, probably from skull base formation stuff. Any thoughts about the genetic component of eustachian tube dysfunction, and embryonic formation and stuff of the Eustachian tube? What are your thoughts about that?

DR. SANTOS-CORTEZ - So there are a lot of known genetic conditions that contribute to eustachian tube dysfunction. Cleft palate is the most common. We already know that if your palatal muscles don't work, it contributes to eustachian tube dysfunction, then you can not drain the fluid from your middle ear. And that causes otitis media. There are other conditions of the craniofacial structures. What we found, for example, in A2ML1, we know that this looks normal from the outside, but in the mice, we have some preliminary data wherein there are some, there's some changes in the dimensions of the skull of the mice, suggesting that being humans might also have some differences in their eustachian tube structure. So you cannot really operate on them.

There have been some trials on how to do operations in animal models, with eustachian tube deficits, but this has not been applied directly to humans. For now, what we do really is surveillance, try to minimize effects of the infection on their hearing, by putting in tubes, trying to diagnose infection early. This is really what's going on. We can't do much more, right, Dr. Lalwani? I wish there was more.

DR. LALWANI - There's another very interesting question, which is, is there any link between climate change and otitis media?

DR. SANTOS-CORTEZ - This is very new. There's only a few articles that have come out in this. I think there will be more in the future. They're saying that it does have a difference, whether it's the smoke inhalation from wildfires, for example, that might contribute to otitis media, or increasing pollution. And there are only a few, I wish there were more studies coming out in the next few years. You'll probably see more of those associations.

DR. LALWANI - Well, I like to thank you for a wonderful talk. It's opened up our ears and eyes to what otitis media can do, its long-term consequences, what causes it, but more importantly, how genetic influences could impact otitis media, really very cutting edge stuff. And I know that HHF is very proud to have supported your work, and we take credit for all your wonderful, wonderful stuff you're doing. And thank you for all, everybody who's attending, for attending the presentation.

And of course, Dr. Santos-Cortez for this informative research presentation on chronic childhood ear infections and related hearing loss. Hearing Health Foundation is really so, so fortunate to be able to fund this important research with your help. Remember that you can donate to our efforts to advance better treatments and cures for hearing imbalance conditions at hhf.org\donate. Thank you again. Thank you, Dr. Santos-Cortez. Thank you to our attendees, please enjoy the rest of the day.

DR. SANTOS-CORTEZ - Thank you.