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Failure of antibiotic therapy in acute otitis media

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Abstract

The aim of this retrospective study was to determine the possible causes of failure of antibiotic therapy in children with acute otitis media (AOM). Thirty-nine samples of middle-ear fluid were obtained by myringotomy from 31 children suffering from AOM, unrelieved by antibiotic therapy administered for over 48 hours. The samples were analysed by the usual microbiological techniques, including cultures, tests for beta-lactamase producing strains and the determination of the minimal inhibitory concentration of penicillin for *Streptococcus pneumoniae*. In 14 samples, no bacterial strains were detected in the cultures of middle-ear fluid; and in two samples the cultures revealed two strains of bacteria. The bacteria most frequently identified were *Haemophilus influenzae*, found in 11 samples, and *Streptococcus pneumoniae*, found in seven samples, of which four produced strains with reduced susceptibility to penicillin. The failure of antibiotic therapy in AOM appears to be related to the increased resistance of *Haemophilus influenzae* and to the reduced susceptibility of *Streptococcus pneumoniae* to penicillin. Other factors contributing to the failure of antibiotic therapy in AOM may be the viruses or the bacteria that produce multiple pathogens in the middle ear.

Key words: Otitis Media; Antibiotics; Treatment Failure

Introduction

Acute otitis media (AOM), a very common infantile ailment, leads to about 4.5 million consultations each year in France.[1] Although the disease resolves spontaneously in 81 per cent of the cases, antibiotic therapy is often used in AOM to avoid the risk of complications such as meningitis, mastoiditis and facial paralysis.[2] However, the recent emergence of antibiotic-resistant bacteria seems to be increasing the risks of relapse.

The aim of our study was therefore to identify the causative organisms involved in AOM after failure of antibiotic therapy, and to determine their characteristics.

Materials and methods

The study covered 31 patients treated for AOM from June 1996 to June 1999 in the Department of Otolaryngology – Head and Neck Surgery, Caen University Hospital, Caen (France).

The patients included in the study suffered from acute suppurative otitis media with effusion behind an intact eardrum. In spite of antibiotic therapy for at least 48 hours, all showed systemic signs and symptoms of infection, i.e. temperatures higher than 38°C, impaired functional status, and gastrointestinal disturbances. Myringotomy was performed either immediately in emergency cases of severe earache, or under general anaesthesia in milder cases. The procedure, carried out under an oto-microscope, consisted of an incision in the antero-inferior quadrant of the tympanic membrane using a sterile, single-use myringotomy knife. Uncontaminated samples of middle-ear fluid were collected using a #6 flexible tracheal suction catheter. Each sample was made up to a 1 ml volume with normal saline before being sent to the microbiology laboratory. Bacteriological analyses included direct microscopic examination, culture studies, antibiograms, tests for beta-lactamase producers, and the determination of the minimal inhibitory concentration (MIC) of pencillin for *Streptococcus pneumoniae.*

Results

Thirty-nine myringotomies were performed on 31 children (18 male and 13 female). Bilateral myringotomy was carried out in eight of these cases. The mean age was 25.5 months (range: six to 108 months), and 23 of the 31 children were under two years of age. Empiric antibiotic therapy given before myringotomy is shown in Table I.

Of the 39 samples of middle-ear fluid put into culture, 23 developed one potential bacterial pathogen each, two developed two bacterial strains, and 14

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TABLE I
ANTIBIOTIC THERAPY ADMINISTERED BEFORE MYRINGOTOMY

Antibiotic therapy	Cases
Amoxycillin 50 mg/kg/day	2
Amoxycillin-clavulanic acid 50 mg/kg/day	7
1st generation cephalosporins	3
Cefadroxil 25 mg/kg (2 cases)	
Cefatrizine 30 mg/kg/day (1 case)	
2nd generation cephalosporins	2
Cefuroxime-axetil 30 mg/kg/day	
3rd generation cephalosporins	12
Cefpodoxime proxetil 8 mg/kg/day (8 cases)	
Cefixime 8 mg/kg/day (4 cases)	
Trimethoprim 80 mg/day	2
+ Sulfamethoxazole 400 mg/day	
Erythromycin 50 mg/kg/day	3
+ Sulfafurazole 150 mg/kg/day	

were sterile (Table II). The distribution of pathogens was as follows: 11 samples contained *Haemophilus influenzae*, including four beta-lactamase-producing strains, seven contained *Streptococcus pneumoniae*, including four strains with reduced penicillin susceptibility (MIC>1 mg/L), five contained *Pseudomonas aeruginosa*, two contained beta-haemolytic streptococci and two contained *Staphylococcus aureus*.

