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Acute Otitis Media: Translating Science into Clinical Practice

Edited by

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These discussions reflect the experience and opinions of the panellists and do not necessarily reflect the opinions of the Royal Society of Medicine or the recommendations of Lupin Pharmaceuticals, Inc.



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Introduction

The management of acute otitis media is a continually changing field. Much discussion surrounds the relevance of new developments in scientific understanding, as well as the most appropriate approach to the management of this troublesome condition, which, if untreated or treated inappropriately in children under 2 years of age, can lead to serious complications. While treatment of acute otitis media with antibiotics is not always essential in the older and non-symptomatic patient, antibiotics do resolve symptoms more often in the first 4 days; and in almost half of patients, effective antibiotic therapy more rapidly sterilizes the middle ear fluid of offending pathogens compared to no antibiotic treatment.

The spectrum of acute otitis media pathogens is rapidly changing, and clinicians – physician extenders, family physicians, paediatricians, and ear, nose and throat (ENT) specialists alike – can find it hard to keep abreast of the current situation and to determine the most appropriate treatment choice. Despite these concerns, this is an interesting time for acute otitis media, as new knowledge about its pathogenesis and the immune system emerges, patterns of resistance change, and the use and impact of new vaccines open up new possibilities and close the door on some management options. The treatment of children with respiratory tract infections (RTIs), particularly mucosal upper respiratory tract infections, is thus a real challenge.

In July 2006, a number of physicians with differing special interests in the field of acute otitis media met to attempt to translate the science into clinical practice. Their objectives were to:

- review the scientific literature specific to antibacterial resistance and susceptibility in acute otitis media
- discuss the shift in pathogens that has occurred since the introduction of the pneumococcal 7-valent conjugate vaccine (pneumococcal capsular polysaccharides conjugated to diphtheria CRM197 protein)
- discuss how to translate scientific data into clinical application

- discuss the role of other therapeutic alternatives in the current environment and their position in the treatment armamentarium.

The following papers are a representation of the presentations and discussions that took place during this meeting.

Susceptibility and resistance of acute otitis media pathogens

MICHAEL R JACOBS

Many physicians assume that an organism will be susceptible to an antibiotic because it has not developed resistance to that antibiotic, but this is a common misconception. In fact, the drug must have adequate pharmacokinetic characteristics to treat baseline or wild-type organisms, and some organisms have intrinsic resistance to antibiotics. This is often overlooked, as acquired resistance, which can develop through a variety of mechanisms¹ (Box 1), has been the focus of most research in this field.

Box 1 Mechanisms of resistance development. Adapted from Sinus and Allergy Health Partnership.¹

- Enzyme inactivation of the antibiotic
 - β -lactamases
- Altered target sites for antibiotics
 - Penicillin-binding proteins
 - Ribosomal binding sites
 - Dihydrofolate reductase
 - DNA gyrase and topoisomerase
- Antibiotic efflux pumps

In vitro activity

Minimum inhibitory concentration and breakpoints

To make decisions on prescribing in clinical practice, the *in vitro* susceptibility of the bacterium (or the drug's potency against it) must first be measured in the laboratory. This is achieved by inoculating a series of test tubes containing antibiotic solutions of increasing antibiotic concentration with a known bacterial inoculum. The test tubes are incubated

overnight, and the lowest concentration of drug that results in the inhibition of visible growth of the micro-organism – the minimum inhibitory concentration (MIC) – is then identified. This simple technique is universally applicable to almost every known antibiotic, can be translated into clinical practice and has proved to be the most reliable method despite the subsequent development of other methods.

A population of bacteria with no acquired mechanism of resistance produces a distribution of MIC values – the baseline MIC range, which graphically usually has one peak, similar to a bell-shaped curve. The MIC₅₀ is the concentration of antibiotic needed to inhibit 50% of the strains in a population and the MIC₉₀ the concentration needed to inhibit 90% of strains. It is important to note that these MIC₅₀ and MIC₉₀ values do not indicate 50% or 90% inhibition of one strain. Even when the MIC₉₀ is low, some strains may still be resistant. When a mechanism of resistance is developing in a population of bacteria, a bimodal population, which has two peaks, is usually produced and widely separated MIC₅₀ and MIC₉₀ values provide a clue that this may be the case. Unfortunately, the literature usually only provides MIC₅₀ or MIC₉₀ values rather than the full MIC distribution.

Susceptibility breakpoints are discriminatory antimicrobial concentrations used to differentiate MICs into susceptible, intermediate and resistant categories. Susceptibility breakpoints should be based on clinical studies where actual bacteriological outcome is determined, and studies where this was determined will be reviewed and correlated with MICs.

Development of resistance

When antibiotics were first discovered and penicillin became available, *Streptococcus pneumoniae* was described as ‘exquisitely sensitive’ to penicillin, with just 0.015 µg/ml of penicillin needed to inhibit this organism. In the 1960s and early 1970s, a few strains were described as ‘slightly resistant’ to penicillin, including some strains from Papua New Guinea, which had MICs up to 0.25 µg/ml. As these were not particularly common, they aroused little interest at the time. In 1977, however, two groups in South Africa began to find *S. pneumoniae* with MICs in the range of 2–8 µg/ml.² These strains were not only highly resistant to penicillin but were also resistant to chloramphenicol, trimethoprim–sulfamethoxazole, macrolides and lincosamides. Investigation of these multidrug-resistant *S. pneumoniae* also showed that as the MIC increases for penicillin, it also increases proportionately for all other β-lactam antibiotics, including cephalosporins and carbapenems.

S. pneumoniae becomes resistant to penicillin not through production of β -lactamase but because of mutations in its three penicillin-binding proteins (PBPs). The natural function of PBPs is to knit the organism's cell wall together. Clinicians take advantage of this by blocking this action with β -lactams, which causes the cells to lyse. Each PBP contains three regions that create the penicillin-binding site when the protein is folded.³ Wild-type (baseline) strains with MICs of 0.01–0.06 $\mu\text{g/ml}$ are penicillin-susceptible and have no changes in their PBPs. When one change occurs in one of the PBPs, the MICs increase up to 10-fold, and the more PBPs affected and the more mutations, the higher the MIC becomes.³ The current breakpoints for penicillin G against *S. pneumoniae* are $\leq 0.06 \mu\text{g/ml}$ susceptible, 0.1–1 $\mu\text{g/ml}$ intermediate, and $\geq 2 \mu\text{g/ml}$ resistant.

While PBP changes occasionally account for decreased β -lactam susceptibility of *H. influenzae*, β -lactamase production is the usual mechanism of resistance to aminopenicillins such as amoxicillin in this species. Most cephalosporins are not affected by these β -lactamases, and addition of a β -lactamase inhibitor to amoxicillin overcomes this resistance mechanism.

Aside from penicillins, the other major group of antibiotics used in outpatients and some inpatients with respiratory tract infections is the macrolides. As with the penicillins, pneumococci were initially susceptible, but various resistance mechanisms resulted in the development of resistance.⁴ In two-thirds of macrolide-resistant organisms, the resistance involves an efflux pump, which gives MICs in the range of 1–16 $\mu\text{g/ml}$.⁴ In the other one-third of macrolide-resistant organisms, the resistance develops through ribosomal methylase mechanisms, which also give cross-resistance to clindamycin.⁴ Occasionally, mutations, rather than foreign genes, are responsible for macrolide resistance, but these are extremely rare.⁴ The only mechanism that affects clindamycin is the ribosomal methylase coded for by the *ermB* gene.⁴ Virtually all strains of *H. influenzae* have an intrinsic macrolide efflux pump, resulting in this species being intrinsically resistant to this and related drug classes such as azalides (e.g. azithromycin).³

A study compared strains of pathogens from a collection of middle ear isolates recovered between 1973 and 1985 with strains from isolates isolated between 1985 and 1998.⁵ For *S. pneumoniae*, the MIC₉₀ value for amoxicillin had increased from 0.03 $\mu\text{g/ml}$ to 2 $\mu\text{g/ml}$, for cefuroxime from 0.5 $\mu\text{g/ml}$ to $>4 \mu\text{g/ml}$, for cefprozil from 0.5 $\mu\text{g/ml}$ to 16 $\mu\text{g/ml}$, and for macrolides from 0.03 $\mu\text{g/ml}$ to $>2 \mu\text{g/ml}$ and from 0.12 $\mu\text{g/ml}$ to $>4 \mu\text{g/ml}$ for clarithromycin and azithromycin, respectively. Percentage susceptibility decreased from 98–100% for all antibiotics tested for pre-1985 isolates, to 50–91% for post-1985 isolates. The results for *H. influenzae* showed 84% susceptibility to amoxicillin before 1985, which indicates that 16% of these organisms produced β -lactamase, while by 1998, 54% of the

strains were β -lactamase producers. For the remaining antibiotics tested, the MIC values and percentage susceptibility remained the same.

Two changes in the patterns of pathogens have occurred since the introduction of the pneumococcal 7-valent conjugate vaccine across the USA in 2000. The first is an increase in treatment failures for acute otitis media caused by *H. influenzae*. The second, which developed subsequently, is an increase in a specific *S. pneumoniae* serotype not included in the vaccine – serotype 19A. One of the serotypes contained in the vaccine is serotype 19F, but unfortunately this does not provide cross-reacting immunity to serotype 19A.⁶ Many strains of serotype 19A are multidrug-resistant, showing resistance to amoxicillin, oral cephalosporins, macrolides, clindamycin, trimethoprim–sulfamethoxazole and, in some cases, ceftriaxone – in other words, every oral antibiotic used to treat acute otitis media. The serotype 19A strains used to be resistant to penicillin but not amoxicillin, but their PBPs have been altered to the extent that they are now resistant to amoxicillin as well. This has resulted in increased rates of bacteraemia, acute otitis media and empyema with these strains,^{7,8} which is well illustrated through the results of a study at our institution (University Hospitals of Cleveland) in which the serotype distribution of isolates of *S. pneumoniae* predominantly taken from invasive bacteraemias was assessed.⁹ We used to see 100–120 cases of invasive pneumococcal disease per year, but a dramatic decrease followed the introduction of the pneumococcal 7-valent conjugate vaccine in 2000, mirroring results across the USA, and the predominant serotypes included in the vaccine (14, 19F and 6B) have decreased or almost disappeared.⁹ However, one of the non-vaccine types (serotype 19A), which was previously a very small percentage of isolates, is now predominant (Figure 1). Furthermore, the first two cases of multidrug-resistant serotype 19A were isolated at the hospital in 1999, but 40 isolates were identified during 2005.

In vivo activity

A recent paper assessed whether or not physicians were following the American Academy of Pediatrics and American Academy of Family Physicians 2004 guidelines on the management of acute otitis media.^{10,11} Unfortunately, the paper showed that although the guidelines for the initial treatment of acute otitis media, in general, were followed well, adherence to the guidelines was very low for second-line treatment – for example, in patients who failed treatment with amoxicillin.¹¹ No particular rationale seemed to be followed for switching from one antibiotic to another and, as the number of treatment failures indicated, most patients were switched to antibiotics that did not or were unlikely to work.

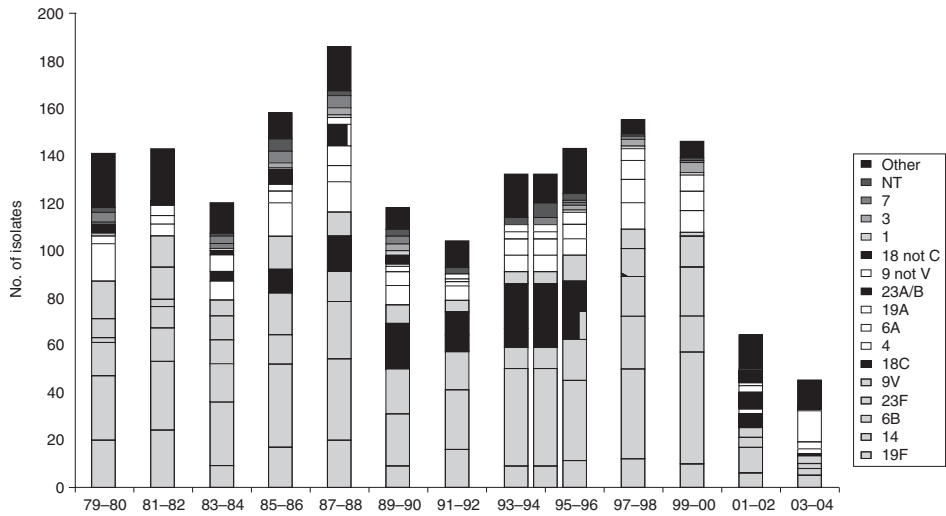


Figure 1 Serotype distribution of invasive *Streptococcus pneumoniae* in Cleveland from 1979–2004 in two-year increments. Adapted from Jacobs.⁹

The most important determinant of clinical outcome in an infectious disease is eradication of infection, as bacterial survival is likely to lead to clinical failure. Two factors are important in overcoming bacterial infections: host defences and antibiotics. Without host defences, antibiotics cannot eradicate bacteria – they kill or inhibit most of the bacteria but never eradicate the entire population. The role of an antibiotic, therefore, is to aid host defences. With respiratory tract infections treated on an outpatient basis, it is difficult to show whether or not antibiotics have a significant impact, as these diseases have high rates of spontaneous resolution. Most *clinical* outcome studies are comparative and do not include placebo arms. Unfortunately, therefore, such clinical studies without a placebo-controlled arm are unable to demonstrate the efficacy of antibiotics. Studies that determine *bacterial* outcome can show differences between agents.

Pharmacokinetics and pharmacodynamics

A drug's pharmacokinetics (PK) consider its serum concentration profile and penetration to the site of infection, providing an indication of the drug's fate after administration – when the drug is absorbed, enters the bloodstream and reaches the various sites of infection. This means that blood levels of the drug, which can be measured easily, can be used to predict drug levels in the tissues and at infective sites. After administration of a drug with a regular dosing interval, the parameters of relevance to bacterial killing are the time to maximum

concentration (T_{\max}), maximum concentration (C_{\max}), trough concentration (C_{\min}), half-life ($t_{1/2}$) and area under the curve (AUC).

A drug's pharmacodynamics (PD) consider its *in vivo* efficacy, based on whether it produces concentration- or time-dependent killing and whether it has persistent (post-antibiotic) effects. For drugs that act via time-dependent killing only, the time during which the serum concentration of unbound (free) drug is above the MIC is important (protein binding must be taken into account when performing calculations), while for drugs that act via concentration-dependent killing, the key parameter is the AUC, with the ratio of AUC to MIC predicting outcome.

Integration of PK and PD parameters has allowed us to predict *in vivo* efficacy based on *in vitro* susceptibility and the PK/PD interactions discussed above.

TIME-DEPENDENT AGENTS

For time-dependent agents *in vivo* killing does not occur until the serum concentration of unbound drug reaches the MIC. After the concentration reaches the MIC, organisms are killed until the drug concentration falls to below the MIC, and the population then increases until the next dose is given and the concentration again reaches the MIC. Studies have shown that as long as the serum concentration is above the MIC for 30–50% of the dosing interval (depending on the drug class), the antibiotic will be successful and the host defences will control the remaining bacterial population; however, if the time above the MIC is too short – for example, only 25% of the dosing interval – not enough organisms are killed to prevent them continuing to increase in number, and this results in treatment failure unless host defences themselves are able to eradicate the organisms.

