MAJOR ARTICLE

Association of Clinical Signs and Symptoms with Bacterial Findings in Acute Otitis Media

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In acute otitis media (AOM), a means of prediction of the bacterial pathogen based on symptoms and signs would be valuable in selecting appropriate antimicrobial treatment. Children in the control arm ($n = 831$) in the Finnish Otitis Media Vaccine Trial were prospectively observed in a study clinic setting from the age of 2 to 24 months. In patients with AOM, myringotomy with aspiration was performed, and middle ear fluid samples were cultured for bacterial pathogens. Symptoms and signs of respiratory infections were thoroughly recorded. *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae* were the most common bacterial pathogens. Pneumococcal AOM was associated with more-severe AOM characterized by fever and earache. AOM due to *H. influenzae* was associated with eye symptoms and findings. Accurate prediction of a bacterial cause of infection based on symptoms and signs of AOM was not possible, but a specific cause was predicted in some situations, with a high probability of applicability to clinical practice.

Various bacteria and viruses have been documented as pathogens in cases of acute otitis media (AOM). The major bacterial pathogens in AOM are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis;* the previously important *Streptococcus pyogenes* group A (Strep A) has become uncommon [1–6].

Of the 3 major pathogens, *S. pneumoniae* has been associated with the greatest virulence and the most severe findings in AOM [7–9]. It is also a common finding in complications of otitis media [10–12]. *H. influenzae* AOM has been reported to occur more commonly as a bilateral disease [7] and concomitantly with eye symptoms [3]; the latter was referred to as "otitis-conjunctivitis syndrome" by Bodor [13]. *M. catarrhalis* is considered a less virulent pathogen in AOM [14]; it is also uncommon in purulent complications of otitis media [10–12].

Thus, different pathogens may be associated with different clinical syndromes of AOM [6], and the clinical characteristics could be helpful in predicting which bacteria are present in the middle ear fluid (MEF) of the patient. This might be useful in the management of the disease.

In the Finnish Otitis Media (FinOM) Vaccine Trial, clinical symptoms and signs of AOM were thoroughly documented, and the bacterial cause of AOM was verified by culture of MEF samples obtained from children, who were observed from 2 to 24 months of age. The large amount of data collected formed a basis for assessing the association of clinical symptoms and signs with bacterial cause of AOM.

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MATERIALS AND METHODS

Study subjects. The control group of the FinOM Vaccine Trial [15] constituted the subjects of this study. The FinOM Vaccine Trial was conducted from 1995 through 1999. During the enrollment period, 55% of 2-month-old children born in the study area were enrolled in the trial. Informed consent was obtained from

every subject's parents or legal guardians at the time of enrollment in the study. The guidelines for human experimentation (Good Clinical Practice and national and local regulations) were followed in the conduct of clinical research. One-third of the children ($n = 831$) were randomized to receive hepatitis B virus vaccine (the control group), and two-thirds received 1 of the 2 experimental pneumococcal conjugate vaccines.

Follow-up for AOM. The children were prospectively observed in special study clinics from the age of 2 months to the age of 24 months. Full-time study physicians and nurses conducted the scheduled visits at 2, 4, 6, 7, 12, 13, 18, and 24 months of age. In addition, the parents were advised to bring the child to the study clinic whenever the child had symptoms suggestive of AOM or respiratory infection (i.e., a "sick visit"). Pneumatic otoscopy and tympanometry were used for the diagnostic assessment of AOM. AOM was defined by abnormal otoscopical findings (with regard to color, position, and/or mobility) suggesting that MEF was present, concomitantly with acute symptoms ($\geq$1 of the following: fever, earache, ear pulling, ear discharge not due to external otitis, excessive crying, vomiting, diarrhea, and other acute respiratory symptom). When the signs suggesting that MEF was present were detected in otoscopy, the diagnosis of AOM was confirmed by myringotomy with aspiration. The aspirate was cultured routinely for the major bacterial pathogens. All attacks of AOM were treated with antibiotics.