The outcome was favourable in all cases within 48 hours after myringotomy, with the resolution of fever and a definite reduction in earache. The clinical criteria, including major signs of infection and impaired functional status, led to the continuation of antibiotic treatment after the operation in 16 children. Six of these children were considered to have previously received appropriate antibiotic medication, which was therefore maintained. Infection due to penicillin-resistant pneumococci (PRP) was suspected in 10 children, eight of whom had received high doses of amoxycillin (150 mg/kg/day) and two had received intravenous antibiotic therapy (ceftriaxone) (Table III). At the follow-up visit, 10 days after myringotomy, most children still showed some signs of recent middle-ear infection, such as infiltration and residual effusion, but none of the patients were given any further treatment since the clinical condition of all 31 patients was considered reasonably satisfactory.

TABLE II
RESULTS OF BACTERIAL CULTURES

Bacteria	Samples of middle-ear fluid
Haemophilus influenzae	11 (of which 4 contained beta-lactamase producers)
Streptococcus pneumoniae	7 (of which 4 had an MIC > 1 mg/l)
Pseudomonas aeruginosa	5
Beta-haemolytic streptococci	2
Staphylococcus aureus	2
Sterile cultures	14
Total	41*

*Of the 39 samples of middle-ear fluid put into culture, 14 were sterile, 23 contained only one bacterial strain each, but two contained two strains, leading to this total.

TABLE III
ANTIBIOTIC THERAPY ADMINISTERED AFTER MYRINGOTOMY

Antibiotic therapy	Cases
Amoxicillin 150 mg/kg/day	8
1st generation cephalosporins	3
Cefadroxil 50 mg/kg/day (2 cases)	
Cefatrizine 50 mg/kg/day (1 case)	
Cefuroxime-axetil 30 mg/kg/day	3
Ceftriaxone 1 g/day	2

Discussion

In European medical practice, empiric antibiotic therapy for AOM is based on bacterial epidemiology, the main pathogens involved being considered to be *Haemophilus influenzae* and *Streptococcus pneumoniae*.[3]

The current first-line treatment of AOM in children includes the administration of one of the following drugs: amoxycillin (100 mg/kg/day), amoxycillin-clavulanic acid (80 mg/kg/day), cefuroxime-axetil (30 mg/kg/day), cefixime (8 mg/kg/day), cefpodixime-proxetil (8 mg/kg/day), first-generation cephalosporins (25 to 50 mg/kg/day), co-trimoxazole (30 mg/kg/day of sulfamethoxazole) or erythromycin-sulfafurazole (50 mg/kg/day). The usual duration of the treatment is from eight to 10 days.

The initial treatment for children at risk of infection with penicillin-resistant pneumococci (PRP) (Table IV) includes the administration of one of the following drugs: amoxycillin (150 mg/kg/day), amoxycillin-clavulanic acid (80 mg/kg/day), cefpodoxime-proxetil (8 mg/kg/day) or cefuroxime-axetil (30 mg/kg/day). The second-line treatment is instituted following documentation of specific bacterial pathogens in samples of middle-ear liquid, and administered during 48 to 72 hours after the first-line antibiotic therapy. It usually comprises parenteral administration of ceftriaxone (1 g/day) for three days.[4]

The epidemiological and clinical causes of the failure of antibiotic treatment in children with AOM are multifactorial. Age is a predictive factor of therapeutic failure in paediatric cases. Thus, Harsten *et al.*[5] and Carlin *et al.*[6] observed a peak failure rate in the first year of life. In our study, 23 of the 31 children (74 per cent) were under two years of age. Attendances at day-care centres, temperatures above 38°C, and earache have also been reported to be predictive factors of treatment failure.[7] Although all the children in our study had been

TABLE IV
PENICILLIN-RESISTANT PNEUMOCOCCI (PRP) RISK FACTORS

Age < 2 years
Temperature > 38°5 C
Earache
Attendance at day-care centres
History of AOM
Recent use of antibiotics

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TABLE V
VIRUSES IN THE MIDDLE-EAR FLUID OF PATIENTS WITH ACUTE OTITIS MEDIA (AOM)

