[MUSIC PLAYING]

ALEJANDRO HOBERMAN: It's a pleasure for me to present to friends and colleagues about our work over the recent years in the diagnosis and management or acute otitis media. I have to disclose that through the University of Pittsburgh, I hold two pending patents in this area. As a framework for this presentation, I will use the American Academy of Pediatrics 2013 diagnosis management guideline.

This is a frequently occurring problem. It's the most common reason for children to be prescribed an anti-microbial. Acute otitis media accounts for 18% of ambulatory visits, 11 million visits every year. There are about 280,000 tube operations being done yearly in children less than three years.

There is a direct cost for management of this condition of $2 billion a year. The peak incidence is during the first two years of life. 60% to 70% of children experience an episode of acute otitis media before their first birthday. Onset during the first six months is associated with the likelihood of recurrent acute otitis media. And recurrent acute otitis media occurs in about 20% of children.

This is an old slide, but I like it. Otitis media is like life. We know where it starts, we know where it ends. The difference is the quality of what happens in between. The red dotted line shows that every child will experience spontaneous resolution, even in the absence of anti-microbial therapy. The goal of anti-microbial therapy is to eradicate pathogens from the site of infection, so that symptoms will resolve sooner, and that's the delta one, or that at any given time, fewer children will experience symptoms.

Going back to the American Academy of Pediatrics practice guidelines, this was the section on diagnosis. It has 1A, 1B, and 1C. C 1A basically says that clinicians should diagnose acute otitis media in children who present with moderate to severe bulging of the tympanic membrane or new onset of otorrhea not due to otitis externa. So moderate or severe bulging, you don't need anything else.

1B is that clinicians should diagnose acute otitis media in children who present with mild bulging of the tympanic membrane. But now you need to have something else.

You need otalgia, evidenced by holding, tugging, rubbing of the ear, or intense erythema of the tympanic membrane.

So moderate or severe bulging, nothing else is needed. Mild bulging, you need something else, pain or intense erythema of the tympanic membrane. And most importantly, 1C, we should not diagnose acute otitis media if the children do not have middle ear effusion.

Now, over the years, our group has developed serious multimedia tools to improve the accuracy of diagnosis in acute otitis media. I am not certain we have internet connection in the room now, so I'm not going to play with them and try to show you anything. I'm just going to tell you where to find them.

The New England Journal of Medicine has videos in clinical medicine. There is two that we have developed, one on a otoscopy and cerumen removal, the second one on diagnostic tympanocentesis. There are many modules on the peds education .pitt.edu website under the ePROM modules, funded by the AAMC and the CDC.

ePROM stands for Enhancing Proficiency in Otitis Media. And we have worked in algorithmic thinking about how to diagnose otitis media. This was the latest iteration of the algorithm published by my colleague, Nader Shaikh, that first we have to make a decision whether the ear drum is bulging, yes or no. If the ear drum bulging, we have acute otitis media. If the eardrum is not bulging, then the question is, is it opaque or do you see an air fluid interface?

If you do, it's otitis media with effusion. If you don't, it's no effusion. Keeping in mind always, as my mentor Jack Paradise says, that this is a disease continuum. It starts in acute otitis media or in otitis media with effusion and it goes in both directions. And where you catch it sometimes may be somewhere in the middle.

So these are examples of a normal tympanic membrane. A mild bulging of the tympanic membrane, or 1-plus bulging, as we call it, generally. Moderate bulging of the tympanic membrane, you don't see the short process here any more of the malleus. And distinct or severe bulging of the tympanic membrane, when the whole thing is gone and all you see looks like a bagel or a donut, and it's umbilicated in the center. It has this central concavity that is characteristic.

This is what I mean when I say intense erythema. I'm not talking about vessels, like the spokes of a wheel from the center to the periphery. We're talking about patches of hemorrhage on the tympanic membrane or petechiae on the tympanic membrane.

And this is the 1C statement of the American Academy of Pediatrics, that we should not diagnose acute otitis media with a pink or red tympanic membrane in the absence of middle ear effusion, understanding that we will miss some children. That this could be time zero for otitis media in most instances, but most children with a viral illness will have a little bit of a red eardrum, particularly after they are crying for a little while, while you are trying to look at the ears.

So on the right side of this slide, you have the acute otitis media severity of symptom scale. Nader Shaikh has become they world expert in the patient-reported outcome tools, and he has developed one for acute otitis media. This is called the AOM-SOS, severity of symptom scale, one for acute sinusitis and another one for acute pharyngitis.

This one has five items. And the five items, in case you cannot read them, are, is the child tugging, rubbing, or holding the ear? Is the child crying more than usual? More irritable or fussy than usual? More difficulty sleeping and having fever? So this is zero points, one point, or two points, so maximum ten on this version of the scale. The one I'm going to share with you in some of our work had seven items. We dropped two items because they were not as sensitive as these five items.

