Antibiotic Resistance Among Pediatric Acute Bacterial Conjunctivitis and Otitis Isolates: 2014 Update

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Conjunctivitis in children is frequently associated with acute otitis media (AOM). This comorbidity is known as conjunctivitis/otitis media syndrome. Acute otitis media occurs in as many as 35% of children who have conjunctivitis and is indicative of a bacterial etiology.[1] An acute inflammation of the middle ear, AOM is usually caused by bacterial infection, although it is believed that damage to the mucosa by a concurrent viral infection frequently precipitates the pathogenic behavior of the bacteria.[2] Acute otitis media is the most common affliction associated with antibiotic therapy for children younger than 5 years in the United States.[2] The most frequently isolated organism in AOM associated with conjunctivitis is *H. influenzae*. Investigators in France sampled 465 children who had purulent conjunctivitis and AOM, and isolated pathogenic bacteria in 419 of them.[3] Non-typeable *H. influenzae* (NTHi) was present in 371 (89%) in the isolates, followed by *S. pneumoniae* in 72 (17%) and *M. catarrhalis* in 23 (5%). Paired *H. influenzae* isolates from conjunctival exudate and middle ear fluid were identical strains.

Non-typable *H. influenzae*, which lacks a capsule and cannot therefore be identified by capsular serotyping, is of increasing concern in both conjunctivitis and AOM. This organism is normally commensal in the human pharynx, but can become pathogenic if it attaches to the host epithelium.[4] NTHi is a major cause of mucosal infections, including otitis media and conjunctivitis, and the incidence of invasive NTHi is steadily increasing worldwide.[5] Infection by NTHi is associated with high mortality; β-lactamase production is the predominant mechanism of resistance, although ampicillin-resistant strains are emerging in many parts of the world. In Japan, NTHi was identified as the causative organism in 62% of children with conjunctivitis-otitis media syndrome.[6] The remainder of isolates consisted of *S. pneumoniae* (28%) and *M. catarrhalis* (19%). The most commonly isolated pathogens were β-lactamase non-producing ampicillin-resistant strains of NTHi, which were identified in 72% of conjunctival isolates, and penicillin-resistant *S. pneumoniae* occurred in 74% of isolates. Identical strains were found in the eye and ear in 90% of *H. influenzae* infections and all of the pneumococcal isolates.

The American Academy of Pediatrics (AAP) criteria for the diagnosis of AOM underwent a substantial change in the recently revised guidelines published in 2013.[7] Previous guidelines required a history of acute onset of signs and symptoms, the presence of middle ear effusion, and signs and symptoms of middle-ear inflammation for a definitive diagnosis, the current guidelines use a simpler approach. The key diagnostic feature is a bulging tympanic membrane (TM). AOM is diagnosed if there is moderate to severe bulging of the TM. Mild bulging together with recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM is also diagnostic. Additionally, new onset of otorrhea not due to acute otitis externa permits a diagnosis of AOM.

In addition to the bulging position of the TM in AOM, its appearance is opaque and red, yellow, or cloudy. Mobility will be reduced, but immobility may not be complete; that is, the TM may respond to positive pressure on pneumatic otoscopy. Effusion may be present.[8]

In the case of otitis media with effusion (OME), the TM may be translucent or opaque, and is generally gray or pink in color. The TM is neutral in position or retracted. Mobility is usually reduced as a consequence of the effusion, and on pneumatic otoscopy (if retracted), the membrane may respond with negative pressure. Fluid may be present in the middle ear space, and signs and symptoms of acute infection (other than reduced hearing) may be absent.[9]

Epidemiologic studies from our center and from others show that children below the age of 3 years who present with earache, approximately 2/3 have AOM, and approximately 1/3 have OME, or simply a retracted eardrum without fluid. Misdiagnosis of otitis media occurs frequently, and there is a tendency among pediatricians and otolaryngologists to over-diagnose AOM.[10] In fact, a correct diagnosis is made only 45% to 60% of the time by these specialists. During the 2000s, educational seminars were conducted with pediatricians, otolaryngologists, pediatric residents, their teachers, and nurse practitioners on

Table 1. Signs and Symptoms of Conjunctivitis According to Etiology (% of Cases)

Symptom	Etiology		
	Allergic	Viral	Bacterial
Redness	38	**81***	**83**
Purulent discharge	N/A	25	28
Mucoid discharge	18	19	17
Irritation/foreign body sensation	**52**	19	17
Watery discharge/tearing	48	**50**	39
Itching	**86**	38	33
Follicles present	8	47	42

*Symptoms seen in half or more cases of a particular etiology marked in bold.