	Patients with AOM	Patients with viruses in middle-ear fluid	AOM patients with viral infection
Klein, *et al.*[14]	53	13	25%
Sarkkinen[15]	137	24	18%
Arola *et al.*[16]	143	16	11%
Chonmaitre, *et al.*[13]	271	66	24%
Heikkinen, *et al.*[17]	456	188	41%

previously prescribed appropriate treatment, the doses of the drugs used were frequently insufficient, and the method of administration was inadequate in some cases. Moreover, despite interviews with the parents, it was difficult to be sure that medical recommendations were being fully complied with, since child-care institutions, such as day nurseries, and caregivers frequently failed to administer the prescribed drugs correctly. The intensive use of amoxycillin in anti-infection therapies could favour the development of resistant pneumococcal strains, particularly serotypes 23F, 6B, 14 and 9F.[8] The efficacy of third generation cephalosporins needs to be more fully evaluated since, in our study, 12 of the 31 children (39 per cent) failed to respond to this initial antimicrobial therapy.

Up to now, there have been very few microbiological or viral studies in AOM after failure of antibiotic therapy. In a 1981 study, Teele *et al.*[9] performed tympanocentesis on 31 children initially treated for AOM with either ampicillin or amoxycillin. Twelve of the 31 samples (39 per cent) showed signs of bacterial infection in the middle-ear fluid: seven *Haemophilus influenzae* were detected alone, and two *Streptococcus pneumoniae* were found together with *Haemophilus influenzae* and *Staphylococcus aureus*.[9] In contrast, Cohen *et al.*[10] found 158 bacterial strains in 147 of the 293 children treated for AOM. *Streptococcus pneumoniae* was the most frequently recovered pathogen, being isolated from 81/158 (51 per cent) of bacteriologically documented cases; resistance or reduced susceptibility to the prescribed antibiotic was found in 70/81 (86 per cent) of the *Streptococcus pneumoniae* isolates; and *Haemophilus influenzae* were detected in 65/158 (41 per cent) of the bacterial strains.[10] In a prospective study conducted in the Paris Region, Gehanno *et al.*[7] evaluated 186 children with AOM after failure of antibiotic therapy. Cultures of 141 samples obtained from 126 children yielded 170 strains of bacteria; 67/170 (39 per cent) were *Streptococcus pneumoniae* strains, among which 52/67 (78 per cent) had reduced susceptibility to penicillin; 61/170 (36 per cent) were *Haemophilus influenzae* strains, among which 30/61 (49 per cent) were beta-lactamase producers; and eight out of 170 (five per cent) were *Moraxella catarrhalis* strains.[7] These findings are similar to those of our study (Table II), except for the *Moraxella catarrhalis* strains. Teele *et al.*, found no bacterial strains in 19/31 (61 per cent) of the samples of middle-ear fluid,[9] and Cohen *et al.* found none in 146/293 (50 per cent) of the samples.[10] In our study, no bacterial strains were found in 14/39 (36 per cent) of the samples of middle-ear fluid.

Neither the epidemiological and clinical factors described above, nor the development of resistance to antibiotics, explain all the cases of failure of antibiotic therapy in paediatric patients with AOM. The presence of two bacterial strains in the same specimen is likely to be a contributing factor (there were two such cases in our study). Concomitant or isolated infection of the middle ear by a respiratory virus is an additional factor[11–13] and, in any case, the role of viruses as active pathogens in AOM is well established.[13–17]

Table V sums up several studies that have reported the presence of viruses in the middle-ear fluid in cases of AOM. It is noteworthy that in the recent study bearing on the largest number of cases,[17] the percentage of patients with AOM in whom viruses were detected was as high as 41 per cent. The viruses involved, e.g. rhinovirus, respiratory syncytial virus, influenza A and B viruses, parainfluenza virus (type 3), and adenovirus, commonly cause respiratory infections and were found in the nasal secretions as well as the middle-ear fluid of the patients.[17] This suggests that the viruses interact with the bacteria present, and that the persistence of viruses could be an aggravating factor in causing AOM. These conditions may explain some of the failures encountered with antibiotic therapy in acute otitis.

Thus, the failure of antibiotic therapy in children suffering from acute otitis media may be attributed to epidemiological, clinical and biological factors. The high percentage of sterile cultures obtained should prompt physicians to seek the precise causes, e.g. viruses or atypical bacteria leading to this frequent childhood pathology.

The identification of the bacterial and viral pathogens involved in acute otitis media would provide the basis for setting up regional epidemiological surveillance centres and allow improved management of patients when the usual antibiotic therapy fails to produce satisfactory results.

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