β -lactams have been shown to be time-dependent agents. On the basis of free drug levels, the relationship between time above MIC and efficacy in animal infection models with *S. pneumoniae* showed that the β -lactam concentration needs to be above the MIC for 40% of the dosing interval for penicillins and 50% for cephalosporins.¹² That this translates into humans in clinical practice was confirmed in studies of patients with acute otitis media treated with a wide variety of β -lactams: when concentrations of antibiotic were above the MIC for 40–50% of the dosing interval, greater than 90% bacterial eradication was achieved (Figure 2). Furthermore, the efficacy of drugs against penicillin-susceptible *S. pneumoniae* varies considerably, and, as spontaneous resolution occurs in about 15–20% of cases in placebo studies with *S. pneumoniae*, any drugs that achieve 20% eradication are no more effective than placebo, with the host defences in fact eradicating the bacteria. The

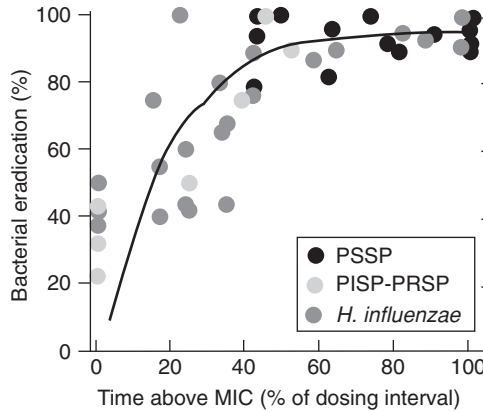


Figure 2 Relationship between time above MIC and bacterial eradication with β -lactams in studies of acute otitis media in humans. Reproduced with permission from Craig.¹² PSSP, penicillin-susceptible *S. pneumoniae*; PISP-PRSP, penicillin-intermediate and penicillin-resistant *S. pneumoniae*.

situation is similar with *H. influenzae*, for which placebo studies show spontaneous resolution in almost 50% of cases.

CONCENTRATION-DEPENDENT AGENTS

For concentration-dependent agents, once an inhibitory concentration is reached, bacterial killing begins; this is followed by a post-antibiotic effect by which killing or inhibition continues. Only when the post-antibiotic effect stops can the bacterial population begin to increase again. With concentration-dependent agents, the 24-hour AUC:MIC ratio needs to be greater than 30 to achieve bacterial killing. Macrolides and quinolones have been shown to be concentration-dependent agents.

SUSCEPTIBILITY BREAKPOINTS BASED ON PK/PD PARAMETERS

For time-dependent agents, the breakpoint that will differentiate between clinical susceptibility and resistance is the free serum concentration present for 40–50% of the dosing interval. For concentration-dependent agents, such as macrolides and quinolones, the breakpoint is the unbound serum AUC₂₄ divided by 30. According to guidelines for the treatment of acute bacterial rhinosinusitis, antimicrobial susceptibilities of isolates at PK/PD breakpoints of drugs typically used to treat infections due to *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis* show that amoxicillin, co-amoxiclav (amoxicillin-clavulanate), clindamycin and quinolones used in respiratory infections are effective against *S. pneumoniae* (although clavulanic acid confers no additional benefit over amoxicillin alone);

co-amoxiclav, cefixime, cefpodoxime and quinolones used in respiratory infections are effective against *H. influenzae*; and co-amoxiclav, cefixime, macrolides and quinolones used in respiratory infections are effective against *M. catarrhalis* (note that quinolones used in respiratory infections, while active against respiratory pathogens are currently not approved for use in children due to concerns about toxicity).¹ Cefixime is an excellent drug for *H. influenzae* and *M. catarrhalis* but is effective only against penicillin-susceptible *S. pneumoniae* (Table 1).¹ It is important to note, however, that these data were reported before the introduction of the pneumococcal 7-valent conjugate vaccine.

Table 1 Susceptibility of isolates at pharmacokinetic/pharmacodynamic breakpoints. Adapted from Sinus and Allergy Health Partnership.¹

Drug	Susceptible PK/PD breakpoint (µg/ml)	Percentage of strains susceptible at PK/PD breakpoint		
		<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>M. catarrhalis</i>
Co-amoxiclav	2†	92	98	100
Co-amoxiclav	4‡	95	100	100
Amoxicillin	2†	92	70	7
Amoxicillin	4‡	95	70	7
Cefaclor	0.5	20	4	9
Cefixime	1	66	100	100
Cefpodoxime	0.5	75	100	85
Cefprozil	1	72	23	9
Cefuroxime axetil	1	73	83	51
Cefdinir	0.25	69	78	78
Azithromycin	0.12	71	2	100
Clindamycin*	0.25	91	0	0
Levofloxacin	2	99	100	99
Trimethoprim–sulfamethoxazole**	0.5†	64	78	19

*Based on NCCLS breakpoints

†Based on amoxicillin at 45 mg/kg/day

‡Based on amoxicillin at 90 mg/kg/day

**Based on trimethoprim component.

Clinical studies

When considering the results of clinical studies, it is important to take into account spontaneous resolution of disease, time to resolution, relation between clinical and bacteriological outcome, and clinical study design.

It is important to remember that bacteriological cure and clinical cure are very closely related in acute otitis media. Two entirely different data series showed that if bacteria are

eradicated from the middle ear after 4–6 days of treatment, clinical cure is seen in $\geq 90\%$ of patients, but if bacteria persist, the risk of clinical failure is 37%.^{13,14}

These observations led to a sophisticated analysis that may be the key to understanding acute otitis media and the best ways to study this condition. Marchant *et al* showed very elegantly that a comparison of the bacteriological efficacies of theoretical drug A and theoretical drug B could be used to determine the sample size needed to distinguish between a drug with differing activities by calculating bacteriological efficacy of theoretical drug A versus B (%) against the number of patients required.¹⁵ The results showed that studies that use bacteriological diagnoses and outcomes (where a repeat tap is taken after 4–6 days) need to include about 660 patients to show a difference between a drug with 80% bacteriological efficacy and one with 90% bacteriological efficacy, but only about 100 patients to show a difference between a drug with 60% bacteriological efficacy and one with 90% bacteriological efficacy (Figure 3). For a study involving a bacteriological diagnosis but a clinical outcome after 7–10 days (and initial tap but clinical criteria for outcome), about 250 patients are needed to distinguish between a good drug and placebo, while about 800 patients are needed to distinguish between a good drug and a mediocre drug. With the weakest study design, where both diagnosis and outcome are judged on clinical terms only, 540 patients are needed just to distinguish a good drug from placebo. Most studies in acute otitis media use this last study design, but if a study includes fewer than 500 patients, it is not powered to show a difference – irrespective of the efficacy of the drugs compared.

In an interesting although small study by Ruohola *et al* in Finland, children with acute otitis media and tympanostomy tubes were given co-amoxiclav or placebo.¹⁶ As is typical

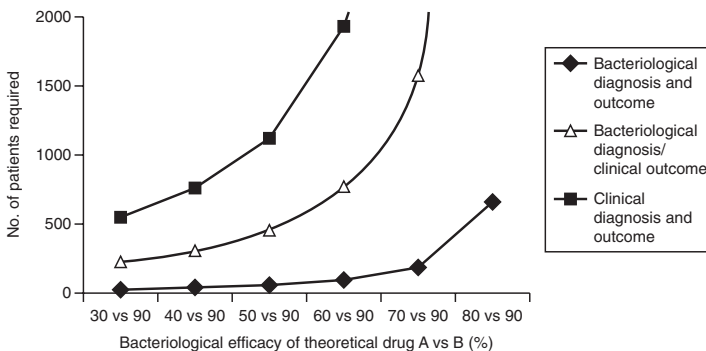


Figure 3 Sample sizes required to detect differences between theoretical antibiotics for acute otitis media based on study design and bacteriological efficacy of antimicrobials. Half the patients would be in each arm of a study. Adapted from ref 15.

for studies in which taps are taken, 80% of patients had bacteria recovered from their ears. Spontaneous resolution was seen in about 30% of patients by day 7. When co-amoxiclav was effective, it had typically eradicated the bacteria by day 3, but if bacteria persisted by day 3, they also persisted up to day 7. This study provides good evidence that the double-tap study design is valid, and it also shows that more studies should include patients with tympanostomy tubes because they are easier to study as tympanocentesis can be avoided.

The results of a study in which Fonseca *et al* gave children amoxicillin orally at a dose of 15 mg/kg/day three times a day or 25 mg/kg/day twice a day (45–50 mg/kg/day) and measured serum drug levels can be used to show the application of pharmacokinetics.¹⁷ When the PK/PD parameter for amoxicillin is applied (i.e. serum concentration greater than the MIC for $\geq 40\%$ of the dosing interval) to these amoxicillin dosing regimens (45–50 mg/kg/day in divided doses), a serum drug concentration of 1 $\mu\text{g/ml}$ was present for $\geq 40\%$ of the dosing interval in 99% of subjects. A serum drug concentration of 2 $\mu\text{g/ml}$ for $\geq 40\%$ of the dosing interval was achieved in 82% of subjects. These results support the use of the susceptible amoxicillin breakpoint established for a dose of 45 mg/kg/day in divided doses at 2 $\mu\text{g/ml}$, while a breakpoint of 4 $\mu\text{g/ml}$ can be achieved at a dose of 90 mg/kg/day in two divided doses.

These data predict that isolates with MICs of up to 2 $\mu\text{g/ml}$ would be eradicated by amoxicillin at 45 mg/kg/day. Indeed, in a study by Dagan *et al*,¹⁸ eradication of *S. pneumoniae* was achieved in most patients, with only a few failures seen at amoxicillin MICs of 2 and 4 $\mu\text{g/ml}$ (Figure 4a). An increase in the dose of amoxicillin from 45 mg/kg/day to 90 mg/kg/day would be expected to improve on these results, and, indeed only occasional failures were found (Figure 4b).¹⁹ With the azolide azithromycin,²⁰ the calculated breakpoint (based on AUC_{24} of free drug $\div 30$) is 0.1 $\mu\text{g/ml}$; when organisms were resistant with MICs > 0.1 $\mu\text{g/ml}$ (through an efflux pump or ribosomal mechanism), the failure rate was about 80% (Figure 4c) – exactly the same as was found in initial placebo studies. Even with azithromycin-susceptible strains, more failures occurred around the breakpoint than with amoxicillin. This shows that azithromycin is not as effective as amoxicillin against susceptible strains.

Figures 5 and 6 show bacteriological failure rates from all published studies in acute otitis media with a bacteriological outcome obtained via tympanocentesis on day 2–6 of treatment.^{18–23} For *H. influenzae*, as described earlier, placebo resulted in 52% bacteriological failure, and the figures show that many agents have efficacy only as good as or even worse than placebo, with the macrolides clarithromycin, erythromycin and azithromycin, as well as cefprozil, being shown to have no activity against this organism.

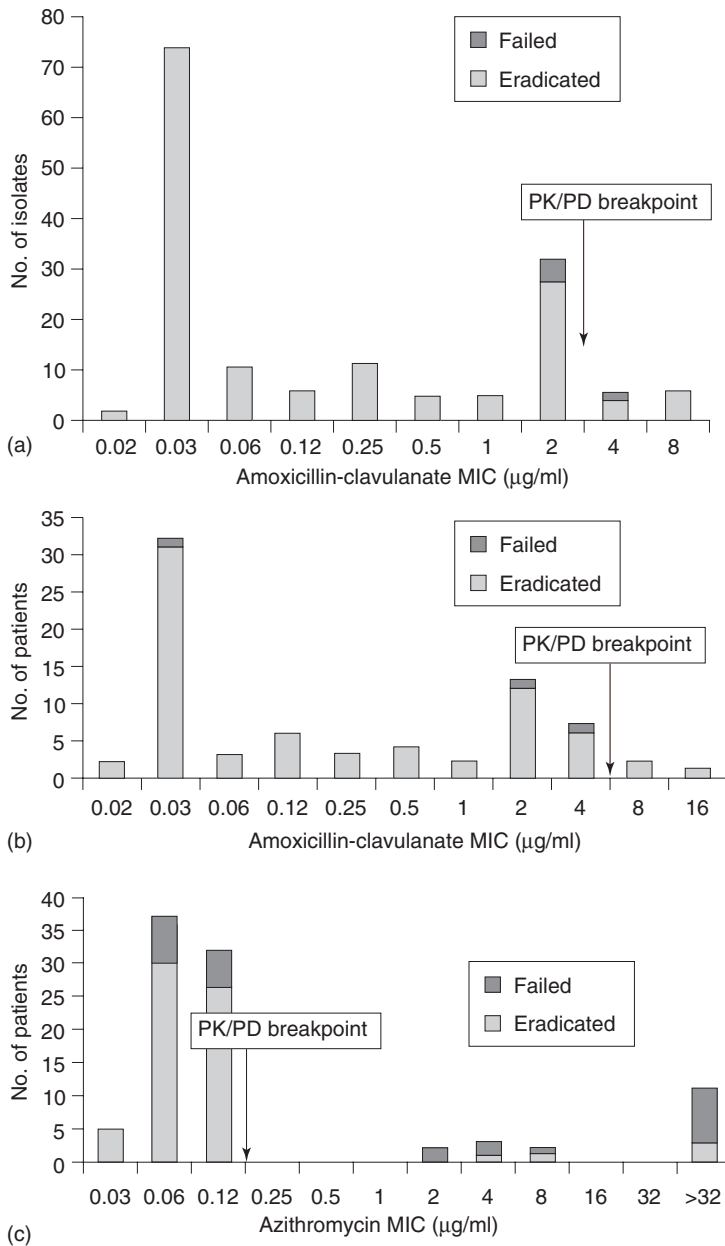


Figure 4 Acute otitis media: eradication of *S. pneumoniae* with amoxicillin-clavulanate (co-amoxiclav) (45/6.4 mg/kg/day, n=149) (a), amoxicillin-clavulanate (90/6.4 mg/kg/day, n=75) (b) and azithromycin (10 mg/kg on day 1, 5 mg/kg/day on days 2–5, n=92) (c). PK/PD, pharmacokinetic/pharmacodynamic. Adapted from Dagan et al,¹⁸ Hoberman et al¹⁹ and Hoberman.²⁰

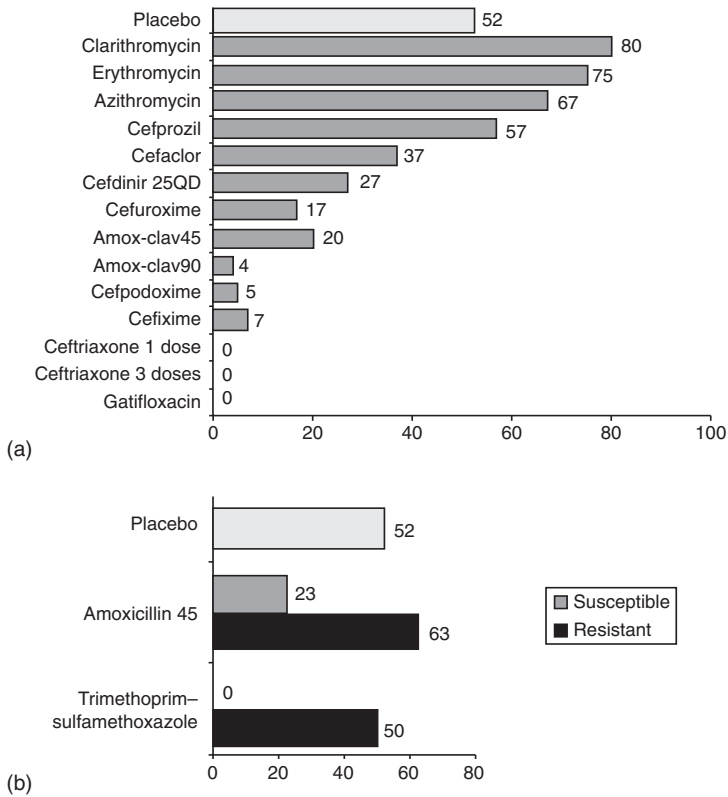


Figure 5 Bacteriological failure rates in studies of acute otitis media: *H. influenzae* for antibiotics excluding amoxicillin and trimethoprim-sulfamethoxazole (a); and for amoxicillin and trimethoprim-sulfamethoxazole (b).¹⁸⁻²³