Source: Fitch CP, et al. *Ophthalmology.* 1989;96(8):1215-1220; Solomon AS. *Arch. Ophthalmol.*1985;103(7):891; Kosrirukvongs P, et al. *Asian Pac J Allergy Immunol.* 2001;19(4):237-244.

the subject of improving the diagnosis of otitis media. In the course of the seminars, the ability of the participants to correctly diagnose otitis media were evaluated.[10] Thirty-second videos, including pneumatic otoscopy, were shown of 9 ear examinations. Participants then indicated the diagnosis using an audience response system (Table 1). The percentage of pediatricians who selected the correct answers remained at or close to 50% across the 5 papers in the series, while otolaryngologists increased to about 85%. Interestingly, pediatric residents and their teachers each scored 48%, although the sample size was deemed to be too small for inclusion in the published papers.

Given this scenario, practitioners who, on average, diagnose AOM in more than 2/3 of patients aged under 3 years with earache, would benefit from a review of their diagnostic technique in the light of the new AAP guidelines. In particular, careful attention should be paid to the position of the eardrum in AOM relative to other types of otitis media, keeping in mind that a bulging position of the TM or new onset of otorrhea not due to acute otitis externa is required for the diagnosis.

The fact that such a large percentage of experienced pediatricians have difficulty with the accurate diagnosis of otitis media indicates that it is difficult to achieve. Barriers to effective diagnosis have been identified.[9] Some practitioners place too much reliance on an inaccurate or incomplete history from the parent, coupled with an inadequate examination of the tympanic membrane. There may be a failure to remove sufficient amounts of cerumen to view the tympanic membrane. Redness of the TM may be due to the child screaming or crying, or by efforts to remove cerumen from the ear. If the light provided by the otoscope is inadequate, perhaps as the result of failing batteries, it will not provide an adequate view of the middle ear, and can diminish the physician's ability to make a correct assessment of the middle ear. Clinicians also may tend to use a small speculum to avoid causing distress to the child, but an inappropriately sized speculum will prevent an adequate seal. This can impair the physician's determination of TM mobility. It is recommended that the largest speculum that will fit into the ear canal be used. Inexperienced health care providers often misdiagnose AOM due to failure to recognize the condition. Most pediatricians fail to evaluate tympanic membrane mobility with the use of pneumatic otoscopy. This procedure determines the mobility of a patient's TM in response to pressure changes. Middle ear effusion immobilizes the TM, and visualization of this with pneumatic otoscopy can reveal the presence of effusion even when examination of the TM shows no indication of middle ear pathology.

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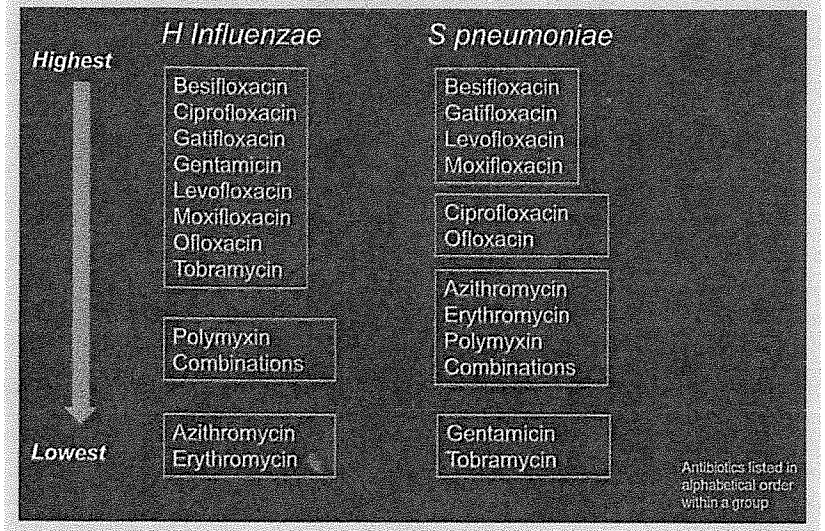
Tympanometry, although not used routinely, can be helpful to assist a difficult diagnosis. The tympanometer provides additional, quantitative information about the mobility of the TM by measuring the reflectance of a tone at different pressures. This can be helpful in differentiating between AOM and OME.