At the sick visit, the accompanying parent, guardian, or caregiver was interviewed regarding the child's symptoms using a structured questionnaire. Questions about the presence of each symptom (fever, cough, runny nose, eye symptoms [discharge or redness], earache, ear pulling, ear discharge, crying, restless sleep, vomiting, or diarrhea) were specifically asked, and if the symptom was present, its duration was documented. The clinical findings and general status, including measurement of rectal temperature, pneumatic otoscopy, and tympanometry (Grason-Stadler GSI38 Autotymp [16]), were determined by a physician's examination. When the color of the tympanic membrane was assessed, only the main finding (i.e., whether it was opaque, yellowish, red, or normal) was recorded. All relevant data were recorded on structured case report forms.

Bacteriological investigation. The practices and methods used for the bacteriological investigation were described in detail previously [6]. In brief, MEF samples were cultured immediately on selective sheep blood agar containing gentamicin, 5 μg/mL, and on enriched chocolate agar plates that were incubated overnight at the study clinics and transported daily to the bacteriological laboratory for examination and for the identification of the main pathogens and other bacteria by generally accepted methods.

The MIC of penicillin was determined for *S. pneumoniae* strains using agar dilution method. Production of β-lactamase for *H. influenzae* and *M. catarrhalis* strains was tested using nitrocefin discs (12 μg/mL; AB Biodisk).

Data analysis and definitions. Recurrence of AOM is common. Because we focused on the cause of AOM in this population, we included all events in the analyses. Selection of a single event per child may have resulted in inefficient and biased population average estimates during the follow-up because of complicated interdependence between recurrence and age. Because children with preexisting perforations in the tympanic membrane(s) usually present with ear discharge irrespective of other symptoms, the data for these events were excluded from the analysis of symptoms. Furthermore, for analysis of tympanic membrane findings, data from patients whose ears had discharge (obscuring more detailed assessment) were excluded.

The analysis of the data was descriptive. Thus, the reported differences should be interpreted on the basis of their clinical relevance. No statistical testing was performed, mainly because a huge sample size may lead to statistically significant but clinically irrelevant differences. Furthermore, a differing number of recurrences at unequal age intervals results in a complex dependence structure between repeated events, to the extent that interval estimates (such as confidence intervals) that rely on assumptions of independence, or even commonly used correlation structures, are unlikely to be valid.

The bacteriological results are presented by ear and event. For the results presented by event, the culture results for both ears are combined. The main pathogens (*S. pneumoniae, H. influenzae, M. catarrhalis,* and Strep A) are included in their own category only when detected as single isolations. Different combinations of pathogens found in mixed cultures are considered a single category of mixed culture, unless stated otherwise. Bacteria other than the main pathogens are of doubtful pathogenic significance in AOM or were rare findings. For analytic purposes, these were combined with negative findings in a culture-negative category. "Culture positive" AOM was defined as a culture that tested positive for the main pathogens. When the findings associated with a specific pathogen were compared with those for all other culture findings, mixed culture categories were excluded.

RESULTS

Study Visits and Samples

The present study included 831 children (403 girls and 428 boys) at enrollment, of whom 587 (71%) experienced $\geq$1 documented AOM-related event during the follow-up period (figure 1). At least 1 MEF sample was available from 1819 AOM events (samples were from 2595 ears). These events form the data set for the present study.