Cefaclor and cefdinir have reasonable activity, and cefuroxime produces slightly better results. In terms of co-amoxiclav at 45/6.4 mg/kg/day, some treatment failures are seen for *H. influenzae*, while efficacy against *S. pneumoniae* is high. Increasing the co-amoxiclav dose to 90/6.4 mg/kg/day resulted in a dramatic improvement in bacteriological success rate against *H. influenzae* (increasing from 77% to 94%). Cefixime and ceftriaxone are highly active against *H. influenzae*, with very low bacteriological failure rates. For amoxicillin and trimethoprim-sulfamethoxazole, bacteriological outcomes with β -lactamase-producing or trimethoprim-sulfamethoxazole-resistant strains are no better than with placebo, while the failure rate for 45 mg/kg/day amoxicillin against susceptible (β -lactamase-negative) strains is similar to that for co-amoxiclav 45/6.4 mg/kg/day (about 20%). Amoxicillin 90 mg/kg/day alone has not been studied, but the results (β -lactamase-

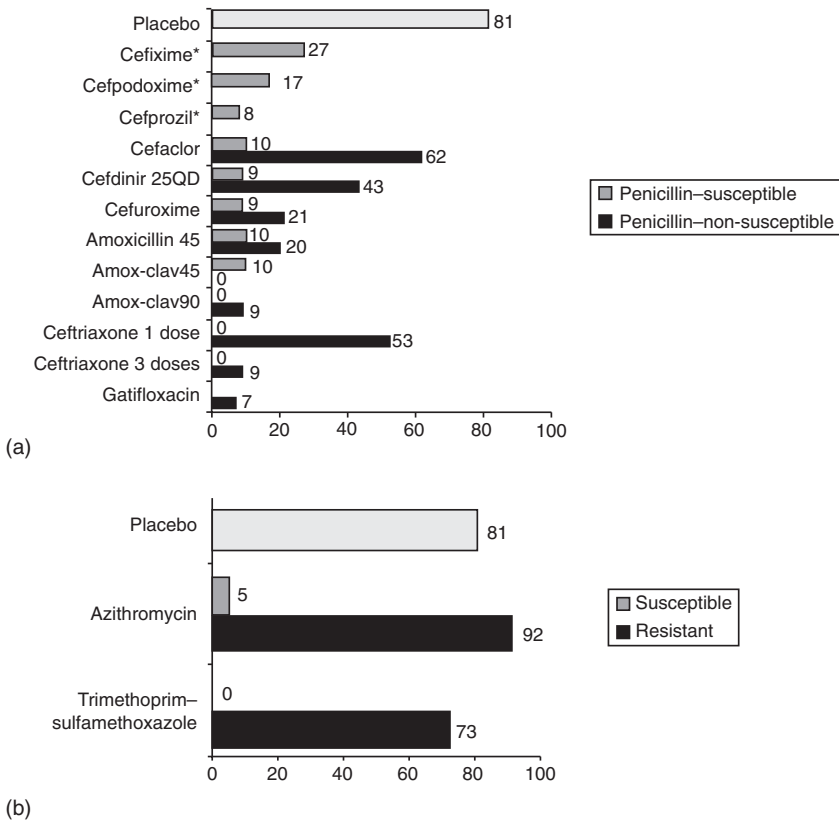


Figure 6 Bacteriological failure rates in studies of acute otitis media: *S. pneumoniae* for antibiotics excluding azithromycin and trimethoprim-sulfamethoxazole (a); and for azithromycin and trimethoprim-sulfamethoxazole (b).¹⁸⁻²³ *, No penicillin-non-susceptible isolates in these studies.

negative strains) would be expected to mimic those with co-amoxiclav at 90/6.4 mg/kg/day, which produced a bacteriological eradication rate of 94%.

In terms of *S. pneumoniae*,^{21,22} the failure rate for placebo is about 80% (see Figure 6). When the results are divided into subsets of penicillin-susceptible and penicillin-non-susceptible strains, most of the cephalosporins have relatively good efficacy and amoxicillin excellent efficacy against penicillin-susceptible strains, but for penicillin-non-susceptible strains, many of the antibiotics show failure. This is not surprising, as penicillin-non-susceptibility also predicts non-susceptibility to oral cephalosporins. Even one-dose ceftriaxone was not adequate to treat some penicillin-non-susceptible *S. pneumoniae*.

Table 2 Bacteriological failure rates in acute otitis media.¹⁸⁻²³

Drug	Bacteriological failure rate (%)			
	<i>S. pneumoniae</i>		<i>H. influenzae</i>	
	Penicillin-susceptible	Penicillin-non-susceptible*	β -lactamase-negative	β -lactamase-positive
Amoxicillin				
45 mg/kg/day	10	20	23	63
Co-amoxiclav				
45 mg/kg/day	10	0		23
90 mg/kg/day	0	9		6
Cefaclor	10	62		37
Ceftriaxone				
One-dose	0	53		0
Three-dose	0	9		0
Cefuroxime axetil	9	21		17
Cefdinir ^{22,25}	9	43†		27
Cefprozil	8	ND		57
Cefixime	27	ND		4
Cefpodoxime	17	ND		5
Azithromycin	5***	92****		67
Clarithromycin	0	ND		80
Trimethoprim-sulfamethoxazole	0‡	73**	0‡	50**
Garufloxacin		7		0

ND, not determined.

*Intermediate or resistant.

†32% penicillin-intermediate; 57% penicillin-resistant.

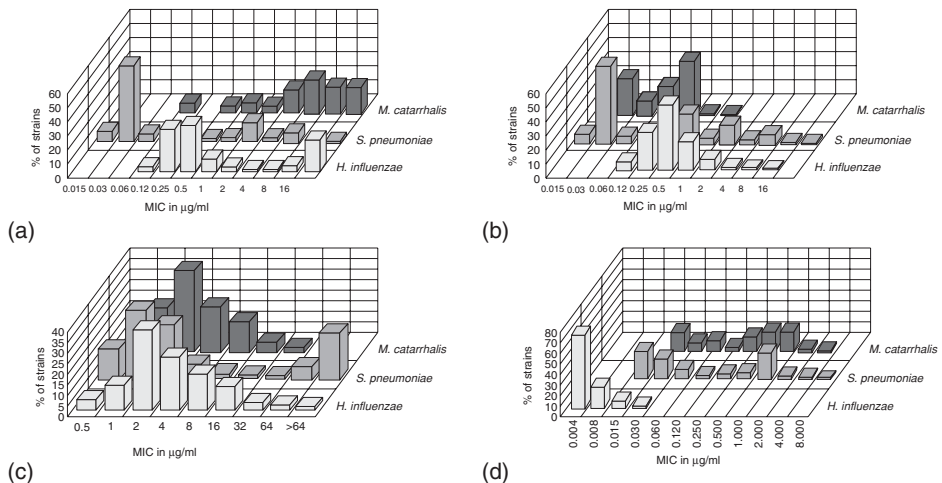
‡Trimethoprim-sulfamethoxazole-susceptible.

**Trimethoprim-sulfamethoxazole-resistant.

***Azithromycin-susceptible.

****Azithromycin-resistant

Table 2 summarizes bacteriological failure rates for 13 antibiotics in acute otitis media studies where bacterial eradication was determined.¹⁸⁻²³ Figure 7 shows MIC distributions of acute otitis media pathogens against these 13 antibiotics.²⁴⁻²⁶



(Continued)

SUSCEPTIBILITY AND RESISTANCE OF ACUTE OTITIS MEDIA PATHOGENS

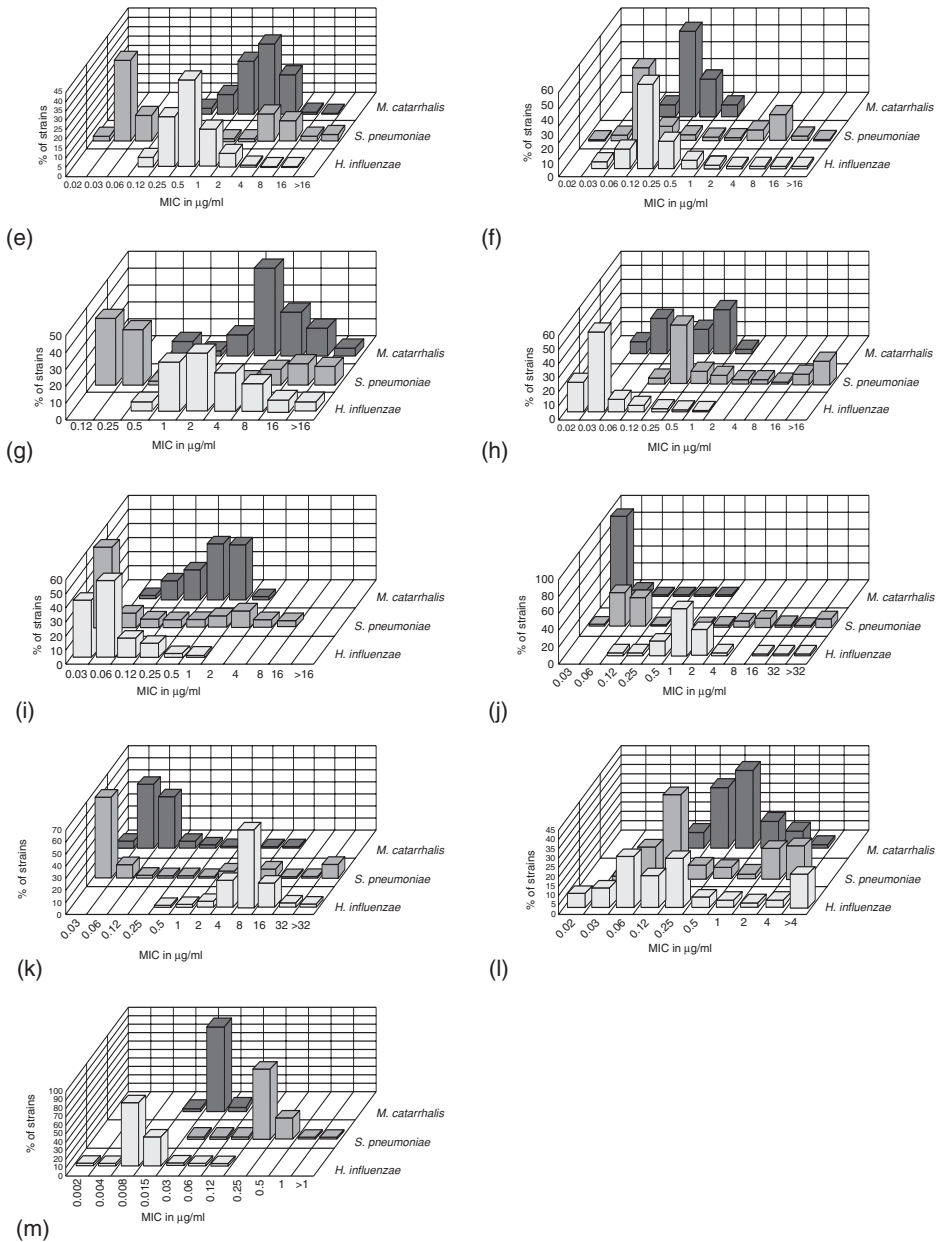


Figure 7 MIC ranges and susceptible PK/PD breakpoints against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (susceptible breakpoints are shown in parentheses after each agent) for: amoxicillin (2 µg/ml for 45 mg/kg/day and 4 µg/ml for 90 mg/kg/day) (a); co-amoxiclav (2 µg/ml for 45 mg/kg/day and 4 µg/ml for 90 mg/kg/day) amoxicillin component (b); cefaclor (0.5 µg/ml) (c); ceftriaxone (no breakpoint defined) (d); cefuroxime axetil (1 µg/ml) (e); cefdinir (0.25 µg/ml) (f); cefprozil (1 µg/ml) (g); cefixime (1 µg/ml) (h); cefpodoxime (0.5 µg/ml) (i); azitromycin (0.12 µg/ml) (j); claritromycin (0.25 µg/ml) (k); trimethoprim-sulfamethoxazole (0.5 µg/ml trimethoprim component) (l); and gatifloxacin (0.5 µg/ml) (m).

Summary

In vitro susceptibility can be accurately interpreted on the basis of PK/PD parameters. The principles of pharmacokinetics and pharmacodynamics can be used to:

- develop effective dosing regimens for antimicrobials
- develop new formulations and dosage regimens
- contribute to guideline recommendations

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Discussion

Albert Collier: It is important to realize that more prescriptions are written for acute otitis media than for any other infectious disease – it is the most common reason for children attending a paediatrician in the USA today.

Michael Jacobs: The resistance that has developed in acute otitis media pathogens has been driven by the antibiotics given to children younger than five years. These organisms do not generally become resistant in adults but become resistant in children and then spread to adults.

Jeremias Murillo: It is difficult in practice to apply the guidelines and individualize them to individual patients, as a number of factors that are involved are not included in the guidelines – for example, whether or not the family is able to ensure compliance and whether or not follow-up is feasible.

Michael Jacobs: Guidelines can sometimes be too theoretical and perhaps need to be more practical.

Albert Collier: Cefixime oral suspension had not been available in the USA and it has only recently been included again in the current edition of the *Physicians' Desk Reference (PDR)*.¹ Many paediatricians are not aware that cefixime oral suspension is again available. Cefixime is a standard of care for febrile urinary tract infections in children and, especially with the evidence on cefixime sensitivities for *H. influenzae* and *M. catarrhalis*, it should be used more routinely for patients with acute otitis media.

Jeremias Murillo: The diagnosis of acute otitis media is clinical and empirical; a reliable tool for diagnosis of viral cases of acute otitis media is needed.

Albert Collier: Historical evidence of untreated acute otitis media developing into mastoiditis often leads physicians to be reluctant to diagnose empirically a viral infection and avoid antibiotics through fear of the complications of untreated acute otitis media.

Michael Jacobs: The introduction of the pneumococcal 7-valent conjugate vaccine has increased our understanding of acute otitis media and highlighted how little is understood about this condition. That β -lactamase-producing *H. influenzae* would be the most likely cause of treatment failures with oral amoxicillin was not surprising, but the fact that the vaccine would select non-vaccine amoxicillin-resistant serotypes of *S. pneumoniae* was not predicted, despite how obvious this now seems.

Michael Haggmann: Many patients are likely to be suboptimally dosed. Can this in some cases help the host's defences or is this always detrimental as far as selection of resistant organisms is concerned?

Michael Jacobs: It depends on the 'safety margin' between MIC and breakpoint, because if the safety margin is large, suboptimal dosing will not make any difference. Although the focus is often on whether or not the dose is adequate at the site of infection, all administered antibiotics put selective pressure on normal floral sites and wide variation is seen in terms of concentrations, for example, in the mucous membranes or in the bowel or urine. More important, therefore, are subinhibitory levels at these body sites. This is increasingly being examined, with studies in patients with acute otitis media looking at the effects on the flora in the nasopharynx and gastrointestinal tract. The ideal drug would be as effective in the nasopharynx as in the ear or have no effect on normal flora in the nasopharynx; most drugs lie somewhere in between, and these are producing resistance – but at the level of the nasopharynx not the ear.

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The changing microbiology of acute otitis media

CHRISTOPHER HARRISON

Introduction

When clinicians choose to use an antibiotic to treat acute otitis media (AOM), it is critical that they have a clear understanding of the patterns of antibiotic resistance in their geographic area and the advantages or adverse effects of the candidate antibiotics. Because cultures are rarely obtained in routine practice, susceptibility patterns for middle ear pathogens are usually found only during investigations of antibiotic efficacy and are quite often sponsored by pharmaceutical companies. There are also surrogate studies for antibiotic resistance, which include surveillance of respiratory pathogens whether they come from the middle ear or not. Therefore resistance patterns found in the literature can vary by the population of patients that is studied as well as by the era in which the studies are performed. Over the last 30 years there have been changes in protocol design as well as the addition of newer antibiotics that have led to frequently changing recommendations for empiric therapy of AOM based in part on changing microbiology.

Over the years, there have been three major middle ear pathogens, *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Moraxella* is much less difficult to treat and therefore the focus for choosing antimicrobials has been directed by resistance patterns among pneumococcus and non-typeable *H. influenzae*. Beginning in the 1970s, resistance to commonly used antibiotics for treating AOM began to appear. Much of the resistance appeared to be driven by antibiotic use, but it also became clear that the increasing use of daycare allowed for resistant strains to be more easily transmitted, and recently the addition of pneumococcal 7-valent conjugate vaccine has modified resistance patterns as well.