Acoustic reflectometry is a sonar-based technology that permits the assessment of middle ear fluid in pediatric patients, occurring in the context of AOM and OME. Modern hand-held acoustic reflectometry devices, suitable for in-office use, are available. Creating a seal in the ear canal is not necessary, and the device can be used as long as the ear canal is less than 50% occluded by cerumen. The rate of return of

the reflected signal is reduced by the presence of effusion fluid behind the TM, allowing the amount of fluid to be measured, although the device cannot determine whether or not the effusion is infected. The sensitivity and specificity of acoustic reflectometry devices is in the 90% to 95% range. This tool provides very useful diagnostic information, and the nurse practitioner or physician assistant can use it to take a reading prior to the pediatrician examination.

Figure 1. Relative *in vitro* Activity of Antibiotics Against Resistant Conjunctivitis Bacterial Pathogens



Treatment for conjunctivitis is usually selected empirically, so it is necessary to consider which organisms are most likely to be present and treat accordingly.

Source: Pichichero ME. *Clin Pediatr.* 2011;50(1):7-13.

Bacterial Resistance

In order to be effective, antibiotics must be selected with consideration for resistance rates in the target organisms found in the population to be treated. Treatment for conjunctivitis is usually selected empirically, so it is necessary to consider which organisms are most likely to be present and treat accordingly. In Figure 1, the relative levels of *in vitro* activity of ophthalmic antibiotics against the 2 most common causative pathogens of bacterial conjunctivitis.[11] The relative activity of the drugs against these organisms has not changed since the 2011 publication of this data.

In Figure 1, *H. influenzae,* the commonest pathogen in bacterial conjunctivitis, is equally susceptible to the fluoroquinolone antibiotics and the aminoglycosides. However, aminoglycosides are ineffective against the second most common organism, *S. pneumoniae.* In addition, the older generations of fluoroquinolones have less activity against *S. pneumoniae* than do the newer agents in this class. Besifloxacin, gatifloxacin, levofloxacin, and moxifloxacin provide the best coverage against both organisms.

S. aureus is a less common cause of conjunctivitis in children, although it is the principal cause of blepharitis. Methicillin-susceptible *S. aureus* (MSSA) has a similar antibiotic resistance profile to that of *H. influenzae.* Methicillin-resistant *S. aureus* (MRSA), which is increasingly common in pediatric practice, is similar to *S. pneumonia*, its susceptibility to the newer fluoroquinolones is greater than to earlier generations (Figure 2).[11] However, the absolute susceptibility of MRSA to all of the fluoroquinolones is substantially lower than that of the other organisms discussed.