So I'm going to talk about this scale a little bit more later, too. Now, when I was in the early 90s, I was still a fellow in ambulatory pediatrics with Jack Paradise. My other mentor was Ken Rogers. And Ken used to tell me that when he-- the story, when he was stationed as a physician during the Second World War in the Philippines, the planes would come by, and he will have to make a split instant decision whether they were allied or enemies.

And he wondered if some of our thinking about acute otitis media was similar, in which we get a glimpse of the eardrum, sometimes a split second, because the wax closes in or the speculum moves or the child moves or the holder is not-- or there is no holder, as another option. And then we make a quick decision.

So for the millennial generation, we created the otitis media game.

[LAUGHTER]

I can try to play it, but I'm not sure we have internet connection here today. Let's see if it works. Oh, yeah, it works. This is on the peds education website. And if you want to play along with me, you are more than welcome.

And the goal here is going to be to yell A if you think it's acute otitis media, O if you think it's otitis media with effusion. No if it's no fusion, and if you don't know, you can say, "oh no."

[LAUGHTER]

Don't worry about it. We're not dealing with blades here. The lives are fake otoscopes. So if you make a mistake and you lose a life, you're losing a fake otoscope. Or And after you lose the five otoscopes, then you get a score, and then you can compete with each other in the future.

[LAUGHTER]

But this is about the time that we get when we are looking at the eardrums many times. I'm going to let one go, so I lose a life. OK. So you see the amount of time that we get. We're going to say no.

AUDIENCE: No.

ALEJANDRO HOBERMAN: OK. Good. A.

OK.

[LAUGHTER]

AUDIENCE: O.

ALEJANDRO HOBERMAN: You got to tell me fast.

AUDIENCE: A.

ALEJANDRO HOBERMAN: You're good.

AUDIENCE: A.

O.

A.

ALEJANDRO HOBERMAN: That was O.

OK, let's lose the last slide. There we go. So we've got a score. We didn't do that good. But we can do better. You can keep playing.

[LAUGHTER]

OK.

So the management guideline, going back to the American Academy of Pediatrics guideline, had recommendations in children less than two years. If they had otorrhea with acute otitis media, antibiotic therapy should be indicated. If they have unilateral or bilateral acute otitis media with severe symptoms, and severe symptoms means otalgia, moderate or severe, or fever more than 39 degrees centigrade, the child should be treated with antibiotics.

If they have bilateral disease without otorrhea, they should be treated. But they had this point here, unilateral acute otitis media without otorrhea, where they open the option of observation.

I did not like-- I was sitting on this committee. I did not like it very much. Because we were sitting on data. In those days, I was sitting on data from Pittsburgh, and there was a parallel study that had been done in Finland that basically did not indicate that unilateral otorrhea was any different than-- unilateral disease was any different

than bilateral disease.

So we warned, I sat at that committee. I says, don't say this. Don't say this. I was ignored to the committee. I was the only voice that was against this, so I lost. They had to put it very clear that I did not agree with this in the bottom of the recommendation. AH is me.

[LAUGHTER]

OK. And then we went on to report this study. So this study we've done was funded by NIAID. And this is-- I'm sorry, as large the font as I could get for you to be able to do it. But I read you the numbers, so you can see them.

We screened 1385 children. This was a placebo-controlled study. Of those children, about 500, 498, were eligible to participate. Of those, we enrolled 291. And they were divided half and half between amoxicillin clavulanate at 90 per kilo and a placebo. And they were followed at 4 to 5, 10 to 12, and 21 to 25 days.

We're pretty good at getting these children back and seeing them. We do intention to treat analysis, so all children are included. This was published in New England Journal of Medicine in 2011.

The population of children that I'm going to show you in the series of studies is always going to be the same. These are studies in children under age two years. If you want to do otitis media research and show that things always work, do it on three and four-year-olds, everything works. If you want to really find out, you have to stay under age two.

And now the FDA requires that all studies need to be under age 24 months. So in our case, 50-some percent of children, no differences between the two treatment groups, were under one year. The other half were between one and two years.

Showing the inferiority of the gender, always you get more boys than girls having acute otitis media. There's no differences in race and health insurance and maternal level of education. Half the kids are exposed to other children on a regular basis in daycare.

This is the 14 item scale, so these are 7 items. So we get a maximum of 14. They

get a baseline score of about 8 in each of the two treatment groups. Half the kids have bilateral disease, and 3/4 of the kids have moderate or severe bulging of the tympanic membrane.

