



## *Otitis Media in Latin America*

*Adriano Arguedas*

I would like to discuss some important data on otitis media in Latin America. First I would like to highlight some general aspects, as well as some data on microbiology worldwide and in Latin America. I am also going to discuss about resistance patterns in our countries, but not antimicrobial therapies, however, I would like to show some results of studies with different vaccines, one of them already available and two that are being evaluated in phase 3 studies in different countries, many of them in Latin America.

Otitis media is one of the most important pathologies in the pediatric population, children — especially those with less than 5 years of age.<sup>1</sup> In Latin America, we do not actually have data on the incidence of the disease, we are gathering data in a study we have underway in Panama. In the United States alone, it is known that there are over 30 million cases of otitis media in children each year, and that approximately 2/3 of the children in studies followed up prospectively by doctors Teele<sup>2</sup> and Klein<sup>3</sup> had at least one event of otitis media before the age of three and that 25% of three year olds had three or more events; this represents in the United States high numbers which mean very high costs.

The microbiology of what can be found behind the eardrum up to the 90's, probably, it was fairly stable, and when we isolated bacteria we knew that the most frequently isolated microorganism in the USA was *Streptococcus pneumoniae*, and the second most common organism was *Haemophilus influenzae*. I would like to stress that **when we talk about *H. influenzae* in the middle ear, we mean non-typeable *H. influenzae***. I want to stress this because in a study concluded with 2,000 pediatricians worldwide, only 40% of them knew that when we talk about *H. influenzae* in the middle ear we are talking about the non-typeable *H. influenzae*, and this is important. We also knew that the third organism was *M. catarrhalis*.

However, after the introduction of the vaccine against *S. pneumoniae* there was a shift on the proportion of cases of otitis media caused by pneumococci and *H. influenzae* in the United States<sup>4-6</sup>. Before the introduction of the Prevenar vaccine (PCV7), 48% of the bacteria isolated from the middle ear were *S. pneumoniae*, 41% were *H. influenzae*; but after the PCV7, there was a reduction in the proportion —not in the number of cases, but in the proportion of cases of pneumococci isolated from the middle ear, with an increase up to

56% in the number of cases of non-typeable *H. influenzae* stains producing otitis media in the USA. Data we have from the USA, data from Sih from Brazil <sup>7</sup>, data from Chile <sup>8</sup> also showed that between 1998 and 1999 our microbiology was not that different, just that in Latin America, similarly to what happens in many other countries, *S. pyogenes* was more frequent than *M. catarrhalis*. In Costa Rica, from 2002 to 2007 we performed approximately 1108 tympanocenteses in children that came to our clinic with otitis media, and we divided them into three groups: Children with acute otitis media, children with recurrent otitis media, and children with failed treatment, and we saw how in these two groups ***S. pneumoniae* was more frequent — in acute otitis media and recurrent otitis media** — and we saw how **patients that had failed therapies had more frequently *H. influenzae*** (probably due to the biofilm that *H. influenzae* can produce in the middle ear) than *S. pneumoniae* — similar data to those presented in other countries, where **non-typeable *H. influenzae* was the most frequent**.

We observed, when comparing these thousand tympanocentesis with a similar percentage of tympanocentesis we performed from 1991 to 2001, how *M. catarrhalis* in our country and — and similar to what happened in Mexico—is increasing, surpassing *S. pyogenes* in this period, at least in our region. When we talk about the microbiology of otitis media and the choice of antibiotic, it is important to know the pattern of sensitivity in the bacteria found in the middle ear. In the USA how between 1983 and 1988 the percentage of beta-lactamase producer strains of *H. influenzae* in the middle ear was only 10% and how this has increased up to 35% to 40% nowadays.

In Latin America the percentage of beta-lactamase producer strains is different: data from Chile indicated that in 1998-1999 only 10% — similar to figures in the USA many years ago — of *H. influenzae* were beta-lactamase producers.

In Costa Rica we observed an interesting phenomenon: at the same time, in year 2003, only 5% of *H. influenzae* were beta-lactamase producers. In 2007 this number increased and, currently, in our country 14% of *H. influenzae* are beta-lactamase producers; and this changed or altered up to a certain point the antimicrobial recommendations in our country <sup>9</sup>.

Why? We have seen not only in Costa Rica, but also in Mexico, a considerable increase in beta-lactamase producers strains, and I believe that this is connected with the increase and bad use of antimicrobials in our countries. There is an increase, throughout the years, of *H. influenzae* beta-lactamase producers, and in our countries (Mexico and Costa Rica) there was a substantial rise in the use of amoxicillin within social security — it wasn't available for social security before—when the use of amoxicillin grew, there was also an increase in the percentage of beta-lactamase producers strains.

*S. pneumoniae* is also a great concern and it is important to recognize the percentages of resistance in our countries — there are data on middle ear strains from data published by Sih from Brazil <sup>7</sup>— in Costa Rica <sup>9</sup> we have approximately 20% of resistance, most are intermediate strains, in Chile <sup>8</sup> the percentages in 2007 was approximately 40%.

We have also managed to serotype pneumococci strains from middle ear, data yet to be published, from children with otitis media, 110 strains of pneumococci isolated from children with otitis media, 207 isolated from the nasopharynx and oropharynx of small children, of which most — 65% — were less than 2 years old. From this data, the most frequent type is type 14, and for our surprise, in our country we observed a large increase in serotype 3.