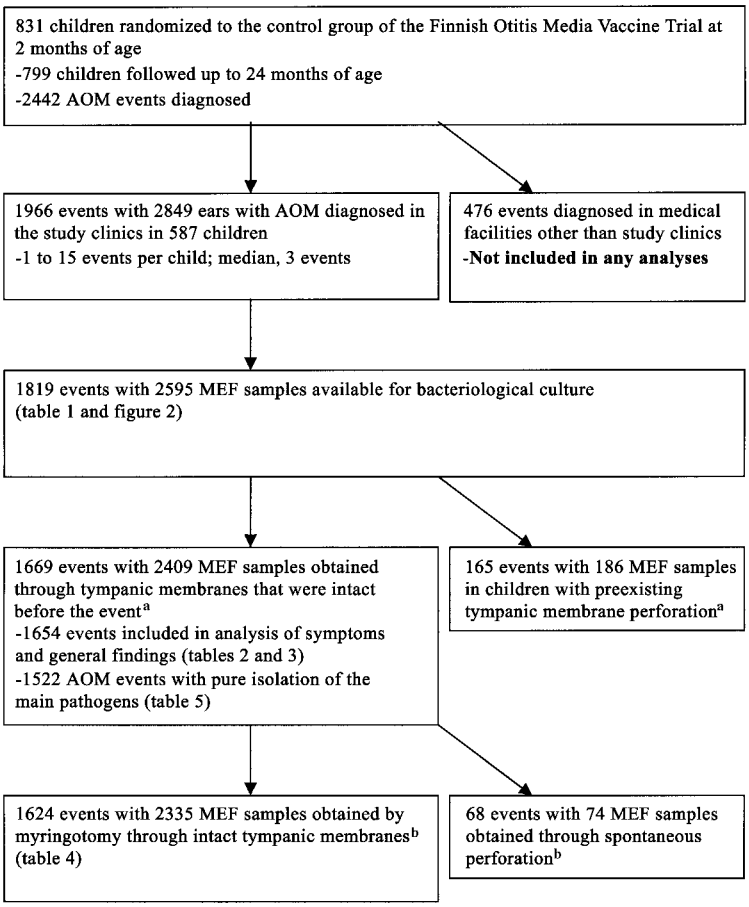

Figure 1. Flow chart of acute otitis media (AOM) events and middle ear fluid (MEF) samples used for data analyses in the present study. [a]Fifteen events with MEF obtained through an intact tympanic membrane from one ear and through preexisting perforation from the other are included in both categories. [b]Twenty-three events with MEF obtained through an intact tympanic membrane from one ear and through preexisting perforation from the other are included in both categories.

Bacteriological Findings

The bacterial categories for AOM-related events and for ears, according to the isolation of the bacterial pathogens and their combinations, are shown in table 1. *S. pneumoniae* was the most common pathogen; it was the single pathogen for 414 events (22.8%), and it was present in mixed culture for 121 events (6.7%), for a total of 535 events (29.4%). Only 6 (0.8%) of the 709 *S. pneumoniae* isolates were resistant to penicillin (MIC, $\geq$2 μg/mL), and 36 (5.1%) were intermediately resistant to penicillin (MIC, 0.1–1.0 μg/mL). A total of 124 (25.3%) of the 490 *H. influenzae* isolates and 547 (94.8%) of the 577 *M. catarrhalis* isolates produced β-lactamase.

Association of Clinical Findings with Bacterial Etiology

Figure 2 shows the proportion of the etiologic categories, according to the status of the tympanic membrane. The bacterial cultures of the 74 MEF samples obtained through spontaneous perforations revealed a higher proportion of pneumococci (35%) and lower proportions of *M. catarrhalis* (3%) and mixed cultures (3%) than did the other MEF cultures. MEF samples obtained through tympanic membranes with known preexisting perforations (mainly due to patent tympanostomy tubes) were more likely to grow *H. influenzae* (30%) and mixed pathogens (18%) and were less likely to be culture negative (16%) than were samples originating from ears with intact or spontaneously ruptured tympanic membranes.

Below, we focus on the events that were diagnosed in children with previously intact tympanic membranes and for which $\geq$1 MEF sample was available for bacterial culture (1654 events and 2409 ears of patients with AOM).

General epidemiologic factors. The median age of the children at the time of the AOM-related event was 13.3 months, and the median age was highest for the 248 children with *H. influenzae* AOM (14.0 months). The incidence of AOM was lower during the summer months (June through August). However, *S. pneumoniae* AOM showed less seasonal variation

Table 1. Bacterial culture findings for children aged 2–24 months with acute otitis media (AOM), by events and ears.

Etiologic category[a]	AOM events[a]	Ears of children with AOM[a]
Main pathogen alone		
Streptococcus pneumoniae	414 (22.8)	574 (22.1)
Moraxella catarrhalis	326 (17.9)	430 (16.6)
Haemophilus influenzae	298 (16.4)	411 (15.8)
Strep A	7 (0.4)	8 (0.3)
Mixed culture of the main pathogens		
All	161 (8.9)	176 (6.8)
S. pneumoniae and *M. catarrhalis*	84 (4.6)	96 (3.7)
S. pneumoniae and *H. influenzae*	26 (1.4)	28 (1.1)
S. pneumoniae and Strep A	1 (0.1)	1 (0.0)
S. pneumoniae, M. catarrhalis, and *H. influenzae*	10 (0.5)	10 (0.4)
M. catarrhalis and *H. influenzae*	40 (2.2)	41 (1.6)
Negative culture or other bacteria yielded	613 (33.7)	996 (38.4)
Total	1819 (100)	2595 (100)

NOTE. Data are no. (%) of events or ears. Strep A, *Streptococcus pyogenes* group A.