Symptomatic response. The FDA in those days was very interested in time to event analysis. We did not like time to event analysis. Under the advice of our senior biostatistician Howard Rockette, it's kind of a shaky outcome in the sense that children get better and then eventually, the symptoms pop up again.

So time to event getting a score of 0, 1 once was not significant. So Howard pushed us to say time to event two times. They want to have a consistent resolution of symptoms. So that finding was significant.

And now the FDA, after discussion and Howard and I went and met with them multiple times, agreed that the best outcome is actually the generalized estimated equation approach of actually measuring the scores, the mean scores every day and then computing that over a period of time.

So this is the mean scores over time. That gives you a one value with a standard deviation, a confidence interval, a p-value, and you can compare the two treatment groups as to what were the symptoms overall over that period of time.

Now, the main outcome of this study, the presence of a treatment, the categorisation of treatment failure at day 4 to 5, 3% treatment failure in the antibiotic group, 23% in the placebo group. At the end of treatment, 16%. Remember that number.

That's what we get when we finish treatment with the best antibiotic we have in the market now, amoxicillin clavulanate. You still get 16% of children that have bulging tympanic membranes at the end of treatment and most of them with symptoms. And placebo was 51%. And those findings were significant.

There were no differences in the response to antibiotics between severe and non-severe otitis media. Of course, the severe children tend to have higher failure rates. But there is a three time increase of failure rates when you do not treat, whether it's severe or non-severe. So 20% goes up to 60% and 15% goes to, like, you know, 45%.

So it's literally a three time-- a higher likelihood of treatment failure if they are not

treated with antibiotics. And of course, if have clinical success at the end of treatment, the scores go down. If they don't, the scores stay relatively up.

We looked at prognostic factors that help us predict who may end up having a treatment failure, and there were four that were significant. Exposure to other children, having a score of more than eight, having bilateral disease, and having marked bulging of the tympanic membrane.

And all of those were significant, and the effect of these prognostic factors were additive. So if you had one, if you were treated with placebo, 27% of children will have treatment failure. I'm sorry.

If you had zero, 27%. If you had one, 30%. Two, 60%. Three, 71%. Four, 100%. That means that a child who is in daycare, who has a score of more than eight, who has bilateral disease and a bulging tympanic membrane, and you don't treat them with antibiotics, 100% of those are going to fail at the day 12 to 14.

Of course, if you treat with antibiotics, you get adverse effects. And children who did not receive antibiotics, one child had mastoiditis. Diarrhea was more common among children who received amoxicillin clavulanate, 25% versus 15%.

Actually, it was 7% with a placebo, but then they get rescue treatment, and it goes up to 15%. More diapers dermatitis necessitating the prescription of an anti-fungal cream, and more thrush. And children who did not receive antibiotics were most likely to have perforation of the tympanic membranes.

These are the data I was sitting on and why we told the American Academy of Pediatrics, don't go on and recommend option of observation in children with unilateral disease. And these data, at the same time we did our study, the Finnish were doing their own study, Paula Tahtinen and Aino Ruohola.

And they [INAUDIBLE] on the same issue of the New England Journal of Medicine. And then we put together our data with their data, restricting their data to children under age two, because they went up to age three originally.

And we classified the ear infections from the least severe to the most severe. So we have unilateral non-severe, unilateral severe, bilateral non-severe, bilateral severe.

Combined the data from the two clinical trials, and the relative risk, as you see, there is no difference between these treatment groups. It's 0.3, 0.4. And the absolute risk reduction is 0.3 pretty much across, and the number needed to treat is the same.

So there is no difference between unilateral, bilateral, severe, non-severe. The benefit of anti-microbials in children under two was noted in across the board.

With regards to anti-microbial treatment, the guideline is pretty straightforward. It basically says amoxicillin, amox-clav, ceftriaxone. That's the order. Nothing else should be allowed.

So amoxicillin if the child has not received amoxicillin in the past 30 days, does not have allergy to penicillin, and doesn't have conjunctivitis. Amox-clav if you need better lactamase coverage, if they've received amoxicillin within 30 days, they have purulent conjunctivitis or a history of recurrent acute otitis media, which has not responded previously to amoxicillin properly.

And of course, we should be available to talk to them in 48 to 72 hours and determine if a change of therapy is needed. So this is the steps. If amoxicillin fails, you go to Augmentin. If amox-clav fails, you go to ceftriaxone. This in the middle, cephalosporins, is just in case there is true penicillin allergies.

It doesn't work to switch from amox-clav to Omnicef or Cefdinir, assuming that you are going to be using a new class of antibiotics, and in this case, it's going to make a difference.

And if you use ceftriaxone, we'll talk about what's probably the right dosing. Why don't I like Omnicef or Cefdinir as a choice in antibiotics? In the mid-2000s, whenever Abbott had Omnicef and it wasn't generic, they tried the same thing as the amox-clav people tried, double the dose and see if we can cover the penicillin resistant streptococcus pneumonia, and it did not work.