When critically reviewing the efficacy of antibiotics in the treatment of AOM, it is first important to understand that the rate of spontaneous cure of AOM is pathogen-dependent. The rate of spontaneous cure is also likely to be dependent on age of the patient (more commonly > 2 years of age), status of the immune system, and function of eustachian tube. If we are to review the shifts in the dominance of pathogens in AOM, it therefore becomes important to specifically define the spontaneous cure rate for each.

The seminal study on spontaneous resolution of AOM was performed by Howie and Ploussard in 1972. It compared the persistence of pathogens in patients who received placebo or antibiotic treatment to determine spontaneous remission rates.¹ *S. pneumoniae* had the lowest spontaneous remission rate, nearly 20%, while the spontaneous remission rate for *H. influenzae* was nearly 50%. When a physician considers the data on efficacy of each antibiotic, this differential in spontaneous cure between the two pathogens needs to be considered. It is likely to be a reflection of the immune system's expected contribution to the success rate against each pathogen.

It has long been clear that pneumococcus has additional ways of evading the immune system in young infants in that the polysaccharide capsule of pneumococcus does not naturally stimulate antibody production in the first 18 to 24 months of life. Therefore, serotypes of pneumococcus did not induce immunity when they cause AOM in this age, leading to possible repeated infections with the same serotype. Recently a pneumococcal 7-valent conjugate vaccine (PCV-7) came into universal use in the USA in the first six months of life, and this vaccine does produce neutralizing antibody against the seven most common disease-producing pneumococcal serotypes, with efficacy appearing initially one to two months after the third dose.

This vaccine was originally studied in relation to AOM in Finland, where Eskola *et al*² identified a reduction in pneumococcal (especially vaccine) serotypes in middle ear isolates causing AOM. They noted compensatory serotype substitution (non-vaccine strains increased among AOM pathogens in immunized children), as well as an increase in *H. influenzae* and *M. catarrhalis*. Although these changes in *H. influenzae* did not reach statistical significance, they were the first indication that the vaccine could combat the serotypes included in the vaccine but might not solve the problem of AOM in the long run. Thus, new serotypes became colonizers in the nasopharynx of immunized children. Because age-associated eustachian tube dysfunction is not modified by immunization, whatever strains remain in the nasopharynx when eustachian tube dysfunction occurs would be expected to be pathogens when AOM developed. It was not clear whether these data would translate directly to the USA because these studies in Finland involved a population with a uniform genetic background that lacks the genetic diversity seen in the USA.

The distribution of middle ear pathogens in AOM and the resistance patterns that they possess have usually been somewhat different in the USA than in Finland. So data from the USA become important and the mechanisms of resistance for each of the major middle ear pathogens become the focus.

For example, a major mechanism of antibiotic resistance in pneumococci is penicillin resistance conveyed by alterations in penicillin-binding proteins. These altered proteins also convey resistance to the cephalosporins proportional to the degree of penicillin resistance. Penicillin resistance also increased the likelihood that the same strain would contain acquired resistance to trimethoprim-sulfamethoxazole and to macrolides. Among isolates in Louisville, Kentucky, a recent survey confirmed that a majority of respiratory pneumococcal strains were penicillin non-susceptible. Further, the more resistant the organism was to penicillin, the more likely it was to be a vaccine serotype (Harrison C, unpublished data). Because many highly or intermediately resistant *S. pneumoniae* strains were vaccine strains, it stood to reason that penicillin-non-susceptible strains might be affected out of proportion to penicillin-susceptible strains by the vaccine, thereby lowering the rate of penicillin resistance (and concomitant cephalosporin resistance). There was also the hope that resistance to other antimicrobials among pneumococci might decline as well.

β -lactamase production has been the major mechanism of resistance among non-typeable *H. influenzae* in the USA for the last 30 years. A review by Leibovitz *et al* showed rising rates of β -lactamase production in middle ear isolates, ranging from zero in the 1970s up to 35–40% in the 1980s, when β -lactamase-producing *H. influenzae* was the major cause of treatment failures.³ The initial peak for this as the cause of treatment failures in the 1980s was followed by a decline, but the number of β -lactamase-producing *H. influenzae* isolates increased again around the year 2000, rising to higher proportions even before the pneumococcal vaccine had a major impact.

Along with these changes in resistance rates were changes in the dominance of pneumococcus or non-typeable *H. influenzae* among pathogens obtained from the middle ear of patients with AOM, with notable shifts occurring approximately every 10 years.

Otopathogens in the 1970s

A study in Dallas showed that *S. pneumoniae* was the dominant pathogen in infants with AOM in 1976.⁴ At that time, however, none of these organisms showed penicillin resistance, and none of the *H. influenzae* produced β -lactamase. That soon changed and was first reported by Schwartz *et al* from Washington DC, showing that *H. influenzae* and

S. pneumoniae both accounted for 30% of isolates.⁵ At this time however, 17% of *H. influenzae* produced β -lactamase. Interestingly, spontaneous remission occurred in only 16% of patients with β -lactamase-producing *H. influenzae*. This paper brought into question whether 50% was always the true rate of spontaneous remission with all *H. influenzae*, as reported by Dr Howie, whose isolates were nearly all non- β -lactamase producers. This rate of spontaneous remission reported by Schwartz *et al* with β -lactamase-producing *H. influenzae* is remarkably similar to that reported by Howie and Ploussard for *S. pneumoniae* (16%),¹ which suggests that spontaneous remission may be influenced by virulence factors, such as β -lactamase production among *H. influenzae*.

Traditional belief in the 1970s was that *H. influenzae* did not cause AOM in children older than three years. However, Schwartz *et al* found that non-typeable *H. influenzae* accounted for at least one-third of middle ear isolates in 18 children older than three years.⁶ As a result, physicians became aware that *H. influenzae* needed to be considered in children of any age with AOM.

Otopathogens in the 1980s

Because β -lactamase-producing *H. influenzae* was now becoming more common, β -lactamase stable drugs were thought to be necessary unless one could be sure that pneumococcus was the pathogen. This led to investigations to see whether clinical clues could make one more confident that pneumococcus was the middle ear pathogen so that narrower spectrum antibiotics might be useful. It was also unclear just how many patients with AOM actually suffered from infections due to an *H. influenzae*. One clue was provided by a small emergency room series of 30 'painful ears' reported by Friedman *et al* in Philadelphia. They found that most painful AOM cases were caused by *S. pneumoniae*.⁷ This was the first study to suggest that highly symptomatic painful ears were more likely to be caused by *S. pneumoniae* than *H. influenzae* or *M. catarrhalis*.

Most tympanocentesis studies up to the mid-1980s were performed in children who were not pre-treated with antibiotics and therefore were not likely to be representative of patients with recent treatment or failure while on therapy. However, a study of 75 middle ear aspirates in 1984 considered the effect of pre-treatment with sulfisoxazole (the drug of choice for prophylaxis in the early 1980s).⁸ *H. influenzae* was the dominant middle ear pathogen in children on prophylaxis, whereas *S. pneumoniae* was the dominant pathogen in children who were not on prophylaxis. So pre-treatment, at least in the early to mid-1980s, led to *H. influenzae* predominance, whereas it was more likely that patients not previously treated had pneumococcus as their middle ear pathogen. This study also showed that 20%

of *H. influenzae* isolates produced β -lactamase. Interestingly, only one *S. pneumoniae* isolate was penicillin-non-susceptible. These researchers further investigated whether or not patients who had repeat infections had the same or different strains. While 17 patients had the same species, more careful analysis by either serotyping or biotyping showed that 7 of those 17 were really different strains. In addition, when the infection was due to the identical strain, the recurrent AOM was more likely to recur closer to the end of therapy than episodes with different strains (2.5 weeks vs 5.7 weeks).

Another study, which compared recently treated AOM to AOM in patients who had not recently received antibiotics, showed more pneumococcus than *H. influenzae* in previously untreated AOM, but increased numbers of *H. influenzae* in recently treated patients. The *H. influenzae* isolates from recently treated AOM were more likely to produce β -lactamase (45%), and the *S. pneumoniae* were more likely to be penicillin-resistant (18%). This showed that recent antibiotic use selects for antibiotic resistance and enriched for *H. influenzae*. It was also the first study to show more than an occasional pneumococcus with some form of penicillin resistance.⁹

Later in the 1980s, two studies from different sites investigated drugs no longer recommended for use in patients with AOM – loracarbef and cefprozil. Investigators from Dallas, Texas, treated 92 patients with loracarbef and found approximately equal numbers of *S. pneumoniae* and *H. influenzae* isolates in patients, but 40% of *H. influenzae* produced β -lactamase.¹⁰ A multicenter study, partly undertaken in the south-eastern USA, showed that in 137 patients treated with cefprozil, *S. pneumoniae* was detected at almost twice the rate of *H. influenzae* isolates.¹¹ Thus, in the same relative timeframe but in a different geographic area, differences were reported with respect to the proportions of the two major pathogens that cause AOM. Overall at this time, however, *S. pneumoniae* usually dominated, with an occasional study reporting equal numbers of *S. pneumoniae* and *H. influenzae* isolates.

In the late 1980s, a multicenter study comparing cefixime with cefaclor found that *S. pneumoniae* predominated and that 42% of *H. influenzae* isolates produced β -lactamase.¹² Interestingly, no β -lactamase-producing *H. influenzae* were identified from Rochester, New York in the north-eastern USA, but more than 50% of *H. influenzae* in Cincinnati, Ohio and Omaha, Nebraska produced β -lactamase. This study emphasized the fact that geographic differences in antibiotic resistance could be large.

Finally, in a large review of thousands of isolates obtained throughout the 1980s in Pittsburgh, Bluestone *et al* evaluated pathogen trends as the 1990s approached.¹³ They found that *S. pneumoniae* was the dominant pathogen in AOM at the close of the 1980s, but that

H. influenzae was the most likely isolate from cultures of middle ear effusions from chronic otitis media with effusion. The authors concluded that over the 10-year period of the 1980s, a significant shift had occurred with an increase in the prevalence of *S. pneumoniae* causing AOM. Although the proportion of *H. influenzae* AOM isolates did not increase, the rate of β -lactamase production did increase during the 1980s (from 10% to 25%).

Otopathogens in the 1990s

In the 1990s, *S. pneumoniae* increased in importance and appeared to be the predominant pathogen in difficult-to-treat AOM due to increasing rates of strains with altered penicillin-binding proteins (PBPs) that reduced susceptibility to penicillin and oral cephalosporins. This led the FDA to request that new investigations of therapy for AOM be designed to include more difficult-to-treat AOM and a larger number of younger children (< 2 years of age). This is the opposite of the majority of prospective protocols used in the 1970s and 1980s, where most children were > 2 years of age and most were not pre-treated. This had the result that most subjects from the 1980s did not have difficult-to-treat AOM. Therefore some of the 'shifts' in AOM pathogens and resistance patterns noted in the 1990s may have in part been due to selection of different patient groups for evaluation.

Consider one multicenter study comparing cefuroxime with amoxicillin-clavulanate, where proportions of *S. pneumoniae* and *H. influenzae* were nearly equal (37% and 33%, respectively). Further, the rate of β -lactamase production among *H. influenzae* isolates was high at 44%.¹⁴ The trend of increasing β -lactamase seen in the 1980s thus continued into the 1990s.

Among nearly 200 pathogens from another mid-1990s multicenter study, *S. pneumoniae* was isolated from middle ear fluid more often than *H. influenzae* (50% vs 40% respectively).¹⁵ This study reflected an ongoing trend toward increased penicillin resistance in the 1990s, with approximately 50% of *S. pneumoniae* resistant, at some level, to penicillin. In addition, increasing amoxicillin resistance among *H. influenzae* by virtue of β -lactamase production was also seen (56%), with some sites in northeast USA also finding increased rates of isolates producing β -lactamase.

In the late 1990s, Block *et al* cultured 134 isolates from 125 patients.¹⁶ Overall, 51% were *S. pneumoniae* but only 33% *H. influenzae*, with 41% of these β -lactamase positive. It is important to bear in mind that these investigators sampled not only treatment failures (as was the case in most other studies this decade) but also enrolled patients with painful AOM and, as discussed earlier with respect to the emergency room study by Friedman *et al*,⁷ such patients may have an increased likelihood of the pathogen being *S. pneumoniae*.

Otopathogens in the 2000s – the effect of PCV-7

PCV-7 came into universal use as part of the infant immunization schedule in the USA, but not other countries, in 2000. This introduction appears to have had a striking impact on middle ear pathogens from patients failing initial antibiotic therapy. This became clear when a study from rural Kentucky and a study from suburban Rochester revealed remarkably similar results when comparing the dominant pathogens and their resistance patterns from before and after introduction of the PCV-7 (Figure 1).^{17,18}

In the pre-vaccine era, *S. pneumoniae* was the dominant organism, accounting for nearly 50% of isolates, while *H. influenzae* accounted for around 40%. Among pre-vaccine *S. pneumoniae*, there were equal numbers of middle ear isolates with high penicillin-resistance, intermediate-penicillin-resistance and penicillin-susceptibility. In the rural Kentucky population, the proportion of β -lactamase-producing *H. influenzae* was higher than in suburban Rochester (about 40% vs 25–30%), reminiscent of the same phenomenon that had occurred 10 years before when comparing the Northeast region to the South or Midwest USA. However, there was a sizeable increase in β -lactamase production in the northeast USA even though it was less than the increase seen in rural Kentucky.

After the introduction of PCV-7, the pneumococcal contribution to AOM pathogens decreased by about one half and the *H. influenzae* contribution increased by about one-third. Among patients who had failed previous antibiotic therapy, non-typeable *H. influenzae* now predominated, making up 56% of AOM isolates both in rural Kentucky and suburban New

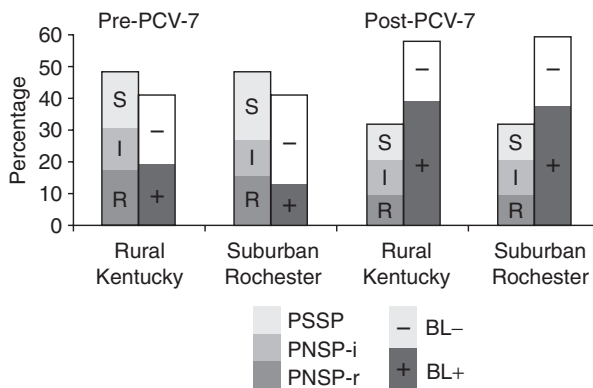


Figure 1 Effect of the pneumococcal 7-valent conjugate vaccine (PCV-7) on otopathogens.^{17,18} PSSP, penicillin-susceptible *S. pneumoniae*; PNSP-i, penicillin-non-susceptible, intermediate; PNSP-r, penicillin-non-susceptible, resistant; BL-, β -lactamase-negative non-typeable *H. influenzae*; BL+, β -lactamase-producing non-typeable *H. influenzae*.

York. In addition, two-thirds of these *H. influenzae* strains produced β -lactamase. A proportional decrease was also seen in penicillin-resistant strains of *S. pneumoniae* in both centres. That these data, which arise from two sites thousands of miles apart, are so comparable gives credence to the change to non-typeable *H. influenzae* being the dominant middle ear pathogen and the increase in β -lactamase-producing *Haemophilus* strains during this part of the post PCV-7 era.

Further confirmation of these changes comes from a separate multicenter, multinational study with almost 500 AOM isolates published in 2003, in which 49% of isolates were *H. influenzae* and 24% of these were β -lactamase positive.¹⁹ *S. pneumoniae* accounted for 45% and *M. catarrhalis* 11%. A caveat is that some sites, particularly those from Israel, have a long history of a scarcity of β -lactamase-positive *H. influenzae*. Most of the isolates from this study also came from countries where universal PCV-7 vaccine was not in universal use and therefore the influence of the pneumococcal vaccine was likely to be diluted. Some experts quote this study as showing that β -lactamase-producing *H. influenzae* are not abundant, but if the Israeli and South American isolates are removed, the proportions from the USA remain at 40–45%.

