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Acute otitis media

Searching for the Holy Grail of acute otitis media

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Use of PCV7 causes a major shift in the microbiology of AOM towards *H influenzae*, but the search for the Holy Grail of AOM still remains elusive

For decades, investigators have been searching for one of the Holy Grails of acute otitis media (AOM)—that is, an easy non-invasive marker that would identify or even suggest the specific pathogen causing AOM. Antibiotic selection by clinicians for almost all episodes of AOM is empirical. Most episodes of AOM usually result from congestion of the eustachian tube by an antecedent virus infection, which then allows one or two of the four typical aerobic bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxiella catarrhalis* or *Streptococcus pyogenes*, to ascend into the middle ear space, causing the painful purulent effusion of AOM. Viruses seem to be an uncommon aetiology of AOM, as positive cultures for viruses being the sole pathogen of AOM occur in only 5–6% of cases.[1 2]

How commonly do bacteria cause AOM? Many multicentre studies report bacterial culture-positive rates between 55% and 75% of children, depending on whether the study is multinational or from a single country or region.[3–7] But, the devil is in the details—that is, the culture methods. Consequently, when microbiologically rigorous clinical studies use a single tympanocentesis with optimal bacterial culture techniques in children with AOM, a bacterial pathogen is obtained in 87–95% of tympanocentesis aspirates.[5–7] Thus, AOM itself is most always found to be caused by bacteria—when stringent criteria to diagnose AOM are used and highly experienced investigators carry out tympanocentesis.

Can any dataset show the Holy Grail of AOM? Can any physical or symptom markers differentiate bacterial from non-bacterial AOM, or *Streptococcus pneumoniae* from *H influenzae* or *M catarrhalis*? Can any set of clinical or otological scores evaluating severity of fever, irritability and tympanic membrane redness and bulging differentiate the specific bacterial pathogens of AOM? Remember that families who participate in a study that includes a single or a repeat tympanocentesis would probably be exceedingly motivated by the severity of symptoms and the investigator's physical findings regarding this particular episode of AOM. So, as would be expected, the mean symptom and tympanocentesis finding scores for any child enrolled in this type of study would initially be high. In addition second tympanocentesis rarely shows much microbiological information as well, as a pathogen is rarely recovered in the second tympanocentesis while receiving antibiotics. On the other hand, over the decades before the heptavalent pneumococcal conjugate vaccine (PCV7) became routine practice, some investigators[8] in the US had noted an almost clinically significant difference between children with AOM who had *Streptococcus pneumoniae* versus those who had Gram-negative pathogens. Children with *Streptococcus pneumoniae* had a tendency towards higher fever and more otalgia, but the observed difference was not enough to suggest that practitioners could ignore the Gram-negative pathogens when empirically selecting an antibiotic for the ''sicker'' child with the AOM.

Enter the routine use of the heptavalent pneumococcal conjugate vaccine since the summer of 2000 in the US (and recently introduced in the UK).[9] Preliminary investigational studies with PCV7 showed merely a 6–7% reduction in rates of overall AOM in the study population,[9 10] hardly perceptible by any clinician. However, as people in entire regions were vaccinated with the PCV7, clinicians began reporting rates of AOM reduction in the magnitude of up to 20% among young children in certain predominantly white populations.[11] Furthermore, our own rural Kentucky general paediatric group has witnessed a nearly 60% reduction in the rates of sinusitis diagnosed in the first 36 months of life (unpublished data).

When PCV7 is routinely used, will it also have an effect on the microbiology of AOM? Resoundingly, yes. In the 1990s, *Streptococcus pneumoniae* was the predominant pathogen of AOM, accounting for nearly 50% of all AOM isolates in the US and European countries, whereas *H influenzae* was usually found in 30–35% of AOM cultures.[12 13] By contrast, although the pneumococcal conjugate vaccine has not been routinely available in Israel, *H influenzae* has, for unknown reasons,been the predominant pathogen recovered in AOM for years.[14]

The beneficial effects of PCV7 on AOM have been further corroborated by the shift in microbiology from two geographically and demographically disparate groups, who were predominantly white and from communities where PCV7 was routinely used. These recent observational studies in the 2000s documented that the microbiology of AOM from tympanocentesis aspirates has shifted markedly towards Gram-negative pathogens among young children who have received PCV7. Casey and Pichichero[15] along with Block and cohorts,[16] respectively, reported that of the AOM isolates recovered, *H influenzae* now accounts for about 56%, *Streptococcus pneumoniae* for 31% and high-level penicillin non-susceptible *Streptococcus pneumoniae* (PNSP) for about 5% of pathogens. Among *H influenzae* isolates, β-lactamase producers were seen in 55% and 64%, respectively, of *H influenzae* as well. The

caveats to these data were that most of the AOM isolates were from children <24 months of age, who had received at least three doses of PCV7 and who also had recurrent or persistent AOM.