So you can see from this slide, we use 25 per kilo. The dose that we prescribe, Cefdinir, is 14 per kilo, not 25. And what we found, these are double tap studies. So we tap, we treat with an anti-- we get an organism, we treat with an antibiotic, and we tap again at day four to six to determine if the germ is gone.

And if the germ is not gone, that's going to be treatment failure. So it worked for penicillin susceptible strep pneumo, 92% eradication. It did not work for the intermediate. It did not work for the resistant. It wasn't that good for Haemophilus influenzae, as we suspected.

And then if you don't eradicate the organisms, the clinical cure rates and in the 50% to 60%. And remember, placebo was 50%. So this is not much better than placebo with regards to clinical cure rates. They are for intermediate or resistant streptococcus pneumonia.

Now, if you use ceftriaxone, it's a different story. It's a very effective antibiotic. It hurts. And the data we have available is for one dose versus three consecutive doses at now and 24 and 48 hours. We don't like that very much.

[INAUDIBLE] that I over the years have switched to using, instead of 50 per kilo that get you those levels you see over there, we use 75 per kilo. And so we get probably a little bit higher peaks than what you see here.

And it doesn't make sense to give another shot at 24 hours when the drug is at its peak. So we usually do it at 48 hours and probably get another peak down here that will get us closer to the nine or ten days of treatment. And the thinking is, in general, with beta-lactam drugs, that you want to stay above the MIC of the organisms, at least 40%, 45% of the dosing interval, to achieve good clinical cure rates.

So if you think of an MIC of one, you really want to stay above that most of the time, as much as you can, at least half the time.

So in the year 2009, the NIAID folks from the Division of Microbiology and Infectious Diseases had a call for applications looking at reduced duration anti-microbial therapy for three conditions, acute otitis media, urinary tract infections-- four conditions. Bacteremia and community acquired pneumonia.

We all applied right away. We got funded on the acute otitis media site to do that. On the second submission, the folks from Philadelphia, and we were included with them. We got funded to do the short duration, long duration treatment for urinary tract infections.

And I have to say that Dr. Judy Martin in the General Academic Pediatrics Clinical Trials Unit got funded this year to do, together with Vanderbilt and Children's Hospital of Philadelphia, to do the community acquired pneumonia. So we're basically participating in all three conditions for the short course versus standard therapy for children with evaluation of anti-microbial resistance.

So this study was a randomized, double-masked placebo controlled study. 600 children were to be enrolled, 6 to 23 months of age. It was supposed to last five years at three sites, here at the primary care center, the emergency department, pediatric Pitt med offices, and Kentucky Pediatrics and Adult Research Bardstown, Kentucky, where my friend Stan Block has been doing otitis media research for many years.

The main outcome was the efficacy. We used a consistent treatment strategy, which means that if the child had acute otitis media multiple times through the respiratory season, every time they had acute otitis media, they would be treated with either the five days or the ten day treatment group in a double blinded fashion.

So we will know at the end of a year later, children who were exposed to half the antibiotics, did they have less adverse effects? Did they have less resistance? And so we compared reduced duration, which was five days of amox-clav, followed by five days of placebo, versus standard duration, which was ten days of amoxicillin clavulanate.

And we looked at the impact on anti-microbial resistance. Every six weeks, we saw them, we swabbed their noses. We analyzed the results, and we continue to analyze the results of what we found longitudinally.

The end points were the proportion of children categorized as treatment failure at day 12 to 14, secondary outcomes included anti-microbial resistance, AOM recurrences within 60 days and within the respiratory season, the number of days of antibiotics during the respiratory season, symptom burden over time with the acute otitis severity of scale.

And again, we only looked at between day 6 and day 14, because this would be the first day that potentially somebody would receive placebo. During the first five days, everybody got on anti-microbial treatment. We looked at the proportion of

recurrences that were categorized as treatment failure, so we saw them over time. So we had another 400, 500, 600 ear infections that we could determine outcome because they were treated in the same way.

And we looked at adverse events. Protocol defined diarrhea, diaper dermatitis, and use of health care resources, and parental satisfaction with treatment.

The results of this manuscript will be published over the next few weeks, and that's as much as I can tell you. There were a total of 1569 children that were assessed for eligibility. Almost 900 were eligible to participate. The ones that are not eligible, they don't have otitis, they don't have enough symptoms, the caregiver is the grandmother and cannot enroll in the study, they don't have pneumococcal vaccine, multiple reasons.