[a] The etiologic category for the event was based on bacterial findings for middle ear fluid samples (1 or 2 per event).

than did the other pathogens; during the summer, 32% of all AOM-related events were due to *S. pneumoniae,* compared with 21% of events during other seasons. For 78% of *H. influenzae* AOM–related events, there was a history of previous AOM-related events (any during the study follow-up), compared with 64% for non–*H. influenzae* AOM–related events.

Symptoms. The symptoms present at the time of AOM diagnosis and/or within the 2 preceding days are shown in table 2. The most common symptoms of AOM were those typical of a concomitant viral respiratory infection: runny nose and/or cough were present with 94% of events.

Fever (rectal temperature, ⩾38°C) and earache were more common with cases of pneumococcal and Strep A AOM than in the remaining AOM events. The parental reporting of earache was less common with the first AOM-related event (23%) than with subsequent AOM-related events (37%), but the age of the child at the time of the AOM-related event did not appear to affect the frequency of earache (data not shown). Eye-associated symptoms (redness or eye discharge) were common in *H. influenzae* AOM (54%), but they were rather uncommon in the remaining events (17%).

General signs. Rectal temperature was measured routinely at sick visits, and fever (rectal temperature, ⩾38°C) was most commonly detected with Strep A and *S. pneumoniae* AOM events (table 3). One-half of the AOM-related events were bilateral. The culture-positive events were more often bilateral (58%) than were the culture-negative events (37%).

Abnormal eye findings (discharge and/or redness) were most commonly associated with *H. influenzae* AOM. The contrast with the other AOM categories was evident, especially with regard to the finding of acutely red purulent eyes (19% in *H. influenzae* AOM but only 2% in non–*H. influenzae* AOM).

Otological findings. The analysis of tympanic membrane findings was based on 2335 AOM ears with MEF samples obtained by myringotomy through intact tympanic membranes (table 4). We could not see any clear association between the color of the tympanic membrane and the bacterium isolated from MEF samples. There were no major differences in the tympanic membrane findings between the 3 major bacterial pathogens, but the culture-positive samples were more frequently associated with bulging, immobile, and fully affected tympanic membranes than were the samples with negative culture results.

Prediction of the cause of AOM based on the findings. To assess the value of the clinical findings in predicting the cause of AOM, the variables above that were found to have the strongest association with specific pathogen groups were selected (table 5). Presence of severe tympanic membrane findings (bulging tympanic membrane or spontaneous perforation) with concomitant fever increased the likelihood of *S. pneumoniae* AOM from the overall prevalence of 25% to 53% (positive predictive value [PPV]). Purulent conjunctivitis was a valuable predictor of *H. influenzae* AOM, increasing the probability of *H. influenzae* AOM from the pretest likelihood of 16% to 67% (PPV). For *M. catarrhalis* AOM, no useful predictors were found. For culture-negative samples, better predictors were