Thus, along with the reduction in the rates of both overall AOM and refractory AOM[15]—the bulk of which occurs in children from 6 to 24 months of age—we are also witnessing an inversion of the proportion of pathogens recovered from AOM among young PCV7 vaccinees in the US. *H influenzae* has now become the predominant player in AOM in the US. Despite the effect PCV7 has had on AOM, *Streptococcus pneumoniae* still cannot be ignored, as it still accounts for nearly one third of organisms causing AOM, which renders the effectiveness of antibiotics such as cefixime and ceftibuten somewhat dubious.

Practitioners often ask: ''Because of the microbiological shift towards *H influenzae*, and specifically β-lactamase-producing types in AOM, should we now initiate first-line treatment with antibiotics that have better β lactamase *H influenzae* coverage than does amoxicillin?''

I believe that amoxicillin should remain the first-line treatment in most cases of AOM, even in children fully vaccinated with PCV7.

Amoxicillin has a long track record of safety, tolerability and effectiveness for first-line treatment. A recent multinational single tympanocentesis study[17] showed an 84% efficacy for high-dose amoxicillin, even when 46% of the isolates were *H influenzae*. The study was limited because only 30% of the patients had received PCV7.

AOM is commonly overdiagnosed.[18] Thus, if clinicians are going to continue to overuse antibiotics—because of parental pressure or the lack of diagnostic accuracy—it is better to limit the mistake to less expensive drugs with a narrower spectrum.[19] Three important keys to improving diagnostic accuracy for AOM centre around the following: diligent cleaning of ear cerumen for better visualisation of the tympanic membrane; use of nickel–cadmium or lithium rechargeable batteries; and the use of original equipment full-length speculums for the Welch–Allyn square-headed otoscope, which are used by most practitioners. (We clean them with alcohol wipes after each patient.) Clinicians should not use disposable speculums for this otoscope.

High-dose amoxicillin (90 mg/kg/day) is preferred over low-dose amoxicillin (40 mg/kg/day) because 15–20% of children have poor gastrointestinal absorption of amoxicillin.[20–22] It should also be given twice daily to improve compliance. Despite these issues, some experts still think that standard-dose amoxicillin has a role in certain low-risk populations.[23]

The microbiology of ''virgin'' AOM has not been reported among children vaccinated with PCV7. The microbiological shift in AOM after PCV7 was ascertained mostly from children who had recurrent or persistent AOM, not ''virgin'' AOM.[15 16] Also, children >2 years will still be more likely to have *Streptococcus pneumoniae* as the predominant pathogen because PCV7 only covers 40% of *Streptococcus pneumoniae* serotypes in this age group.[24]

Clinicians need to be wary about the watchful waiting management of AOM.[25] Studies that compare observation with antibiotic treatment have inherent methodological limits or flaws:

- *Lengthy persistence of symptoms*: Irritability, otalgia or fever were documented in nearly three quarters of untreated young children for up to 2 weeks.[26]
- *Inclusion of children who had middle ear effusion and symptoms*: Most non-treatment studies included children who had either AOM or otitis media with effusion (serous otitis media), as long as they had some ''otitis symptoms''. OME is not expected to respond to antibiotics, thus notably diluting any possible antibiotic response.[27 28]
- *Tympanocentesis studies*: Tympanocentesis, which drains the middle ear effusion abscess, by definition disrupts the natural process of spontaneous resolution.
- *Exclusion of children with AOM who had moderate or severe symptoms*: In one of the more rigorous studies on AOM evaluating non-treatment, at least three quarters of these ''observed'' children did not have bulging or fullness or pus on enrolment.[29] This would limit any claims about generalising the findings to more common cases of bona fide AOM.