520 underwent randomization. Why 520 and not 600? We wanted to go to 600. We were not allowed to go to 600. At the second interim analysis, the Data Safety Monitoring Board of the study concluded that we had accomplished the goals of this study, and it was unethical to continue to randomize children. And they told us to stop this study.

And of the 520, there were five that we mistakenly enrolled that were ineligible after randomization, so we dropped those five. So we're dealing with a total of 257 and 258 in each of the two treatment groups. We follow them over time. And let me share with you the findings.

Again, same population of children. Half are under age one year, the other half are one to two. Always a little bit more of otitis media in boys than girls. Race, there is no difference. Exposure to other children, 50% to 60% of children, in this case, closer to 60%, were exposed to other children on a regular basis. The scores, this is the 14 item scale. Again, eight and eight between the two treatment groups, no difference. Half the kids have bilateral disease and over 80% of the kids have moderate or severe bulging of the tympanic membrane.

Remember the 16% I told you, I reminded you before? We found the same 16% with ten day treatment. No difference. So 16% treatment. However, the five day treatment group, more than twice as many children were categorized as treatment failure. So five days did not work.

And it didn't work. It was sinus and non-inferiority study, and Howard Rockette was shocked by the fact that in a non-inferiority study, we were able to show superiority of one treatment versus the other one, which statistically is very hard to accomplish. So there were so striking differences between the two treatment groups that it was a no-brainer.

With regards to symptoms, there were differences with the symptom burden between day 6 and 14, the symptoms at day 12 to 14, and the proportion of children in whom the symptoms decreased more than 50% from baseline to the end of treatment was higher in the ten day group than the five day group.

There was no difference in the rate of acute otitis media recurrences over time. A little bit more middle ear effusion at the end of treatment in the children who got five days of treatment. And let me tell you one finding of this study that is going to be interesting is that of the kids that have middle ear effusion at the end of treatment, they have fluid in their eardrum, those are most likely to develop recurrences during follow-up.

We are going to be the first time to-- believe it or not, this has never been reported in pediatrics, that the presence of fluid at the end of treatment is the best predictor of recurrence over the next few months. And the number of days of antibiotics, of course, was a little bit higher than the ten day group than the five day group. And there were no differences in diarrhea, no difference in diaper dermatitis. So shorter course of antibiotic, no benefit with regards to adverse events.

We looked at the same prognostic factors that help us predict who's going to have a treatment failure, and only two-- exposure to other children and laterality, bilateral disease, were predictive of a higher likelihood of treatment failure with odds ratio of 1.7 and 2.9. And again, the effect was additive. So if you had one of those, you had 1.4. And if you had the two present, it's four times more likely to result in treatment failures.

Resistance. At entry, they were the same. We looked at only streptococcus pneumoniae and Haemophilus influenzae. The two groups were comparable at entry in the nasopharynx. At the end of treatment, amoxicillin clavulanate is very

good at eradicating some of the-- most of the susceptible strep pneumo. A little bit of the intermediary or resistant are gone. But there is a relative increase of the resistance at the end of treatment, right at the end of treatment, but that actually fades away and disappears immediately afterwards.

Once you look at children at the recurrent episodes, there was no difference between the treatment groups. When you look at them, when you see them healthy, every six weeks, there is no difference between the two treatment groups. When you look at them one year later, June and September, there was no difference between the two treatment groups, even though they were randomized to get five or ten days every time they had an ear infection.

So the presumption that if you use a shorter course of treatment, that would result in reduced anti-microbial resistance, in the case of the study, was wrong. We did not make any kind of advance in shortening the duration of treatment. And we lost a lot with regards to treatment failure rates that were much higher in the five day group.

Haemophilus influenzae is a totally different story. You don't touch Haemophilus influenzae in the nasopharynx. So the colonization rates are the same. Beta-lactamase production is the same, no change. So amox-clav does not affect Haemophilus influenzae in the nasopharynx.

So the conclusion, what you're going to see in print, is going to be that in children 6 to 23 months of age with acute otitis media, reduced duration treatment resulted in less favorable outcomes than standard duration treatment. And in addition, neither the rate of adverse events, nor the rate of the emergence of anti-microbial resistance was lower with a shorter regimen.

Let me digress to another topic now. So this is one of the patents that I actually hold with the University of Pittsburgh, which we're trying to develop a reduced clavulanate, amoxicillin clavulanate concentration. Remember, I told you before that the rate of diarrhea with placebo was somewhere in the 7% rate? And the study by [INAUDIBLE] showed 8%. Another study showed 10%. So 7% to 10%.

If you treat with amoxicillin, you get about 17%. If you treated with amox-clav, you get 25% and above. 25, 27, depending on the studies. And the Finnish study was 48%. So high rates of protocol defined diarrhea when you use amoxicillin

clavulanate at 90 mgs per kilo, 6.4 of the clavulanate component.