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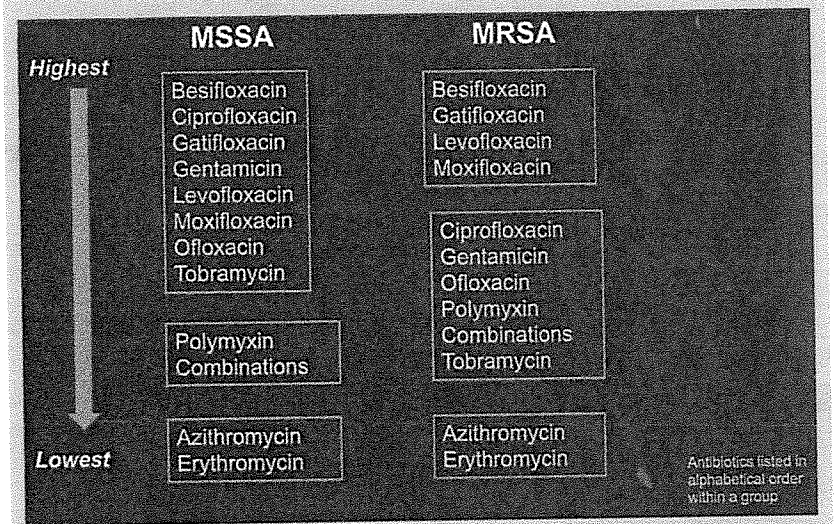
Ocular Tracking Resistance in U.S. Today (TRUST) is a national program that monitors drug resistance in ocular isolates of *S. aureus, S. pneumonia,* and *H. influenzae.*[12] The organisms are evaluated annually against ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, penicillin, azithromycin, tobramycin, trimethoprim, and polymyxin B. Mean minimum inhibitory concentrations that inhibited growth of 90% of the tested isolates (MIC(90)) are classified as susceptible, intermediate, or resistant. In a 2008 report on this program, *S. pneumoniae* was 100% susceptible to gatifloxacin, levofloxacin, and moxifloxacin, while 89.8% of isolates were susceptible to ciprofloxacin. Thus, there was little evidence of emerging resistance to fluoroquinolones despite many years of intensive ciprofloxacin and levofloxacin use as systemic therapy. These findings are in agreement with those from the 2011 study. *H. influenzae* was 100% susceptible to all of the antibiotics except trimethoprim in the Ocular TRUST report.

Of the *S. aureus* isolates examined in Ocular TRUST, 54% were found to be MRSA;[13] previous Ocular TRUST reports had found the predominant type to be MSSA. This increase in the proportion of MRSA among ocular *S. aureus* infections has also been detected by the nationwide Surveillance Network (TSN) database. TSN has reported close concordance between the rates of methicillin

Figure 2. *In vitro* Activity of Antibiotics Against Methicillin Sensitive and Resistant *S. aureus*



The absolute susceptibility of MRSA to all of the fluoroquinolones is substantially lower than that of the other organisms.

Source: Pichichero ME. *Clin Pediatr.* 2011;50(1):7-13.

resistance and fluoroquinolone resistance in U.S. ocular *S. aureus* isolates.[13] According to Ocular TRUST data, MSSA susceptibility to all of the tested fluoroquinolones was very similar, between 79.9% and 81.1%, while MRSA susceptibility was 15.2%.[12] Trimethoprim was the only tested drug that demonstrated strong activity against MRSA. This high degree of *in vitro* MRSA resistance to fluoroquinolones suggests the need to consider alternative therapy when MRSA is a likely pathogen.[13]

The low ability of organisms, such as *S. pneumoniae* and MSSA, to develop resistance to 4th-generation fluoroquinolones is believed to be a result of their mechanism of action. All of the fluoroquinolones inhibit bacterial topoisomerase enzymes, disrupting DNA synthesis.[14] Earlier generations of these antibiotics target topoisomerase IV, while 4th-generation fluoroquinolones additionally inhibit topoisomerase II (DNA gyrase). Simultaneous mutations in both of the genes coding these enzymes are less likely than a single mutation in either one, which may be the reason that resistance to this group of drugs is less likely.[14]

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Acute Otitis Media

The distribution of the causative organisms of AOM has undergone a series of changes during the past 2 decades, as a result of advances in the management of *S. pneumoniae*. The analysis of isolates obtained by tympanocentesis in Rochester, NY has provided accurate information concerning the evolution of otopathogen distribution during this period (Figure 3).[15]