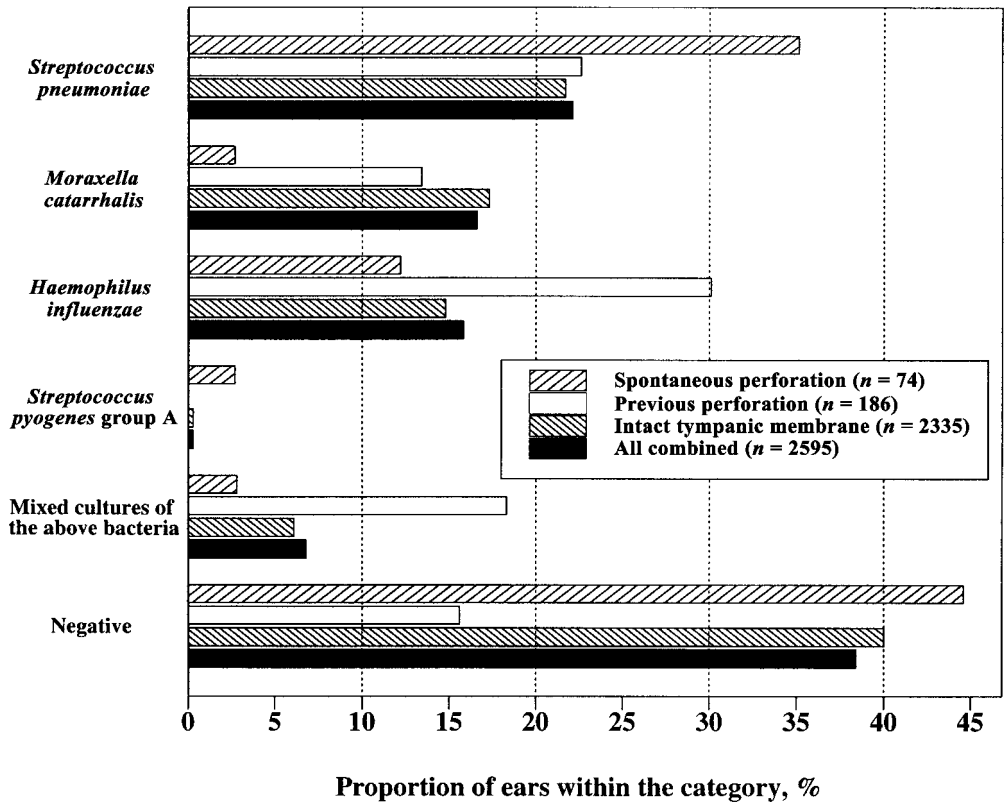

Figure 2. Bacterial culture findings for 2595 middle ear fluid samples, according to the status of the tympanic membrane at the time of diagnosis of acute otitis media.

found for individual culture-negative ears than for culture-negative events.

On the basis of the individual findings above, a combined algorithm was constructed for clinical prediction of the bacterial cause of AOM. First, all events with severe tympanic membrane findings and fever were assigned to the *S. pneumoniae* category. Second, of the remaining events, those with purulent conjunctivitis were assigned to the *H. influenzae* category. Finally, of the events assigned to neither the *S. pneumoniae* category nor the *H. influenzae* category, those involving current antimicrobial treatment, negative pressure in tympanometry, sectorial MEF findings, and/or retracted tympanic membrane noted during otoscopy (the latter 3 findings in bilateral events of AOM present in both ears) were considered to be culture negative. This algorithm picked up 828 events (50% of the total of 1654 events) and predicted the pathogen correctly in 52% of these events.

DISCUSSION

The predominance of the 3 major bacteria as the causes of AOM was confirmed in this study of MEF culture findings for 1819 AOM-associated events that occurred during the first 2 years of life. *S. pneumoniae* was the most common pathogen, but *M. catarrhalis* ranked second: it was more common than *H. influenzae.* The large number of AOM-associated events studied made it possible to analyze the clinical findings in relation to bacteria cultured from MEF samples. Although no absolute pathognomonic findings were identified for any of the bacteria, more-severe symptoms and signs were found for *S. pneumoniae* AOM, whereas conjunctivitis was associated with *H. influenzae* AOM.

This study involved a large, prospective cohort of children observed in special study clinics for the occurrence of AOM. A standardized clinical assessment by the study personnel was performed at all visits. Pneumatic otoscopy includes subjective interpretation of the tympanic membrane findings, and concordant interpretation and documentation of the findings may be difficult to achieve. However, special emphasis was put on uniform recording by using standard operating procedures and specific case report forms.

The compliance was excellent: 96% of the children were observed up to the age of 24 months, thus covering the period when there is the highest incidence of AOM. All AOM-related events during the 22-month follow-up period were included in the analyses, irrespective of previous events or recent anti-

Table 2. Symptoms during the 2 days (unless indicated otherwise) preceding the diagnosis of acute otitis media (AOM), according to the bacteria recovered from middle ear fluid at the time of diagnosis.