We also know that we have no idea what is the level of clavulanate that you need to eradicate Haemophilus influenza. And if you look at babies, and we use a dose of 6.4, that's the approved dosing for amoxicillin clavulanate, we're doubling the dose of what we give to men or women on a per kilo basis of what they receive.

And when the drug was originally developed, the decision was to increase the amoxicillin, leave the clavulanate. Would More is good, that was the thinking. And apparently it was decided by the-- I was told by a CEO of GlaxoSmithKline at a meeting with the scientists at that time.

So the first thing we did is we went to Steve Pelton in Boston, Boston Medical Center, who has this recalcitrant strains of Haemophilus influenzae that have MICs to amoxicillin of 256. So heavy duty beta-lactamase producing strains of a Haemophilus influenzae.

And he tested the current formulation versus a formulation that has half the clavulanate or even less than half the clavulanate. And what we see, a 1:2 dilution is part of the error of the method. In order to see that they're different, you have to see a 2:2 dilution in comparison of the two groups. And some of these were even the same numbers between the 14 to 1 formulation and the 28 to 1 formulation.

So we met with the Food and Drug Administration. Howard Rockette and I went and had a face-to-face meeting with them and discussed with them, what would you need to consider this a reformulation of the drug that may result in the label of a new antibiotic?

And we agreed, after a face-to-face meeting and three teleconferences with the Jack Paradise and Howard Rockette that we needed to do a superiority study versus high dose amoxicillin, because that has never been studied properly. And the FDA always likes to advance a little bit what we know about a condition. And not a single good study comparing high dose amoxicillin versus a amox-clav.

And we concluded that for that study, we need about 1,000 children and that they need to be carefully diagnosed with acute otitis media with symptoms, using this scale that-- by the way, the Nader scale, the AOM-SOS scale, is becoming the

validated scale for Food and Drug Administration purposes for any study that done on acute otitis media.

They wanted me to do tympanocentesis in the event of treatment failure and to use co-primary outcomes, symptomatic response over the seven days. So we're going to use the weighted mean that I shared with you before, and the resolution of bulging at day 12 to 14. And statistically, we'll be able to tell a difference in scores and an 8% difference in treatment failure. And we'll do about probably 90 to 100 tympanocenteses. And we expect that, of the failures on amoxicillin, half are going to be beta-lactamase producing organisms. And fewer would be on the failures of amoxicillin clavulanate.

So at this point, we know that we can get IP and we can get a path for FDA leveling of a new drug. We also know that we have a drug that could eradicate the organisms, and eradication of the organisms results in high clinical cure rates.

Some pharmaceutical companies looked at our preliminary development phase, and they did some market research on their own. And they shared the market research, and we know that hundreds of clinicians were inquired about this. And they say that if there's a drug that has the efficacy of amox-clav and the safety of amoxicillin, they would be likely to move on and use that as a first line treatment for acute otitis media, and so probably would guideline committees.

But we didn't know whether reducing the clavulanate would reduce the likelihood of diarrhea. It was a hunch. So we are not sure. We had no proof that reducing the clavulanate would reduce the likelihood of diarrhea. And that's what we did next.

But we did a study that we took-- and we've met extensively with Howard Rockette and our other senior biostatistician, Jong Jeong, and concluded that we didn't do a randomized study. We can use historical controls. We know what the diarrhea rate for Augmentin is. We've done it on 150 kids in the placebo control group. We've got other 250-some in the ten day group.

So we took those 400 kids, and those are our historical controls. And we enrolled 75 kids and did an open label study with this reduced formulation. The first attempt, we use 90 and 3.2, which was half the dose of clavulanate. And it did not work. We did it on 40 kids.

So I'm glad we did the proof of concept. There was no change in diarrhea with using half the clavulanate. But then we started dosing on the second phase. We started dosing, instead of 90 per kilo, at 90 per kilo, which is within a guideline range of the amoxicillin, using the same formulation developed at the Investigational Drug Service of UPMC. And we now were providing clavulanate at 2.85, 10% less of what we started. And that actually did the trick.

The patients were now-- same patients, half the kids are less than one year. Kids are exposed to other children. Now we have a ten point scale, so the maximum is not eight anymore. It's six. And they have bilateral disease, and they have moderate and marked bulging of the tympanic membrane.

The rates of diarrhea went down from 26% to 18%, which is what you find with amoxicillin. Remember, I showed you 17%. The number of days until 15% of the parents reported protocol defined diarrhea went up to six days instead of four days. The diaper dermatitis went down by a third, from 34% to 22%.

And a clinical failure, and we don't have good understanding of this, was better. So there seems to be some synergy between amoxicillin and clavulanate that less may be best here. And I'm not going to make much out of 72 patients, but we had 12% treatment failure in this group.