Figure 2 shows the trends in the major otopathogens, *S. pneumoniae* and non-typeable *H. influenzae*, over time between 1981 and 2003.^{9,13,17,18,20}

In 1981–83 in Oklahoma, about 18% of *S. pneumoniae* were intermediately resistant to penicillin, with no highly resistant organisms; however, this was one of the first reports of a sizeable proportion of penicillin-resistant *S. pneumoniae* in the USA. The proportion of β -lactamase-producing *H. influenzae* in children not recently treated for AOM was about

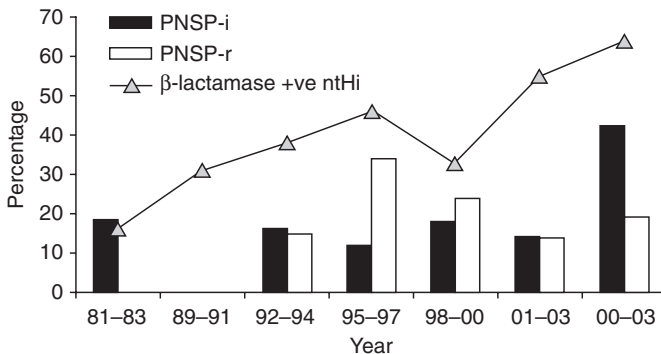


Figure 2 Otopathogens between 1981 and 2003.^{9,13,17,19,20} PNSP-i, penicillin non-susceptible, intermediate; PNSP-r, penicillin non-susceptible, resistant; ntHi, non-typeable *H. influenzae*. (There were no studies during 1989–91 that suitably addressed the issues.)

30%, although the average across all children was about 16% (indicated by the lower left triangle on Figure 2). These data suggest that a child who has an occasional intermittent episode of AOM is less likely to be colonized by β -lactamase-producing *H. influenzae* than a child who has recently been treated. This concept was confirmed in a number of studies in the decade that followed.

No change in non-typeable *H. influenzae* causing AOM was seen after the introduction of the *H. influenzae* type b vaccine in the early 1980s, because the overwhelming majority of *H. influenzae* strains that cause AOM were never type B isolates, but were non-typeable. Therefore no substantial effect was expected either.

After introduction of the pneumococcal 7-valent conjugate vaccine in 2000, the overall rate of penicillin-resistant *S. pneumoniae* among middle ear pathogens did not continue its prior rapid increase that had started in the 1990s. In fact, the proportion of penicillin-non-susceptible *S. pneumoniae* began to decrease more than the proportion of susceptible *S. pneumoniae*, while the proportion of β -lactamase-producing *H. influenzae* continued to rise. One caveat remained, that while penicillin-non-susceptible pneumococci had decreased among AOM pathogens in the post-vaccine era, they had not disappeared and could therefore not be totally ignored as potential pathogens in the most difficult-to-treat patients.

Figure 3 shows a series of isolates from patients with AOM and acute bacterial rhinosinusitis (ABRS) obtained in Louisville during 2000–05 (Harrison C, unpublished data). Prior to full implementation of PCV-7 (2000 to 2001), vaccine types predominated including serotypes 19F, 14, 9V and 6B. Type 4 was observed in small numbers. During 2002–05 when more children had been immunized with PCV-7, serotypes 14 and 9B had disappeared, while serotypes 6B, 19F and 23F had maintained a presence, although at a lower level than before the vaccine was introduced.

Serotype substitution was also observed as non-vaccine serotypes, 3, 11 and 33 became more common after introduction of the vaccine. This confirms the Finnish group's observation that non-vaccine serotypes of *S. pneumoniae* might emerge to take advantage of eustachian tube dysfunction in young children, even when they have antibody against the seven vaccine strains.²

The data from Finland did not suggest that serotypes that were cross-reactive with the vaccine types would emerge. However, these US data obtained since the introduction of PCV-7, revealed that 6A and particularly 19A had become major players among *S. pneumoniae* causing AOM and ABRS in immunized children in the Louisville area.

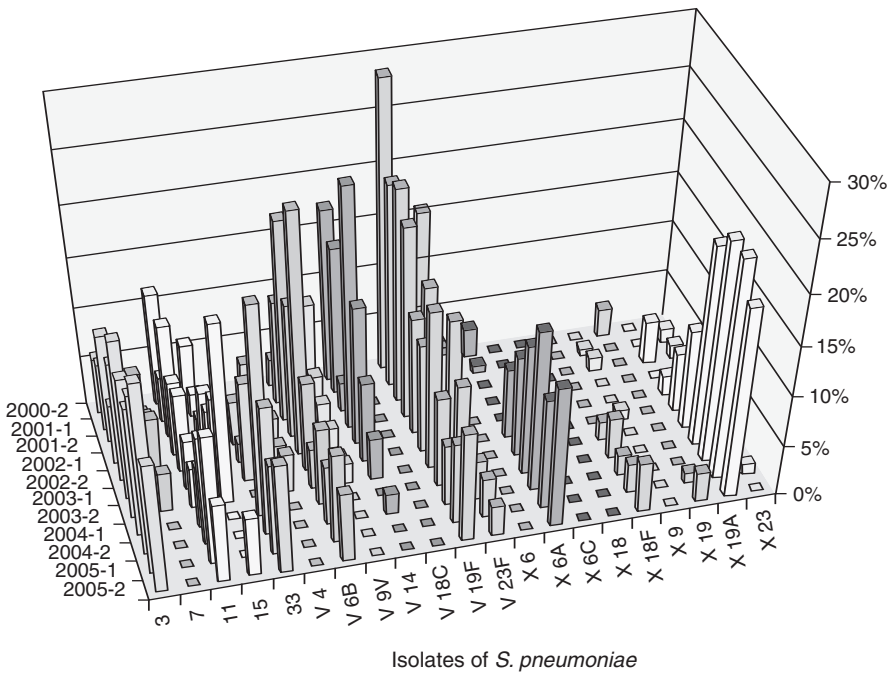


Figure 3 Isolates of *S. pneumoniae* obtained from patients with acute otitis media and acute bacterial rhinosinusitis in Louisville, 2000–05. V designates PCV-7 types and X designates PCV-7 cross-reactive types.

Interestingly, in 2002, serotype 19F alone comprised almost 30% of the total AOM isolates. However, while serotype 19F had decreased by 2005, serotype 19A had increased so that 19A together with 19F now comprised the same 30% of total AOM isolates. Thus it appears that 19A serotype substituted sufficiently for 19F so that no real change in serogroup 19 isolates occurred. Of more concern is that 19A isolates appear to have higher levels of amoxicillin resistance than the prior commonly seen 19F strains.

Summary

In 1970–80, *H. influenzae* was at least as important as, if not more important than, *S. pneumoniae* in AOM. Neither β -lactamase-producing *H. influenzae* nor penicillin-resistant *S. pneumoniae* were seen in clinically important numbers. In the 1980s, a gradual increase was seen in the proportion of cases of AOM caused by *S. pneumoniae*, and β -lactamase-producing organisms (mostly non-typeable *H. influenzae*) became more important in recurrent AOM. Non-typeable β -lactamase-producing *H. influenzae* became the main target for therapy in patients failing previous antibiotic therapy and those patients who suffered frequent recurrences. In the 1990s, the situation changed because of the increase in

penicillin-non-susceptible *S. pneumoniae*. *S. pneumoniae* therefore became the major pathogen in patients with treatment failures and frequent AOM recurrences. β -lactamase-producing *H. influenzae* was still a concern but it had dropped to second place as a cause of treatment failures when compared with penicillin-non-susceptible *S. pneumoniae*. With the advent of PCV-7 universal use in infancy, a decrease in the proportion of penicillin-non-susceptible *S. pneumoniae* was observed, and *H. influenzae* (particularly β -lactamase-producing *H. influenzae*) have become more important causes of AOM treatment failure. Despite this, it is essential to remember that *S. pneumoniae* is still the pathogen involved in about one-third of treatment failures and that about half of those are due to penicillin-non-susceptible *S. pneumoniae*.

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Discussion

Participant: As *H. influenzae* is now the predominant pathogen in patients with acute otitis media, because of the decrease in penicillin-non-susceptible *S. pneumoniae*, would it be logical to assume that the pathogen in patients who fail on amoxicillin is *H. influenzae*?

Christopher Harrison: Two-thirds will be *H. influenzae* and two-thirds of those will be β -lactamase-producing *H. influenzae*, but between one-quarter and one-third will be *S. pneumoniae*, half of which would be penicillin-non-susceptible *S. pneumoniae*. Thus, non-typeable *H. influenzae* is most likely to be the causative pathogen, but penicillin-non-susceptible *S. pneumoniae* cannot yet be dismissed.

Participant: With cefixime oral suspension's good activity against *H. influenzae*, what is your opinion of using this agent as second-line therapy in patients who fail on amoxicillin and of adding the cefixime oral suspension to the amoxicillin rather than switching and stopping the amoxicillin?

Christopher Harrison: That strategy certainly would cover both potential organisms. However, the current opinion of some physicians is that standard-dose amoxicillin can be used as initial therapy instead of high-dose amoxicillin. With this in mind, patients with treatment failure who received 40–60 mg/kg/day should initially undergo a dose increase to 90–100 mg/kg/day to ensure that penicillin-non-susceptible *S. pneumoniae* is covered. Because there is also at least as much chance that a β -lactamase-producing *Haemophilus* could be the cause of treatment failure, cefixime could be added to the amoxicillin as a β -lactamase-stable component. This approach would provide the same, perhaps better, coverage than amoxicillin with clavulanic acid and would definitely provide better coverage than oral second- or third-generation cephalosporins, such as cefuroxime, cefdinir or cefpodoxime, used alone. The combination of amoxicillin plus cefixime however has not been studied in controlled investigations to date.

Participant: Do you consider cefdinir as a second- or third-generation cephalosporin?

Christopher Harrison: The definition of second- versus third-generation has always been 'loose', and different people have different approaches. Some classify on the basis of chemical structure and side chains, while others classify on the basis of activity against groups of organisms. The classic first-generation cephalosporins have poor Gram-negative coverage but very good Gram-positive coverage. The second-generation cephalosporins are active against both Gram-negative and -positive organisms but their efficacy is not the highest against either. The third-generation cephalosporins traditionally had strong activity against Gram-negative but relatively poor activity against Gram-positive. If potency is used as a definition, cefdinir would have to be considered as a second-generation cephalosporin, particularly given a recent report in which it performed worse than expected against β -lactamase-producing *H. influenzae* strains. Having said this, it has been traditionally considered a third-generation cephalosporin.

Participant: Are you aware of any data where the combination of amoxicillin and cefixime has been used?

Christopher Harrison: As noted previously, this combination has not been reported from studies in literature. However it has come to my attention that some clinicians use the combination of cefixime for strong Gram-negative activity and another drug such as clindamycin or high-dose amoxicillin for coverage of penicillin non-susceptible pneumococcus when parents are anxious for their children to receive higher potency therapy for repeated treatment failure.

It is important to consider, however, that failures do not all occur at the same time in relation to the onset of therapy. Three kinds of antibiotic failures can be defined: failures that occur during therapy with the first primary empirical antibiotic, failures in which relapse/recurrence occurs in the first days after antibiotic therapy ceased, and failures where relapse/recurrence occurs 2–3 weeks after treatment stops. A different approach is probably needed depending on the type of failure.

Most published data for treatment of AOM recurrences or treatment failures are from patients who failed more than two weeks post treatment, in which case data suggest that the causative organism will be different from the original infecting pathogen. This means that the patient probably did not fail with the first antibiotic. Rather, the recurrent infection is likely to be due to an organism that survived the initial antibiotic or was acquired since stopping the antibiotic and is colonizing the nasopharynx at the time the AOM recurs.

Patients who fail during therapy may simply have a concurrent viral infection causing many of persisting symptoms (particularly fever and irritability) and do not respond to an

antibiotic. Alternatively, an organism truly resistant to the prescribed drug may be present, in which case a second-line antibiotic is needed with added coverage compared to the first-line therapy. There is, therefore, a three-pronged treatment algorithm depending on the stage at which the treatment failure occurs, with a different emphasis on the basis of the what is the likely breakthrough pathogen, the timing of recurrence and the prior antibiotic.

Participant: Do any symptoms of acute otitis media associate more with *H. influenzae* than *S. pneumoniae*?

Christopher Harrison: Conjunctivitis–otitis syndrome, in which there is purulent drainage from the eyes along with acute otitis media, is caused by *H. influenzae* in 90% of cases. Conversely, a child who looks unwell and has a high fever and otalgia is more likely to be infected with *S. pneumoniae*. Acute media otitis cases due to *H. influenzae* are generally characterized by low-grade, if any, fever.

Clinical application to paediatrics

ALBERT M COLLIER

Immunity in the fetus and young child

The pathogenesis of acute otitis media and the balance between host and pathogen are important in understanding the aims of treatment with antibiotics. Immunoglobulin G (IgG) is an important molecule for immunity, and Figure 1 illustrates the pattern of levels of IgG in a child from conception through to the age of nine years.¹ After the fourth month of fetal age, the pregnant mother begins to pass her own IgG molecules through the placenta, so that, by birth, the baby has a level of IgG greater than 100% of the mother's. Babies born premature and weighing <1000 g are much more likely to survive now than many years ago, but they are still more susceptible to infections because, in part, they have not received the maximum amount of IgG from their mother before birth. After birth and separation from the placenta, levels of IgG decrease very rapidly, with viral antibodies remaining longer than bacterial antibodies. At about 10–11 months, all of the maternal antibodies for bacteria have disappeared. At about 7.5 months of fetal age, the fetal immune system itself begins to manufacture IgG, but the levels increase very slowly, with much maturation of the immune system occurring after birth. Not until the child is aged two years does it have a level commensurate with even 80% of that of its mother. The nadir of IgG concentration is at nine months, which, in longitudinal studies, is the time of the peak incidence of acute otitis media and prior to conjugate (Hib) vaccine of Hib meningitis.²

Otopathogens

Currently, the major pathogens of interest in acute otitis media are *Haemophilus influenzae* and *Streptococcus pneumoniae*. *S. pneumoniae* was discovered in 1880 by Pasteur, who also disproved spontaneous generation and proved the tenet of infectious diseases – that a person must be colonized with an organism before that organism can cause disease. Most often, the organism is acquired through contact with another person infected or colonized with the

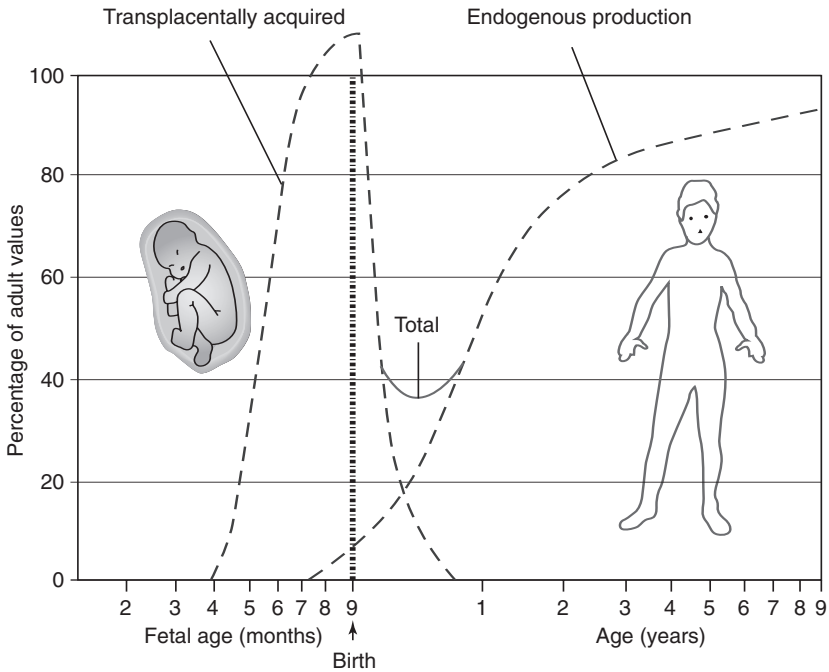


Figure 1 Levels of immunoglobulin G (IgG) at different ages. Adapted with permission from Goldman and Goldblum.¹

organism, which is important in explaining the changing epidemiology of acute otitis media in children. In 1968 in North Carolina, for example, only 1% of children under 5 years of age were in day care and children had little regular contact with other children, perhaps attending Sunday school once a week during the first years of life; in 2006, however, 78% of children under 5 years of age were in day care and thus having regular contact with other young children.