Although amoxicillin is usually recommended as the preferred treatment,[25] in three AOM scenarios with concomitant coinfections, amoxicillin should be sidelined as the first choice in ''virgin'' AOM.

- *Conjunctivitis–otitis syndrome*: β lactamase-producing *H influenzae* tends to be the predominant organism, causing both conjunctivitis and AOM.[30] High-dose amoxicillin–clavulanate (90 mg/kg/day), cefdinir or cefpodoxime would be preferred choices.
- *Ambulatory pneumonia (''walking pneumonia'') and AOM*: As atypical pathogens (*Chlamydia pneumoniae, Mycoplasma pneumoniae*) are such a common cause of milder pneumonias in children >2 years of age, macrolides such as azithromycin or clarithromycin are preferred.[31 32] Erythromycin is suboptimal because of a high frequency of dosing (four times daily), unpleasant taste and gastrointestinal adverse effects.
- *Impetigo or skin infection and AOM*: Typically, impetigo and skin infections are caused by *Staphylococcus aureus* and only rarely by *Streptococcus pyogenes*.[33] *Staphylococcus aureus* in the US uniformly produces β lactamase, rendering amoxicillin useless. Clinicians would be wiser to initiate treatment with a β lactamase-stable antibiotic, such as amoxicillin-clavulanate, cefdinir or even cefuroxime, which possess activity against both methicillin-susceptible *Staphylococcus aureus* and typical otopathogens. Patients whose skin infection does not respond in 24–28 h would then additionally receive either clindamycin or trimethoprim-sulfamethoxale for presumptive methicillin-resistant *Staphylococcus aureus*.

In summary, the Holy Grail of AOM of trying to decipher the clinical parameters that might identify the pathogen of AOM without tympanocentesis will remain elusive—like the Holy Grail itself. Still, the routine use of PCV7 has been shown to cause a major shift in the microbiology of AOM towards *H influenzae*, but not enough to change our overall approach for the preferred treatment. However, recent data suggest that second-line treatment in children vaccinated with PCV7 must definitely have sufficient coverage for β lactamase-producing *H influenzae* to be reasonably effective. Despite our optimism, acceptable rates of spontaneous resolution in AOM seem to be particularly unlikely in younger children, in those with moderate to severe bona fide AOM or in those who have recently received antibiotics.

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IMAGES IN PAEDIATRICS

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Unilateral fixed dilated pupil in a well child

A 19-month-old boy attended the paediatric assessment unit with asymmetrical pupils. This had first been noticed 8 h previously. The boy had asthma for which he was prescribed both salbutamol and ipratropium bromide inhalers, which were given via a spacer and facemask. That morning, inhaler administration had been difficult, as his mother's attempts to deliver the drugs had been resisted. On examination, the child was found to be well with a unilateral left dilated pupil, which did not react to light (fig 1). There were no other eye signs, and systemic examination was unremarkable. The pupil did not constrict when pilocarpine drops of either 0.1% or 1% concentration were applied to the eye, indicating a pharmacological cause for the mydriasis. By the next morning, the symptom had completely resolved.

It can be assumed that the mydriasis was caused by the inadvertent instillation of ipratropium bromide into the affected eye. Ipratropium bromide is an antimuscarinic agent and, like atropine, will cause mydriasis and cycloplegia if applied to the eye.[1] Both nebulised and inhaled treatment have previously been reported to induce this side effect in children.[2 3] An Adie's pupil and third nerve palsy can be excluded, as these will constrict with instillation of pilocarpine eye drops of 0.1% and 1% concentration, respectively.[4] A unilateral dilated pupil can be a worrying sign, requiring thorough investigation. This could occasionally be avoided if the benign differential diagnosis described is considered.

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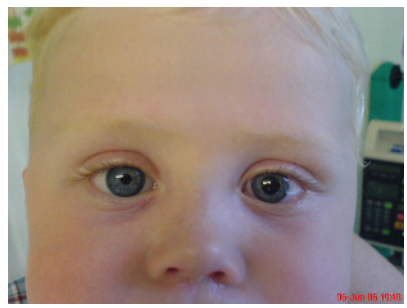

Figure 1 Unilateral left dilated pupil which did not react to light. Parental consent was obtained for publication of this figure.

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Parental consent was obtained for the publication of the child's details in this report.

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