But what we do know is that if we do a confidence interval of the difference, the only way that it could be worse would be 4% worse, minus 4. So in a study of 1,000 patients, this could only be 20% treatment failure, which would be very acceptable if we have a much better safety profile, which is what the FDA also wants to accomplish.

There were no differences in symptoms between the two treatment groups. And we went ahead and did some pharmacokinetics, pharmacodynamics. We drew blood of 50 of these kids at 30 minutes, one hour, one blood draw on each child at different times. And we found very interesting Cmax, Tmax, half-life, and so forth.

The absorption of clavulanate is not linear, so we gave less than half the clavulanate per dose. And we got a little bit of a reduction of the dose that you get. So most importantly, for amoxicillin, if I told you we need to be 40% of the dosing

interval above the MIC, we were 66% of the dosing interval above the MIC. So the levels were very high and appropriate.

And for clavulanate, which connects with the amoxicillin, in an environment of two micrograms of amoxicillin, you need basically to inhibit 93% of the beta-lactamases. You need that level of clavulanate, and we got higher levels than that. So we're comfortable that it will work very well to eradicate Haemophilus influenza that produces beta-lactamase.

So I want to digress to talk about automatic diagnosis of acute otitis media. So we know it's hard. We know that this is a straightforward case of acute otitis media. This is otitis media with effusion and that's a normal tympanic membrane.

We have shown pictures of eardrums to hundreds of trainees and hundreds of practitioners through our time, and we know that this is where we are with regards to sensitivity and specificity. And this is where we are with regards to pediatrician sensitivity and specificity.

So the thinking is that, can we improve? Can we create tools that can aid us in the diagnosis of acute otitis media? Can we go back to that algorithmic thinking and try to develop tools that may help us?

And working with the folks at Carnegie Mellon University and the chair of bioengineering, Jelena Kovacevic. We started working on classification system. Jelena is the queen of classification systems. She is the one that takes the pap smears and determines who has cancer based on a pap smear.

And the first thing we agree is the vocabulary and then the grammar. And the grammar is exactly the algorithmic thinking we talked about. Bulging, no bulging, opacity or air fluid level, to classify into the three categories. And then Jelena hired Anupama. Anupama was a PhD student there who worked for about a year in developing.

First, we did the automatic segmentation of the eardrums, getting rid of the ear canals to be sure that we are only looking at the eardrum. Next, she does what she calls specular highlights, and takes the hairs, the wax, whatever it is. And in my easy thinking of it, Photoshops with the pixels that are around that, so you will get a

picture that will not have hair, wax, or anything else.

Then she looks at the bulging eardrum at the donut and kind of opens up and exposes that central concavity and measures the number of pixels on that central concavity. And finally, she detects the malleus by automatic detection of the malleus. And lastly, looking at images with bulging tympanic membranes, looks at light reflection and topographic maps of the eardrum to help us identify the bulging of the tympanic membrane.

So then we compare that with generic classifiers, with general practitioners, and with the otitis media classifier. And this is the accuracy of general practitioners. This is the accuracy of all the other classifiers. And this is the accuracy of the otitis media classifier, almost 90%.

And with further improvements, we know that it can get up to 95% nowadays. Having said so, Jelena is also good friends with Nikhil Balram who was, until very recently, the CEO of a company in California called Ricoh Innovations. They make copy machines, lenses, cameras, and so forth.

And Ricoh was fascinated about the idea of automatic classification, and they were working on plenoptic cameras, or light field cameras. And what the light field cameras do is, instead of me looking at you through one lens, I'm looking at you through 400 lenses. And that allows a determination of three dimensions.

So now, the picture of the eardrum becomes a reconstruction of the eardrum that allows you to detect the bulging of the tympanic membrane. And to simplify it, it would be like having 400 of these views, a view from the superior area, a ventral view or inferior view that will look different no matter how you look at it. And you reconstruct the eardrum.

And you can see that normal eardrum is pretty flat. The eardrum with middle ear effusion has what they call a valley. And Tim Shope and Nader and I are working with them now and trying to help them apply what Anupama learned from the original classification paper to use this plenoptic camera and enhance it and get even higher levels of accuracy.

And the bulging tympanic membranes will show these mountains and these areas of

bulging that are clearly demonstrable when you're doing 3-D reconstruction. Let me show you how it works.

We've got some images from them. That's a normal eardrum. See how flat it gets? This is what the camera is going to be able to accomplish. At the end of the day, we hope that this would be a device-- let me show you an eardrum with a central valley with otitis media with effusion of retracted eardrum. And finally, the child with acute otitis media, where you can see definitely the bulging of the tympanic membrane, and it rotates the eardrum.