H. influenzae was discovered by Pfeiffer in 1892, when the organism was isolated from a number of patients during the influenza pandemic. The physicians of the time were unaware of viruses and believed that the isolated organism was the cause of influenza, and, as blood was needed in the growth medium, the organism was given the name *Haemophilus influenzae*. In the 1930s, Dr Margaret Pittman, as a project for her PhD in microbiology at the University of Pennsylvania, Philadelphia, was asked to obtain isolates of *H. influenzae* from children with meningitis, produce antisera in rabbits and identify any different serotypes. She identified six types, which she named a–f, by making antibodies to the polysaccharides in the capsules that surrounded the organisms. When the antibodies were added to the

isolates and observed under the microscope, each bacterial serotype could be identified by its reaction to the antisera, with the correct antisera causing the capsule to swell up.

Dr John Robbins and Dr David Smith, who worked in competing laboratories, both isolated the serotype b polysaccharide, which helps the bacteria to evade phagocytosis and remain in the bloodstream long enough to reach the large joints, pericardial space and meninges. They hypothesized that administration of this polysaccharide to children at 2, 4 and 6 months of age – before the peak incidence of meningitis – would encourage the children to produce antibodies against *H. influenzae* type b. Disappointingly, the polysaccharide did not have the desired effect, because children are unable to produce good antibodies to polysaccharide antigens until they reach the age of 18–24 months. The polysaccharide was then linked to a protein, which changed the evoked response from T-cell-independent to T-cell-dependent and resulted in the production of good antibodies against *H. influenzae* type b as early as 2 months of age. The resultant vaccine produced a reduction in cases of *H. influenzae* type b systemic disease from 20 000 cases a year in the USA to around 100 cases in 2005. Although *H. influenzae* is the second most common isolate found in taps from middle ears, the pathogens that cause acute otitis media are non-typeable as they do not have a polysaccharide capsule, and, thus, although the vaccine was extremely effective in preventing systemic Hib disease, it had no effect on surface infections such as acute otitis media.

Of the 90 types of *S. pneumoniae*, seven serotypes were observed to predominate in invasive disease. These seven are the types conjugated to protein carriers in the pneumococcal 7-valent conjugate vaccine (PCV-7). In contrast with the *H. influenzae* type b conjugated vaccine, the same types of *S. pneumoniae* included in the pneumococcal conjugated vaccine also predominate in acute otitis media, so the PCV-7 has had an effect on the incidence of mucosal surface infections such as acute otitis media. Furthermore, a high percentage of these PCV-7 strains were strains (reportedly 30–65%) with penicillin minimum inhibitory concentration (MIC) $>2 \mu\text{g/ml}$. The pneumococcal vaccine not only promotes production of humoral circulating antibodies, but some antibody in the form of IgG appears to reach the mucosa. The surface antibody can prevent attachment and reduce colonization, which, ultimately, prevents disease.

In a 30-year, prospective, longitudinal population study at the Frank Porter Graham Child Development Center in North Carolina, cultures were taken from every child who attended for every respiratory infection for viruses, bacteria and mycoplasmas. Figure 2, when compared with Figure 1, shows an inverse relationship between the incidence of respiratory illnesses by age and levels of IgG antibodies by age in children, with the

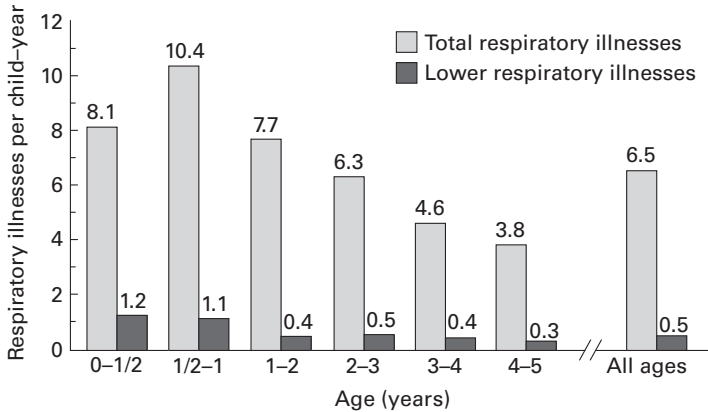


Figure 2 Frequency of respiratory illnesses by age.²

incidence of respiratory illnesses peaking in the second six months of life, when the mother's antibodies are diminishing and the child's own immune system is still maturing, with the IgG levels slowly rising.

In a study of ear taps from children with acute otitis media, no pathogen was isolated in 33% of children.³ This last one-third of children may represent some children with viral otitis media. The situation is further complicated by the fact that an ear affected by a viral infection looks no different from an ear with bacterial otitis media.

When Pasteur discovered *S. pneumoniae*, all of the *S. pneumoniae* were highly sensitive to penicillin, and not until 1960–70 did resistant organisms begin to emerge. Nowadays, about 25% are still highly sensitive, 50% have intermediate resistance and 25% are resistant (MIC >2 µg/ml) to penicillin. A high percentage of *H. influenzae* are resistant because of β-lactamase positivity, with one study showing that 65% of non-typeable *H. influenzae* produced β-lactamases.⁴ Almost all *Moraxella catarrhalis* are β-lactamase-positive.

Figure 3 illustrates the components of the outer membrane of β-lactamase-positive non-typeable *H. influenzae* (Figure 3a). Endotoxin is released in small amounts when Gram-negative rods divide but in large amounts when they are killed. This may be the key to understanding otitis media with effusion (OME).

The peptidoglycan is a very important part of a bacterium, forming its skeleton and giving it shape. The large amount of material packed inside the bacterial cell requires that the cell wall has to be strong to withstand the internal pressure and prevent the cell from 'exploding'.

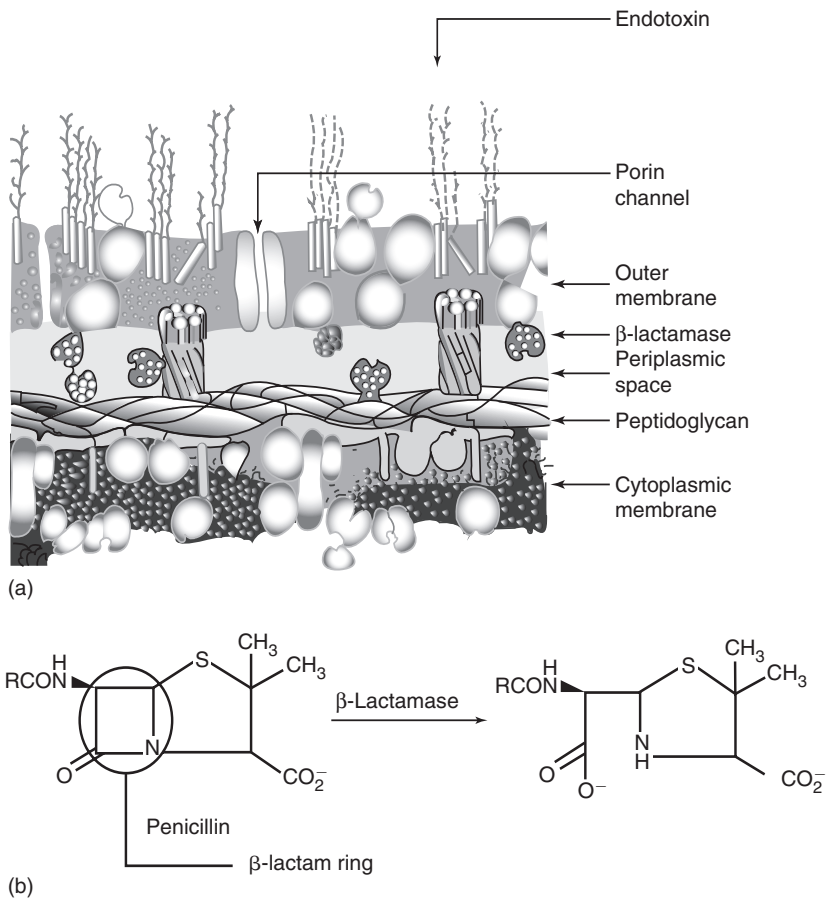


Figure 3 Outer membrane, periplasmic space and porin channels of a β -lactamase-positive, Gram-negative bacterium (a) and the action of β -lactamase on a penicillin (b). Adapted from Neu.⁵

Bacteria can contract viruses, and in the 1970s, a virus infected some *H. influenzae* and inserted a small plasmid (a piece of circular DNA) that coded for an enzyme called β -lactamase, creating β -lactamase-positive bacteria. When this enzyme is present, it attacks the β -lactam ring common to all penicillin and cephalosporin antibiotics, opening up the ring⁵ and altering the structure so that it no longer has the ability to interfere with bacterial cell wall synthesis that would lead to lysis of the bacterial cell wall and death of the bacterium (see Figure 3b). Every time a β -lactamase-positive bacterium divides, it produces progeny that are also β -lactamase-positive. β -lactamase resistance can be overcome through co-administration of a β -lactam antibiotic and a 'suicide molecule' such as clavulanic acid, which blocks the active site of β -lactamase and prevents it breaking down the antibiotic, or through antibiotics, such as some third-generation cephalosporins, such as cefixime, that are resistant to β -lactamase activity.

Evolution of the spectrum of otopathogens

In a review of early double-tap studies after treatment published in 1972, Howie and Ploussard reported that 52% of *H. influenzae*, 84% of *S. pneumoniae* and 25% of *M. catarrhalis* persisted in taps taken 2–7 days after treatment started.⁶ The most virulent pathogen with the most rapid onset was *S. pneumoniae*. In contrast, in 2001, in a study that compared the pathogens that caused acute otitis media in children who received the conjugated pneumococcal vaccine or control vaccine, Eskola *et al* showed that the vaccine reduced the number of episodes of acute otitis media caused by *S. pneumoniae* (217 (28%) vs 414 (35%)).⁷ The vaccine had no effect on episodes caused by *H. influenzae* (315 (33%) for vaccine vs 286 (26.5%) for control vaccine) or *M. catarrhalis* (379 (39%) for vs 381 (35%) for control vaccine). A study of the vaccine coverage of *S. pneumoniae* in Louisville between 2000 and 2004 in terms of penicillin resistance showed that resistance has decreased since the introduction of vaccine (Figure 4) (Harrison C, unpublished data). Although some serotypes have cross-protection, serotype 19F does not provide cross-protection against serotype 19A.⁸

In a review of studies of ear isolates published between 1972 and 2001, Liebovitz *et al* showed that the percentage of β -lactamase-positive *H. influenzae* has changed, with *H. influenzae* becoming more and more β -lactamase-positive.⁹

In a retrospective review of studies in 625 suburban children aged 1 month to 12 years with acute otitis media published between 1975 and 1977, Schwartz *et al* showed that only 16% of cases went into spontaneous remission and 26 of 31 β -lactamase-positive *H. influenzae* failed with ampicillin.¹⁰ Resistance was seen in 8% of all cases of acute otitis media, and 35 (17%) *H. influenzae* isolates were β -lactamase-positive.

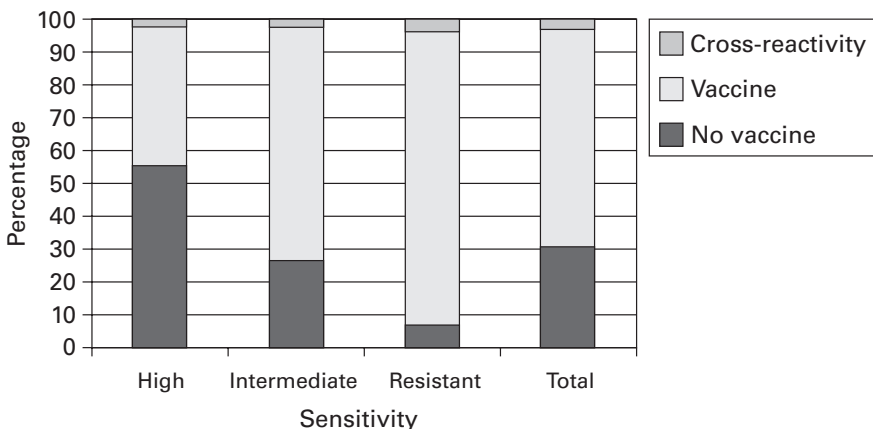


Figure 4 Vaccine coverage of Louisville *Streptococcus pneumoniae* 2000–04 by penicillin resistance.

In the 1970s, general scientific belief was that *H. influenzae* does not cause acute otitis media in children older than three years. By the 1980s, however, and with the publication of a small study in 18 children, in which 35% were infected with *H. influenzae* and 35% with *S. pneumoniae*, *H. influenzae* was recognized as a prominent pathogen behind acute otitis media in children of any age.¹¹

During the 10-year period of the 1980s, statistically significant increases were seen in the prevalence of *S. pneumoniae* causing acute otitis media and there was a progressive rise in the percentage of β -lactamase-producing *H. influenzae*, which increased from 10% to 25%.¹²

In 1993, Harrison *et al* published the results of a study of cefixime versus cefaclor in three centres in the USA.¹³ Of 116 isolates, *S. pneumoniae* accounted for 42 (36%), *H. influenzae* for 24 (21%), with 10 (42%) β -lactamase-positive, and *M. catarrhalis* and *S. pyogenes* (group A streptococci) for 9 (8%) each. Cefixime was more effective against β -lactamase-positive pathogens than cefaclor in this study. In the mid-1990s, in a trial of cefuroxime versus co-amoxiclav (amoxicillin-clavulanate) in 164 patients, before treatment, pathogens were isolated in 120 (73%) middle ear effusion aspirates.¹⁴ Overall, 37% were *S. pneumoniae*, 33% *H. influenzae* (44% of which were β -lactamase-positive) and 8% *M. catarrhalis*. In 265 children aged 2 months to 12 years with recurrent or persistent acute otitis media, 150 (57%) had a single pathogen, 29 (11%) multiple pathogens and 82 (31%) no growth on culturing.¹⁵ Overall, 93 (49%) of isolated organisms were *S. pneumoniae*, with 50 (54%) penicillin-susceptible, 12 (13%) penicillin-intermediate and 31 (33%) penicillin-resistant. Of the 75 (40%) *H. influenzae* isolates, 42 (56%) were β -lactamase-positive. *M. catarrhalis* was isolated from 15 (8%) of children.

A multicentre study in the USA in 177 patients with recurrent or persistent acute otitis media sets the scene for the pattern of organisms before the introduction of the 7-valent pneumococcal vaccine. Overall, 125 children had 134 pathogens: 69 (51.5%) *S. pneumoniae* (11 penicillin-intermediate and 8 penicillin-resistant), 44 (32.8%) *H. influenzae* (18 (41%) β -lactamase-positive), 15 (11.2%) *M. catarrhalis* and 6 (4.5%) *S. pyogenes*.¹⁶ After the introduction of the pneumococcal vaccine, in a study of high-dose co-amoxiclav versus azithromycin, Hoberman *et al* showed that 494 (67.7%) of 730 children had one pathogen and 57 (23%) had more than one pathogen.¹⁷ Of the pathogens isolated, 245 (49%) were *H. influenzae* (23.7% β -lactamase-positive), 229 (46%) *S. pneumoniae* and 53 (11%) *M. catarrhalis*. It is important to note, however, that most of these patients were not from the USA; the non-US children had little use of the pneumococcal vaccine and a lower rate of β -lactamase-positive *H. influenzae* and one-third had recurrent acute otitis media. The study demonstrated the change in otopathogens over time between 1981 and 2003,

highlighting the introduction of the *H. influenzae* type b and pneumococcal vaccines, and the impact of the pneumococcal vaccine on pathogens for acute otitis media in Kentucky in 2003, where the percentage of β -lactamase-positive *H. influenzae* increased considerably and *S. pneumoniae* decreased in terms of susceptible, intermediate and resistant strains after the introduction of the vaccine.