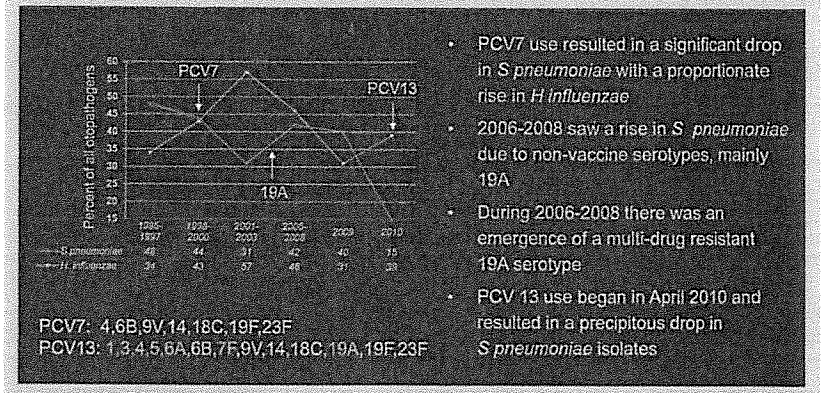
Historically, the predominant causative organism of AOM was *S. pneumoniae*. The introduction of high-dose amoxicillin therapy in the late 1990s led to a decline in *S. pneumoniae* distribution, with *H. influenzae* accounting for a correspondingly higher proportion of infections. The advent of pneumococcal conjugate 7 vaccine (PCV7) in 2001 further accelerated the decline of *S. pneumoniae*. PCV7 consists of capsular polysaccharides from 7 serotypes of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, 23F), conjugated with a diphtheria protein to increase the immunogenicity of the vaccine. The vaccine was very successful, and the 7 serotypes represented were virtually eradicated. The relative contribution of *H. influenzae* to AOM increased during this time. However, during 2006 to 2008, there was an increase in *S. pneumoniae* serotypes not included in the PCV7 vaccine, particularly 19A and 15. Multidrug-resistant 19A became the predominant *S. pneumoniae* serotype, and the proportion of *S. pneumoniae* infections increased once more. PCV13 vaccine, including serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, was introduced in 2010. This vaccine is effective against 19A, and led to a precipitous drop in *S. pneumoniae* isolates.

S. pneumoniae remains at a low ebb. In a recent study of 110 AOM episodes in PCV13-vaccinated children, approximately 20% were caused by *S. pneumoniae,* including new emerging serotypes.[16] Most were penicillin-sensitive. Half of the isolates were *H. influenzae*, 2/3 of which were β-lactamase producing, and the remainder were *M. catarrhalis,* all of which were β-lactamase producing.

~There are signs that *S. pneumoniae* is increasing once again. Martin JM, et al. analyzed nasopharyngeal cultures from 228 children aged 6 through 23 months presenting with a new episode of AOM during 2012 and 2013.[17] All subjects were treated with at least 2 doses

of PCV13. Nasopharyngeal colonization was found in half of the children in the study. Sixty-nine percent of the isolates were non-vaccine serotypes, the most frequently occurring being serotype 15 (23%) and serotype 35B (9%). Serotype 15 was the second most widely distributed type after 19A during the time that PCV7 was in use. Further vaccines are under development to counter this threatened resurgence, including a PCV15, a PCV23, as well as a vaccine that will target pneumococcal surface proteins rather than sugars, thus providing activity against all pneumococcal infections, regardless of serotype.

Figure 3. Otopathogen Distribution 1995-2011, Related to Introduction of PCV7 and PCV13



As a result of advances in the management of *S. pneumoniae*, the distribution of the causative organisms of AOM has undergone a series of changes in the past 2 decades.

Source: Casey JR, et al. *Pediatr Infect Dis J.* 2013;32(8):805-809.

The most effective treatment for AOM caused by *S. pneumoniae* is ceftriaxone.[8] A single injection is sufficient to treat susceptible strains, while resistant organisms require a course of 3 injections. A number of oral drugs also have strong activity against susceptible *S. pneumoniae*, including high-dose amoxicillin, high-dose amoxicillin/clavulanate, and the cephalosporins cefdinir, cefpodoxime, cefprozil, and cefuroxime. Cefixime and ceftibuten, however, are not effective.[8] Conversely, cefixime and ceftibuten are highly active against β-lactamase-positive *H. influenza,* as is ceftriaxone.[8] This organism is resistant to amoxicillin, although high-dose amoxicillin/clavulanate is effective, as are cefdinir, cefpodoxime, cefprozil, and cefuroxime.