So the thinking would be, can we get a device that, as you walk into an emergency department, and nurse can get the temperature in the tympanic membrane or the forehead and then get this into the ear, and if there's not substantial amount of wax, get you an answer, whether it's AOM, OME, or no effusion. And then, before you treat with antibiotics, you're going to have to think twice or you're going to have to go look again to be certain that you can argue with the machine, when the machine hopefully is going to be 90% to 95% accurate.

So we're fine tuning the final steps. We're still gathering some information on children with acute otitis media this season.

I want to finalize talking about recurrent acute otitis media. The recommendations from the guidelines were that we should not prescribe prophylactic antibiotics to reduce the frequency of episodes of acute otitis media. Clinicians can offer tympanostomy tubes for recurrent acute otitis media. If children have three in six months, four in one year, with one episode during the preceding six months, based on a Cochrane review in which tubes reduce by 1 and 1/2 episodes within six months of surgery.

But you know, the caveat of tubes is that, of course anesthesia can result in focal atrophy, tympanosclerosis, retraction pockets, and so forth. We should tell everybody that they should be getting pneumococcal conjugate vaccine. We should use annual influenza vaccine in all children. Exclusive breastfeeding will have an effect in preventing otitis media, and avoidance of tobacco smoke will do us well.

This study we're doing right now, we were funded now by the National Institutes of Deafness and Communication Disorders to do a study looking at the efficacy of

tympanostomy tubes in children with recurrent acute otitis media. We enroll children during a screening phase in which babies that had early onset of otitis media, recurrent otitis media, otitis media during the summer, which is unusual, or they're in daycare and have an episode of otitis media. Once they had three in six months or four in one year, we randomize them to tympanostomy tubes or non-surgical management. And non-surgical management means temporary non-surgical management. If they continue to have recurrent AOM, eventually they will-- after two or three more, they will get tubes.

We will enroll 240 children. My co-PI is in Children's National Medical Center, Dr. Diego Preciado. And we're enrolling children up to 35 months in order to allow those recurrent episodes to occur. And we have two year follow up.

The primary outcome would be the rate of acute otitis media recurrence. We're looking at nasopharyngeal resistance, as well, and cost effectiveness of treatment. And the statistical considerations is we want to try to document that there is a 33% improvement by placing tympanostomy tubes to show that it's worth doing it.

We have, so far, enrolled over the first year of this study, randomized about 61 children until yesterday. So we're like, early beginnings. I would appreciate anybody that you see with recurrent acute otitis media, send them my way. 999-EARS is my phone number. Call me, please.

[LAUGHTER]

So in summary, I hope I told you that acute otitis media is frequently misdiagnosed, that bulging should be required, that there are educational programs that could be used to enhance the diagnostic accuracy, that in children 6 to 23 months old with acute otitis media, anti-microbial therapy is beneficial. It reduces time to resolution of symptoms and symptom burden.

It reduces the rate of persistent otoscopic signs of acute infection, and that's regardless of laterality and likely severity. In children 6 to 23 months old with acute otitis media, reduced duration of anti-microbials showed less favorable outcomes than standard duration, and there was no reduction in adverse events or the emergence of bacteria resistance.

And further research is warranted in improved diagnostics, enhanced safety profile of antibiotics, and the efficacy of tympanostomy tubes for recurrent acute otitis media.

Now, these things are not done alone. This is, all the staff of the Clinical Trials Unit at General Academic Pediatrics, I'm very thankful to each of them. Noel, Nick, Sonika, Katie, Nader, Marianne, Judy, Marcia Kurs-Lasky, Liz Thaxton, Katie. I think that's Michelle in the background. I can barely see it on my screen here.

Megan, Muriel, Marcia, Tim, Megan-- second Megan. Jennifer. We have an old Megan and a new Megan. We have an old Katie and a new Katie now.

[LAUGHTER]

And Gysella and Diana Kearney. And this is Jack Paradise on his 90th birthday last year in Boston. Bob Hickey and I were visiting with him. He turned 91 this year. We continue to work with him on a weekly basis. He gets a phone call from me, from Nader, from Raj. We talk to him all the time. He helped us write the manuscripts.

There's no way to publish a paper in the New England Journal of Medicine unless you have Jack Paradise on your side. There's no way to do it. So we continue to work with him constantly. And if he doesn't hear from me, in about a week, he will come and says, what are you guys doing? Do I have something to do?

[LAUGHTER]

So it's wonderful to have him on board. And frequently we get him to visit with us in Pittsburgh. So I also want to thank the sponsors of all the various studies that generously funded from NIH and Ricoh Innovations and Pediatric Pitt Med that helps us deliver all these studies. Thank you so much. And I want to open up for any questions.

[APPLAUSE]