In Kentucky and New York in 2003, in patients with recurrent/persistent acute otitis media that failed treatment, ear taps led to the isolation of non-typeable *H. influenzae* β -lactamase-positive pathogens in 35% of patients, *H. influenzae* β -lactamase-negative in 23%, penicillin-susceptible *S. pneumoniae* in 12%, penicillin-intermediate *S. pneumoniae* in 3% and penicillin-resistant *S. pneumoniae* in 22%, with other pathogens being isolated in 5% of cases.

In a prospective control study in patients with recurrent acute otitis media who did ($n=38$) or did not ($n=45$) receive one or two doses of 7-valent pneumococcal vaccine, no increase in salivary IgG was seen with one dose of pneumococcal vaccine or control, whereas two doses of the vaccine increased salivary IgG antibodies against serotypes 6B, 14 and 18C, although this was only significant for type 14.¹⁸ The results show that two doses of vaccine were very good at preventing systemic disease, but three or four doses are needed to get a real effect on mucosal surfaces with a non-invasive disease. Repeated dosing is thus needed to increase salivary levels of IgG. In terms of increased salivary IgA levels, local mucosal boosting occurs through normal carriage and recurrent infections, which occurs often in pneumococcal vaccine groups, but it is hard to obtain any real evidence that IgA is produced after the pneumococcal vaccine.

A study by Casey and Pichichero highlights the shift in incidence of pathogens found in patients with persistent acute otitis media and treatment failures (Figure 5). In 1995–7, *S. pneumoniae* was the dominant organism, with *H. influenzae* having a lesser role. By 1998–2000, around the time that the pneumococcal vaccine was introduced, the numbers of cases caused by each pathogen were comparable, but by 2001–03, *H. influenzae* was the dominant organism and *S. pneumoniae* the minor contributor.¹⁹ This shift was also confirmed by a number of other papers reporting from different parts of the USA. For example, Caspary *et al* found that, at the time of placement of pressure-equalization (PE) tubes, children vaccinated with the pneumococcal vaccine were two times less likely to have *S. pneumoniae* and three times more likely to have *H. influenzae* than those not vaccinated.²⁰ In a comparison of middle ear pathogens in children aged 7–24 months from 1992–98 and 2000–03, Block *et al* found that, in children who received the vaccine, the prevalence of *S. pneumoniae* decreased from 48% to 31% and that of *H. influenzae* increased from 41% to 56%.⁴ Finally, Leibovitz *et al* found very similar results in a population of 1077 patients with

acute otitis media from the Negev in Israel, which has a predominantly Bedouin population who live in the desert and do not attend regular schooling, in which 77% of cases were considered treatment successes and 10% recurred in one month, with 28% of recurrences caused by the same organism and 72% by a new organism. Overall, 54% of cases were caused by *H. influenzae*, 45% by *S. pneumoniae* and 1% by *M. catarrhalis*, with all recurrences caused by *H. influenzae* occurring in the first two weeks.²¹

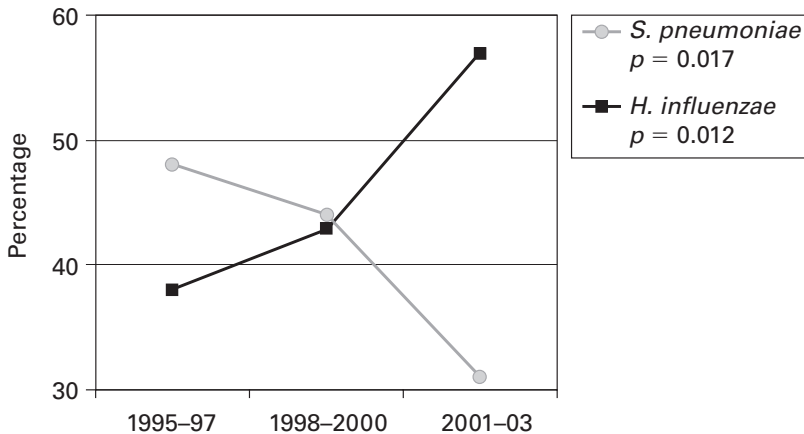


Figure 5 Shift in incidence of pathogens found in persistent acute otitis media and treatment failures. Reproduced from Casey & Pichichero.¹⁹

Summary

In the 1970s, *S. pneumoniae* and *H. influenzae* were common in children with acute otitis media, but there was no penicillin resistance in *S. pneumoniae* and minimal β -lactamase-positive *H. influenzae*. In the 1980s, a gradual increase was seen in *S. pneumoniae* and about 25% of non-typeable *H. influenzae* were β -lactamase-positive, and these were the main pathogens seen in patients with treatment failure or recurrence. In the 1990s, there was an increase in penicillin-non-susceptible *S. pneumoniae*, which became the major pathogen in failures and recurrences. β -lactamase-positive *H. influenzae* remained an issue, but were less important than penicillin-non-susceptible *S. pneumoniae*. The 2000s have seen the conjugated vaccine effect, in which there has been a decrease in the numbers of penicillin-non-susceptible *S. pneumoniae*, although with more of an effect with the intermediate than with resistant *S. pneumoniae*. Increases have been seen in β -lactamase-positive *H. influenzae*, which, again, is the major pathogen in treatment failures and recurrences. It is important to note, however, that penicillin-non-susceptible *S. pneumoniae* have not been completely eradicated, as recent serotype substitution may be occurring. Protection from the vaccine is

thus not 100% and it only protects against the types in the vaccine. It is time to consider adding conjugated type 19A polysaccharide to the pneumococcal vaccine.

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Albert M Collier MD – Financial support disclosure

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Discussion

Michael Jacobs: In the 1970s, the dose of amoxicillin used was 22.5 mg/kg/day, which was inadequate for eradication of *H. influenzae* and most likely explains why so many failures were reported in the retrospective review by Schwartz *et al.*¹

Albert Collier: That is a good point, and if a child with acute otitis media is in day care, particularly with seven or more other children, I start with a higher dose of amoxicillin (90 mg/kg), because they are in an environment where there is more likely to be a resistant organism.

Michael Jacobs: Both the Block and Casey studies were in patients who failed after treatment primarily with amoxicillin, so these studies do not represent initial presentation of patients with acute otitis media but acute otitis media treatment failures, which is a very important distinction. I have heard some investigators recommend giving the polysaccharide pneumococcal vaccine as a booster to children aged 18–24 months, as this is a better immunogen than the conjugated vaccine, in view of additional 16 serotypes covered in it, once children are mature enough to react to it.

Albert Collier: This approach works. The 23-valent polysaccharide pneumococcal vaccine has 16 additional polysaccharide types when compared to the 7-valent conjugated vaccine. You get a better immune response to the 16 additional polysaccharide types when the polysaccharide vaccine is preceded by two doses of the 7-valent conjugated vaccine.

Michael Jacobs: The incidence of pathogens found in children with persistent acute otitis media and treatment failures is now similar for *H. influenzae* and *S. pneumoniae*. Although the data were not strong, one intriguing study on the 11-valent pneumococcal vaccine conjugated to a *Haemophilus* protein D (a surface protein from untypeable *H. influenzae*) showed a decrease in acute otitis media caused by *H. influenzae* as well as *S. pneumoniae*.² A vaccine against acute otitis media caused by *H. influenzae* is a very interesting prospect.

Michael Hagmann: The schedule for vaccinations includes about 20 vaccinations by the age of one year. Has anyone investigated how far the immune system can be pushed with multiple vaccinations?

Albert Collier: Offit published an excellent paper on this subject.³ Although the number of proteins in the immunization pool was halved when the USA switched from the whole cell pertussis vaccine to the acellular vaccine, the immune system seems to be able to tolerate even 100 times more proteins than children are exposed to during immunizations. The main drive currently is to reduce the number of physical injections a child must receive by combining more than one immunization into a single injection. In the USA, the five-in-one vaccine is in common use, and in Europe and in Canada, the *H. influenzae* type b vaccine has been added to the five-in-one vaccine and works well. A major issue with respect to immunization is the cost for parents, as we have a continually increasing number of excellent paediatric vaccines.

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Open discussion

ALBERT M COLLIER, MICHAEL HAGMANN, MICHAEL R JACOBS, JEREMIAS MURILLO

Participant: Dr Jacobs, do you feel that physicians are aware of and are trying to implement the American Academy of Pediatrics/American Academy of Family Physicians' guidelines?¹

Michael Jacobs: Although physicians tend to start patients on appropriate first-line antibiotics, as per the guidelines, second-line treatment tends to involve random cycling between various other antibiotics, with very little logic being applied. A number of pharmaceutical companies have tried to present the guidelines in different, often simplified, formats, but this seems to have had little effect. When the guidelines were in development, I recommended an approach in which patients are started on amoxicillin and are then given an agent effective against *Haemophilus influenzae*, such as cefixime, if they do not respond to the amoxicillin. This approach is based on the fact that no agent is better than amoxicillin against *Streptococcus pneumoniae*, and, therefore, adding an agent effective against *H. influenzae* is probably a better alternative than switching to a compromised drug such as cefdinir, which is much less effective against *S. pneumoniae* than amoxicillin and only marginally better than amoxicillin against *H. influenzae*.

Jeremias Murillo: That concept seems to make sense, particularly when the rapidity of the change between *H. influenzae* and *S. pneumoniae* predominance is taken into consideration.

Albert Collier: I also like this idea. Once the prescription for amoxicillin has been written, it makes sense for the patient to complete the course already prescribed, and, in practice, I often prescribe a second antibiotic when patients fail to respond but ask them also to continue the amoxicillin. This seems particularly sensible now that serotype 19A, which is not covered by the 7-valent pneumococcal vaccine, is becoming an emerging threat.

Michael Jacobs: This approach is particularly attractive for a number of reasons. Many physicians tend to switch to ceftriaxone, which must be given as three daily doses to cover

S. pneumoniae, but breakthrough cases, in which some strains have not responded to three doses of ceftriaxone, have been published. Thus, although ceftriaxone has excellent *H. influenzae* activity, it is much less effective against highly penicillin-resistant *S. pneumoniae* such as serotype 19A.

Jeremias Murillo: In addition, introducing a parenteral medication such as intramuscular ceftriaxone represents a major step-up in the management pathway, and many paediatricians do not feel comfortable giving injections in their office.

Albert Collier: Ceftriaxone should be given for more than one day if used to treat persistent acute otitis media.

Michael Jacobs: On a different note, physicians in Japan use a number of third- and fourth-generation cephalosporins in children that are not used in children in the USA. Unfortunately, however, some strains of *H. influenzae* have developed altered penicillin-binding proteins (PBPs), which has resulted in ceftriaxone and cefotaxime treatment failures in meningitis.

Jeremias Murillo: When the pneumococcal vaccine was first launched, much discussion at national infectious disease meetings suggested that the vaccine was not the best answer, as a shift in serotypes would be the result – as indeed seems to be the case. How complex is the genetic element that predicts serotype switching?

Michael Jacobs: It would be possible to determine this through sensitive sequence typing on strains with housekeeping genes, and some papers have reported definite switches in serotype. My impression is that, overall, very little serotype switching occurs. I have traced some very rare serotypes from different parts of the world, and their lineages can easily be traced back to the same serotype, but it is difficult to trace them back to other serotypes. Interestingly, predominantly only five serogroups of *S. pneumoniae* (6, 9, 14, 19 and 23) have become highly resistant and multidrug-resistant, while the other two types included in the 7-valent pneumococcal vaccine have shown a little progression towards penicillin non-susceptibility but not towards multidrug resistance. Although part of the explanation relates to exposure (strains that have become resistant have had the most antibiotic exposure), this seems unlikely to be the only explanation and perhaps these organisms have different biological mechanisms to explain the disparity.

Participant: Could individual studies based on pharmacokinetic/pharmacodynamic data be undertaken to determine the combined dose of amoxicillin and a second drug, such as

cefixime, that would provide the highest level of killing without increasing the side-effect profile?

Michael Jacobs: Research by Jones and Johnson suggested a possible *in vitro* synergy between amoxicillin and cefixime, but this has not been explored thoroughly.² On a superficial basis, two antibiotics with the same mechanism of action are unlikely to be synergistic, but as they target slightly different PBPs, the combination may produce somewhere between an additive and a synergistic effect. Double-tap studies would be needed to see if clinical synergism is being achieved, and the activity of the standard dosing regimens would be compared with that of combination therapy. Children with tympanostomy tubes are easy to study, as most have several attacks of acute otitis media with drainage out of the tympanostomy tubes while the tube is in place. A study involving this patient population would not need a large number of patients to study multidrug-resistant *S. pneumoniae* serotype 19A and *H. influenzae*.

Participant: As has been mentioned, cefixime oral suspension was not available when the American Academy of Pediatrics (AAP)/American Academy of Family Physicians' (AAFP) guidelines¹ were developed. What procedure would be needed to revisit these guidelines?

Michael Jacobs: The results with cefixime oral suspension would need to be brought to the attention of the AAP and the AAFP. Guidelines on sinusitis published in 2000 and then revised in 2004 recommended amoxicillin (or clindamycin in patients with non-type 1 allergy to penicillins) in combination with cefixime. It is important to remember, however, that although the combination of amoxicillin and cefixime is logical theoretically, it has not been studied in practice. This can lead to reticence on the part of guideline publishers to include the combination in their recommendations.

Jeremias Murillo: Clindamycin looks very promising on the basis of *in vitro* data.

Michael Jacobs: Interestingly, although physicians are comfortable recommending clindamycin, this drug has not actually been studied in patients with acute otitis media, and its efficacy for this condition is thus uncertain. In addition, clindamycin is now known to be a concentration-dependent agent, but its dosage for approval was four times a day, so the optimal dosing regimen is unknown.

Jeremias Murillo: If a physician was going to follow the principle of starting with amoxicillin and following with cefixime, what would the treatment algorithm look like? Would you wait a couple of days with the patient on amoxicillin before cefixime is started?

Michael Jacobs: The current guidelines state that a patient who has not responded well between 48 and 72 hours should be regarded as a clinical treatment failure and a second-line agent should be introduced. It makes sense to me, at that point, to add a second-line agent to the existing first-line drug rather than changing the prescription completely, because only the quinolones and perhaps linezolid would be effective for *S. pneumoniae* and most second-line agents are nowhere near as effective as cefixime for *H. influenzae*. Co-amoxiclav is a second-line agent that is limited by its poor side-effect profile; although the side-effect profile of amoxicillin plus cefixime has not been studied, it is likely to be more tolerable than co-amoxiclav.

Albert Collier: I would also expect adverse effects to be less of a problem with amoxicillin plus cefixime than with co-amoxiclav.

Michael Jacobs: Has the total number of tympanostomy tubes placed nationally in the USA changed since the introduction of the pneumococcal 7-valent conjugate vaccine?

Michael Haggmann: There seems to be a drop in the number of tube placements. Much discussion has surrounded whether or not acute otitis media is a disease that needs antibiotic treatment; many physicians are frustrated by the constant need to switch from one antibiotic to another and there is some controversy in the literature about whether or not the use of antibiotics has achieved anything other than delaying the placement of pressure equalization (PE) tubes. Drainage from PE tubes also raises a number of issues – such as the relevance of immediate versus delayed drainage from the tube. Ototopicals may be an option, as it is assumed that resistance cannot develop because these agents by their nature are administered directly through the tympanostomy tube; however, an increase in colonization of some fungal elements has been reported with the use of ototopicals.