The AAP guidelines for the management of acute otitis media recommend high-dose amoxicillin or high-dose amoxicillin/clavulanate as initial therapy for AOM.[18] If the patient is allergic to penicillin, one of cefdinir, cefpodoxime, ceftriaxone, or cefuroxime may be used. If initial therapy fails, either high-dose amoxicillin/clavulanate or ceftriaxone are recommended. Clindamycin, with or without a third-generation cephalosporin is an alternative choice. The Red Book also recommends high-dose amoxicillin for empiric initial treatment, for a standard duration of 10 days (5 days is permissible for children older than 2 years of age with uncomplicated cases) and high-dose amoxicillin/clavulanate or one of cefdinir, cefpodoxime, ceftriaxone, or cefuroxime following treatment failure.[19]

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However, these recommendations present some difficulties when considered in light of current evidence. For example, the Red Book recommendation for a 10-day duration of treatment with amoxicillin is controversial; a shorter duration may be just as effective. The choice of high-dose amoxicillin as initial therapy in both of the guidelines may have been appropriate when *S. pneumoniae* predominated in AOM, as this organism is highly susceptible to amoxicillin (penicillin resistance is still not seen in current AOM isolates). However, given the current post-PCV13 distribution, with only 20% of AOM due to *S. pneumoniae* versus 50% with a *H. influenzae* etiology,[20] it seems a less than ideal choice. Only 33% of *H. influenzae* infections are susceptible to amoxicillin, and *M. catarrhalis* is 100% resistant, so, in total, only about 30% of AOM infections will respond to amoxicillin therapy. First-line amoxicillin/clavulanate is better suited to current pathogens and resistance patterns. Apart from these questionable issues, the antibiotics recommended by the guidelines have high activity against both *H. influenzae* and pneumococcal infections. *M. catarrhalis* is also susceptible to amoxicillin/clavulanate and third-generation cephalosporins.

Treatment of Conjunctivitis/Otitis Media Syndrome

The treatment of AOM with a well-defined set of systemic antibiotic agents is supported by the literature and clearly laid out in published guidelines. When AOM occurs together with conjunctivitis, as is frequently the case, the question arises as to whether the 2 conditions, which are usually caused by the same organism, can be treated with

one therapy, or whether each condition must be addressed separately. The evidence for treating conjunctivitis/otitis media syndrome is sparse, and many published studies are of low quality. A systematic review of empirical therapy for bacterial conjunctivitis conducted by Epling found no evidence for the effectiveness of oral antibiotics.[21,22] The review found 1 randomized controlled trial that compared 7 days of treatment with polymyxin B sulphate–bacitracin ointment to 3 days of oral cefixime. The trial found no significant difference in clinical improvement or bacteriological failure rates between the 2 regimens in children from 2 months to 6 years of age, but may have been underpowered to detect a clinically important difference between treatments. More studies investigating empirical topical therapy for bacterial conjunctivitis were found, and the evidence was sufficient for the review to conclude that topical therapy is likely to be beneficial. Other treatments, such as ocular decongestants, saline rinses, and warm compresses were not supported by evidence from randomized controlled trials.

Summary

The available evidence supports the conclusion that acute bacterial conjunctivitis requires topical therapy, and therefore should be treated separately from comorbid AOM. Newer topical quinolones are more potent against the commonest causative pathogens for bacterial conjunctivitis than are other classes of topical antibiotics.[12,23] However, cost and formulary issues may force clinicians to use polymyxin combinations as first-line therapy, which is accompanied by a higher probability of resistance. If no improvement is seen after 48 hours of treatment, or if there is severe or recurrent infection, referral to an ophthalmologist should be considered.

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