This is important because serotype 3 has some characteristics. First, usually tends to be a more insignificant serotype, very similar to *Pseudomonas aeruginosa* isolated from patients with cystic fibrosis, compared to the other pneumococci. Furthermore, it tends to be sensitive to antibiotics, and additionally, reports by Ron Dagan suggest that when serotype 3 is detected in the nasopharynx, the relative risk is great to be isolated in the middle ear, which means that it is a serotype that when present in the nasopharynx has a greater predisposition to also go to the middle ear.

What are the goals of the therapy? <sup>10</sup> Actually, vaccines against pneumococci are not the panacea. They are not what will make otitis media infections disappear from the map. And when we talk about conjugated vaccines against *S. pneumoniae*, it is important to remember that we are not talking about the non-conjugated 23-valent vaccine, but we are talking about other kinds of vaccines in which there is a carrier. Currently, there is only one vaccine that is licensed, that is the Prevenar (PCV7) from Wyeth, which contains seven most frequent serotypes in the USA, and not in the rest of the world. The coverage of PCV7 in Latin America oscillates between 60% and 70%, the coverage in Asia is only 40%, so differences in immunogenicity can be expected, as well as differences in the prevention of infection in a country where the coverage is greater than 90% and in another one where the coverage is around 60% and 70% <sup>11</sup>. However, there are other vaccines in research phases, the 10-valent vaccine that is very interesting for the area of otitis media; that is a vaccine that covers the seven *S. pneumoniae* serotypes that are in PCV7 plus three serotypes that are important for the Latin American region: serotypes 1, 5 and 7. Furthermore, it has a carrier, protein D, that is present in the non-typeable *H. influenzae*, which produces sinusitis and also produces otitis media. And there is one other 13-valent vaccine, that is in phase 3 studies. It includes all of these types and also serotype 3, which is the serotype that is producing the replacement in the middle ear in populations that are taking PCV7. It covers against 6A and also covers against the “killer” serotype, serotype 19A that proliferated in the USA and is also antibiotic multi-resistant.

With PCV7, the study that seems to me as the most important – the one with the better design – was a study conducted in Finland <sup>12</sup> showing a reduction of 6% in cases of otitis media, 34% in cases of otitis media positive for *S. pneumoniae*, and 57% in cases positive for one of the serotypes.

The other important thing is that the vaccine also prevents the insertion of tympanostomy tubes (TT), it actually reduces the need for inserting TT.

During the study conducted in Finland, it was observed that there really was not too much difference concerning the number of TT insertion between patients that received PCV7 and the control group. However, in the daily medical practice,

with pediatricians, family doctors, ENT specialists, then there is a difference, and in the patients vaccinated with PCV7 the reduction of TT insertion is of approximately 40%.

To conclude, I would like to mention the data from the 10-valent vaccine, the POET study from Prymula and *cols*<sup>13</sup>. That's the vaccine that protects against *S. pneumoniae* serotype and more potentially against non typeable *H. influenzae*. This was a randomized study conducted in the Czech Republic, in which, with the vaccine there was a reduction of 58% in otitis media events caused by one of the 10 serotypes of the vaccine; there was a reduction of 9% when compared to the control group compared to types that are not in the vaccine; 52% protection in all episodes by *S. pneumoniae*; and most importantly there was a reduction of 37% in cases of otitis media due to *H. influenzae*.

Latin America is currently conducting studies with this vaccine in an attempt to replicate the results of the studies from the Czech Republic. The study has already started in Argentina and Panama, and in two years time we will probably have results of this vaccine, and it could potentially be the ideal vaccine for the treatment of bacterial otitis media.

## References

1. Geenberg D. et al. The burden of acute otitis media on the patient and the family. *Eur J Pediatr*, 162: 576-81, 2003.
2. Teele DW et al. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis*. 1989;160:83-94.
3. Klein, JO. Otitis media. *Clin Infect Dis*, 19(5): 823–32, 1994.
4. Leibovitz E et al. *Haemophilus influenzae*: a significant pathogen in acute otitis media. *Pediatr Infect Dis J*. 2004;23:1142–1152.
5. Murphy, TF. Nontypeable *Haemophilus influenzae* as a pathogen in children. *Pediatr Infect Dis J*, 28(1): 43-8, 2009.
6. Pichichero, ME. Evolving shifts in otitis media pathogens: relevance to a managed care organization. *Am J Manag Care*, 1(6 Suppl): S192-201, 2005.
7. Sih TM. Acute otitis media in Brazilian children: analysis of microbiology and antimicrobial susceptibility. *Ann Otol Rhinol Laryngol*. 2001;110:662-6.
8. Rosenblüt A et al. Bacterial and viral etiology of acute otitis media in Chilean children. *Pediatr Infect Dis J*. 2001;20:501-7.
9. Aguilar L et al. Microbiology of the middle ear fluid in Costa Rican children between 2002 and 2007. *Int J Pediatr Otorhinolaryngol*. 2009 Aug 13. [Epub ahead of print]
10. Segal N et al. Acute otitis media-diagnosis and treatment in the era of antibiotic resistant organisms: Updated clinical practice guidelines. *International Journal of Pediatric Otorhinolaryngology* (2005) 69, 1311—1319.

11. Cripps, AW. et al. Bacterial otitis media: a vaccine preventable disease. *Vaccine*, 23:2304-10, 2005.
12. Eskola J et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344:403– 409.
13. Prymula R. et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae*: a randomised double-blind efficacy study. *Lancet*, 367: 740-8, 2006.