Michael Jacobs: *S. pneumoniae* is the most common typical bacterial cause of pneumonia, and *Mycoplasma pneumoniae* the most common atypical bacterial cause. Increasingly, the recommendations for treating pneumonia separately target each organism; thus, rather than physicians being faced with the dilemma of trying to identify a compromise drug that is best overall, the recommendation is to use the best drug against each pathogen, namely *S. pneumoniae* and *H. influenzae* in acute otitis media.

Albert Collier: Although I tend to start amoxicillin at a higher dose in children with acute otitis media who attend day care with seven or more children, many paediatricians believe that amoxicillin is ineffective in their community; a combination of amoxicillin and oral cefixime suspension might be a useful combination for such physicians.

Michael Jacobs: A number of years ago, Fujisawa began to develop amoxicillin plus cefixime as a commercial combination in Japan. The combination was never pursued, but some papers on synergy and *in vitro* data were published.³

Participant: The formulation of suspensions of cefixime with amoxicillin has poor stability, so the two agents need to be given separately. Does the fact that no new antibiotics are due to become available in the near future have an impact on how physicians use existing antibiotics?

Jeremias Murillo: I think the answer has two aspects. Firstly, physicians need to use antibiotics conservatively – that is, to prescribe antibiotics prudently and for the appropriate indications in order to reduce development of resistance. Secondly, novel combinations of existing antibiotics, such as the combination approach with amoxicillin plus cefixime suggested by Dr Jacobs, need to be considered.

Michael Jacobs: In the UK, primary care physicians promote decreasing antibiotic prescriptions and decreasing visits to physicians for acute otitis media. Parents are thus encouraged not to present their child to their general practitioner until the signs and symptoms of acute otitis media have persisted for 72 hours. This has resulted in a reduction in the incidence of antibiotic prescribing in acute otitis media and rates of resistance in acute otitis media pathogens are much lower in the UK. The downside of this approach is that the incidence of severe complications, such as mastoiditis and meningitis, is slightly higher than in the USA.

Jeremias Murillo: In my inner city setting, I also see an inverse relationship: the longer people wait to seek medical attention, the higher the medical complication rates.

Participant: Do physicians believe that resistance to one third-generation cephalosporin automatically implies resistance to other third-generation cephalosporins, such as cefixime?

Michael Jacobs: Physicians' perceptions do influence their prescribing patterns, but when the minimum inhibitory concentrations (MICs) for the cephalosporins are compared with the breakpoint, cefixime oral suspension clearly has an excellent advantage over many other oral cephalosporins with respect to *H. influenzae*.

Albert Collier: I am amazed by how many physicians have to prescribe from a formulary, which can prevent them using certain antibiotics even though data strongly support their use.

Michael Jacobs: Formularies are a major problem, as many include only first- and second-generation cephalosporins.

Participant: How would you summarize the rationale behind the recommendation to add cefixime oral suspension to amoxicillin in children who have persistent signs and symptoms of acute otitis media after 72 hours on amoxicillin?

Michael Jacobs: The two most common pathogens in patients with acute otitis media are *S. pneumoniae* and *H. influenzae*. Historically, *S. pneumoniae* was the predominant organism, but data then showed that *H. influenzae* had become more important. Now, however, recent data suggest that the introduction of the pneumococcal 7-valent conjugate vaccine has led to the predominance of a specific strain of *S. pneumoniae* (serotype 19A). As the exact organism causing a particular case of acute otitis media cannot be ascertained without culturing and serotyping, and the spectrum of pathogens is subject to rapid and cyclical change, an approach that targets both organisms is logical. The combination of amoxicillin (the currently most effective oral drug against *S. pneumoniae*) and cefixime (currently one of the most effective oral drugs against *H. influenzae*) would be ideal.

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Case study: Newborn hearing screening test, diagnostic approaches, autoinsufflation and otalgia

MICHAEL HAGMANN

Box 1 Case history

An eight-month-old child was referred for ear, nose and throat (ENT) consultation after questionable results on a newborn hearing screening test. The history revealed a first episode of acute otitis media at about 2–3 months of age, which was treated with amoxicillin. A second episode had occurred three months later, at which point the child was given cefdinir. A third episode was treated with high-dose co-amoxiclav (amoxicillin-clavulanate) and a fourth with azithromycin. The child then received intravenous ceftriaxone and was prescribed an outpatient course of oral cefdinir. After five months, between the second and third ear infections, the child had purulent drainage from the left ear. He eventually underwent pressure equalization (PE) tube placement and an adenoidectomy, and now has an occasional discharge from the left ear.

Box 1 describes the history and management of a child with acute otitis media who received multiple antibiotics and experienced multiple recurrences. This case highlights a number of important issues regarding acute otitis media that fails to respond to standard therapy, including the relevance of the newborn hearing screening test, shortcomings in the use of existing diagnostic approaches, autoinsufflation and otalgia.

Newborn hearing screening test

The newborn hearing screening test is a requirement in most US States. In many cases, however, children with an initial questionable newborn hearing screening test are actually experiencing central neural hearing loss or conductive hearing loss from an effusion, particularly in children who undergo the test 2–3 weeks after birth. In those children with effusions, because the exam shows a delay in the early waveforms, it is sometimes confused with a sensorineural hearing loss until the effusion is finally resolved. In this case study, the results of the newborn hearing screening test are questionable, because the initial episode of acute otitis media occurred at 2–3 months, when children are ‘otitis media prone’. Such children, unfortunately, are very likely to need PE tube placement.

Diagnosis

The method used to diagnose acute otitis media is important, and pneumatic otoscopy is essential to differentiate between acute otitis media and chronic serous otitis media (also known as otitis media with effusion). Very few physicians, however, routinely use pneumatic otoscopy to determine whether or not a child’s ears are clear of infection between the second and third ear infections or whether or not the two ‘episodes’ actually reflect a persistent infection without a clear interval.

Drainage

This child had leakage and drainage from the ear as a result of spontaneous perforation due to the high pressure in the middle ear space; this is called a pus-under-pressure (PUP)-type ear. An abundance of purulent material is often expelled during myringotomy in preparation for tube placement, and children with PUP-type ears are very likely to have drainage after tube placement. Although colonization in the nasopharynx is an important issue, however, the respiratory tract, including the middle ear, can be described as one single tract. The patient described in Box 1 had undergone adenoidectomy – as do most patients who have tube placement – and this is likely to reduce a large amount of bacterial colonization. In a recent study of children with adenoidectomy and tube placement, post-tympanostomy tube otorrhoea was dramatically reduced in those who received an adenoidectomy.

Mastoiditis

In patients who have developed mastoid abscesses, immediate tube placement is needed.

Sometimes it is necessary to make an incision over the mastoid area in order to perform a mastoidectomy.

Biofilms

Biofilms can be present in the mucosal spaces of the middle ear, the sinus mucosa and the PE tubes. The existence of biofilms has been proven in the middle ear mucosa of tubed ears and non-tubed ears.

Autoinsufflation

Autoinsufflation is a mechanical approach to ear clearance and allows mechanical expulsion of the fluid in the middle ear. This can be helpful in preventing the build-up of material that can follow a number of courses of antibiotics. The material that results can be very thick and mucoid, even to the point where it cannot be suctioned from the ear. An increase in the use of autoinsufflation could impact on the number of PE tubes needed.

Otalgia

A correlation exists between some of the more-resistant organisms, virulence and otalgia. Some children have badly infected ears but are not uncomfortable or febrile, while others may have a less infected appearance but are in extreme discomfort. Some studies have shown that otalgia coincides with resistant *Streptococcus pneumoniae*. The most common pathogens in immediate post-tympanostomy tube drainage are *Haemophilus influenzae* and *S. pneumoniae*, while *Pseudomonas* is the more common pathogen in children with delayed otorrhoea (about two weeks after tube placement). As far as antimicrobial eradication is concerned, ototopicals are important in eliminating much of this disease.

Discussion

Michael Jacobs: Dr Hagmann, I was interested in your comment about chronic infections and biofilms. Biofilms comprise a slime layer that surrounds metabolically inactive organisms, and antibiotics, which can act only on actively metabolizing and growing organisms, cannot work against inactive pathogen within biofilms. This is an issue for many fields of medicine, including those that involve the use of prosthetic devices, joint replacements and heart valves.

Michael Haggmann: Usually the PE tubes will be removed in children with constant drainage. In children with leaking or draining ears, I prescribe ototopicals, while I tend to use oral antibiotics in children with purulent otorrhoea or another oral or sinus cavity condition.

Michael Jacobs: The first episode in this case illustrates how many physicians seem to choose antibiotics at random, as this antibiotic history does not reflect the recommendations for first- or second-line agents. It also highlights, however, that there are no guidelines on the best approach in cases in whom first-, second- and third-line treatment courses have failed.

Albert Collier: Were cultures of the ear drainage done in this patient?

Michael Haggmann: Our hospital does not culture routinely.

Participant: What message would you give to practising paediatricians in terms of a clinical treatment algorithm?

Michael Haggmann: The data in Dr Jacobs's paper suggest that new recommendations are needed. The initial drug should always be a penicillin such as amoxicillin (unless the patient is allergic to penicillin). If amoxicillin fails to clear the infection, the results of studies and data on minimum inhibitory concentrations (MICs) suggest that cefixime oral suspension should be the first second-line drug, and this could be added to amoxicillin in a combination rather than withdrawing the amoxicillin and prescribing cefixime oral suspension.

Michael Jacobs: Some physicians recommend sequential prescribing of first-, second- and finally third-line therapies if the treatment fails to clear the infection. After such sequential therapy, the physician returns to the start of the treatment algorithm and begins again.

Michael Haggmann: The key issue is whether or not the infection has actually cleared completely between episodes. We consider placing tubes after a child has four or five infections in six months, more than four episodes in one year or persistent acute otitis media. It is important to differentiate acute otitis media, which is the result of a bacterial or viral ear infection, and ears that have been treated with so many different antibiotics that they never become reinfected but the effusion in the middle ear becomes almost solid. At that point, the child is likely to be asymptomatic but falling behind with respect to speech charts. As an ENT specialist, about 30% of my patients have abnormal speech and ears that look healthy – even down the microscope and in the operating theatre; however, the ear drums of these children do not move during tympanogram or pneumatic otoscopy, and a thick, sometimes transparent, effusion drains out when an incision is made.

Jeremias Murillo: Is there a rationale to cycle through a few antibiotics and then return to the start of the treatment algorithm but with a higher dose or longer duration?

Michael Jacobs: One of the recommendations in the guidelines is to do tympanocentesis, but only a small number of mainly specialist paediatric practices undertake tympanocentesis in children with third episodes.

Michael Hagmann: Tympanocentesis is not an easy or quick procedure to perform in an office, and it can be distressing for the child and its parents. Although it provides very useful information, it is understandable that many busy practitioners prefer to prescribe antibiotics.

Case study: Tympanocentesis, cultures and optimal duration of therapy

JEREMIAS MURILLO

Box 1 Case history

A three-year old boy presented to his paediatrician with a two-day history of upper respiratory symptoms associated with fever up to 103°F (39.4°C). On examination, he was found to have a right acute otitis media and was treated with high-dose oral amoxicillin.

On follow-up at 72 hours, he remained febrile with a maximum temperature of 101.5°F (38.6°C) and started to complain of ear pain. He was found to have a bulging right tympanic membrane. He was referred to the ear, nose and throat (ENT) specialist, and tympanocentesis was performed. Culture of the aspirate grew *Haemophilus influenzae* sensitive to cefixime. He was treated with seven days of cefixime and responded with resolution of fever and ear pain.

Box 1 describes the history and management of a three-year-old child with acute otitis media that failed to respond to standard therapy. The case highlights a number of important issues, including physicians' ability to perform tympanocentesis, the ability to culture the sample obtained and the optimal duration of therapy.

Discussion

Tympanocentesis

Jeremias Murillo: Few paediatricians' offices are equipped to perform tympanocentesis, but, with the current issues in terms of pathogens, should physicians be encouraged to undertake this procedure to allow culturing and identification of organisms?

Michael Jacobs: Dr Pichichero has spearheaded an attempt to train physicians to correctly perform the more basic procedure of otoscopy.

Jeremias Murillo: Does the process of change then need to start by encouraging residents in training to undertake these procedures that can lead to better diagnosis?

Michael Hagmann: I feel strongly that residents in training should be encouraged to perform these procedures, but, unfortunately, the paediatric residency in most training programmes in the USA does not rotate through ENT, because it is a surgical specialty.

Jeremias Murillo: Residents in ENT and paediatrics seem to pass through two divergent training experiences, yet acute otitis media is a disease common to both specialties and the care of this condition can eventually merge. The whole training process needs to be improved from the start, so that paediatricians and their offices are equipped for the procedures and patients are referred only when complications develop. Because of the changes in microbial flora that are resulting from pressures from different sources, I think the impetus has to be to begin looking at the ability to culture and identify the causative organisms. In an ideal world, all hospitals should aspire to a benchmark system in which they have the ability to obtain, process and identify the organisms.

Duration of therapy

Jeremias Murillo: Duration of therapy seems to be based on 'belief', as no case-control trials indicate that 7 days is better than 10 days. Dr Jacobs, what is your opinion on the best duration of treatment?

Michael Jacobs: The best answer on the basis of evidence is that we simply do not know. I personally believe that 7 days of treatment is adequate for most patients, but the optimal duration of therapy depends on the severity of the underlying viral infection – if this has caused a lot of damage, treatment may need to continue for 14 days.

Jeremias Murillo: In this era of evidence-based medicine and the problems associated with prolonged antibiotic therapy, it seems surprising that no one has undertaken evidence-based, case-control trials to determine the best duration of treatment.

Albert Collier: Dr Jacobs reminded us that antibiotics only shift the problem more in favour of the host and that the host's immune system takes over. I think that duration of therapy is also dependent on the host – that is, the patient – and should be individualized on a patient-to-patient basis, although, of course, in practical terms it is necessary to determine an 'average' optimal duration.

Pathogen identification

Michael Jacobs: From a clinical point of view, a physician can only take an educated guess at the causative pathogen if a culture is not obtained, which means they also cannot be sure whether or not the infection is a new infection or a relapse or whether or not the treatment has failed for another reason.

Albert Collier: It is so important to obtain a point of reference at the very start of the illness. Each case that is treated has the potential to become a 'problem' case, and identification of the pathogen that causes that initial episode provides such a point of reference. In many cases, this could be achieved easily by taking swabs for culturing during initial diagnostic procedures if tympanocentesis is done or by culturing drainage from the middle ear.

Jeremias Murillo: Such oversights in obtaining critical information that can guide management are common across the board – not just in acute otitis media.

Amoxicillin plus cefixime oral suspension

Albert Collier: Now knowing that β -lactamase-positive *H. influenzae* is so common, controlled studies should be performed employing combination amoxicillin and cefixime oral suspension initially versus prescribing amoxicillin alone in treating acute otitis media.

Michael Jacobs: This approach is most likely to be applied widely to the group of patients the AAP/AAFP guidelines recommend starting on co-amoxiclav, using the combination of amoxicillin and cefixime oral suspension as an alternative to co-amoxiclav. However, the routine initial use of amoxicillin plus cefixime oral suspension would be hard to justify because of the lack of any studies of amoxicillin plus cefixime.

Conclusion

The bacterial aetiology of acute otitis media is constantly changing and evolving, with the spectrum of pathogens changing in response to, for example, immunization practices such as the introduction of the pneumococcal 7-valent conjugate vaccine. The existing recommendations for the management of acute otitis media have some limitations. Although high-dose amoxicillin certainly should be used initially, as per the AAP/AAFP recommendations, physicians need to cover the emergence of resistant organisms, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*, in patients failing antibiotic therapy. Microbiological data suggest that cefixime has distinct advantages in specific situations, such as the treatment of acute otitis media thought to be failing first-line therapy due to β -lactamase-producing *H. influenzae*. Furthermore, a prescription of combination amoxicillin and cefixime oral suspension would bring economic implications in terms of reducing the number of follow-up visits. Clinical studies and evaluation will add credence to this approach.