	Culture finding						
Symptom	*Streptococcus pneumoniae* (n = 376)	*Moraxella catarrhalis* (n = 305)	*Haemophilus influenzae* (n = 248)	Strep A (n = 7)	Mixed culture of the main pathogens (n = 132)	Negative culture or other bacteria yielded (n = 583)	All events (n = 1651)[a]
Fever	60	39	40	86	52	37	45
Cough	66	84	77	57	82	77	76
Runny nose	93	93	90	100	97	90	92
Eye symptoms	15	18	54	0	20	18	23
Earache	43	26	33	43	35	28	32
Ear pulling	51	44	48	57	50	50	49
Ear discharge	7	2	5	14	2	4	4
Excessive crying	77	66	68	100	68	74	72
Restless sleep	77	70	76	100	75	74	75
Gastrointestinal symptoms	24	26	17	14	26	26	24
Any symptoms present for >2 weeks	23	29	26	14	26	25	25

NOTE. Data are percentages of AOM-related events with the specified symptom. A total of 1654 AOM-related events occurred in 573 subjects aged 2–24 months. Strep A, *Streptococcus pyogenes* group A.

[a] Data on symptoms were missing for 3 AOM-related events; consequently, data for 1651 events are reported

microbial treatment, to maintain a high degree of representativeness. Only AOM-associated events involving draining ears were excluded because of evaluation difficulties.

The special study clinics and the emphasis on careful follow-up of the study children could have brought less severe cases of AOM to the attention of the physician than in normal clinical practice, resulting in a potential bias towards less-severe AOM and a higher proportion of culture-negative events. Use of antipyretics for treatment of the symptoms of AOM was not documented.

Because the present study only involved children aged ⩽24 months, the guardian, rather than the patient, was interviewed about symptoms. A high degree of individual variation can be expected in the parental perception, interpretation, concern, and consequent reporting of the different symptoms and signs of the child during a respiratory infection and evolving AOM. Specifically, interpretation of pain and its source (ear or other) is difficult for guardians of children who are not able to express their feelings verbally. The proportion of reported earaches was higher among children with previous AOM events. One explanation would be that, because their children had previously experienced AOM, the parents recognized and reported earache more commonly.

Bacteriological findings in this study were similar to those

Table 3. General clinical findings in patients with acute otitis media (AOM) at the office visit, according to the results of middle ear fluid cultures.

	Culture finding						
General clinical event	*Streptococcus pneumoniae* (n = 376)	*Moraxella catarrhalis* (n = 305)	*Haemophilus influenzae* (n = 248)	Strep A (n = 7)	Mixed culture of the main pathogens (n = 132)	Negative culture or other bacteria yielded (n = 586)	All events (n = 1654)
Fever							
Mean temperature, °C	38.0	37.6	37.7	38.2	37.7	37.6	37.7
Temperature of ⩾38°C	44	26	25	57	41	22	30
Abnormal auscultation finding	16	23	15	14	23	18	18
Any eye discharge or redness	7	12	40	0	16	13	16
Purulent red eyes	2	1	19	0	4	3	5
Bilateral AOM	57	57	55	43	67	37	50

NOTE. Data are percentages of AOM-related events with the specified symptom, unless otherwise indicated. A total of 1654 AOM-related events occurred in 573 subjects aged 2–24 months. Strep A, *Streptococcus pyogenes* group A.

Table 4. Relation of tympanic membrane (TM) findings to the bacterial cause of acute otitis media (AOM).

Factor	Culture finding						
	Streptococcus pneumoniae (n = 506)	*Moraxella catarrhalis* (n = 403)	*Haemophilus influenzae* (n = 346)	Strep A (n = 6)	Mixed culture of the main pathogens (n = 140)	Negative culture or other bacteria yielded (n = 934)	All ears (n = 2335)
TM color							
Yellow	23	28	25	0	29	24	25
Opaque or cloudy	72	70	73	100	69	69	71
Color on >50% of TM	80	74	76	100	74	64	72
TM position							
Normal	45	55	50	83	52	63	55
Bulging	44	32	40	17	36	16	30
Retracted	11	13	10	0	12	21	15
TM mobility							
Normal	5	7	6	0	11	10	7
Decreased	51	50	52	17	45	54	52
Immobile	44	43	42	83	44	36	41
Tympanometry finding							
Type B curve	80	72	77	100	71	60	70
Negative pressure (less than −100 daPa)	4	8	6	0	9	17	11
MEF quality							
Purulent[a]	74	68	73	100	64	47	62
Mucoid	14	21	14	0	27	25	20
Serous/blood	12	11	13	0	9	28	18
MEF quantity low[a]	12	9	10	0	8	32	19

NOTE. Data are percentages of AOM-related events with the specified symptom. Middle ear fluid (MEF) samples were obtained after myringotomy through previously intact tympanic membranes (discharging ears excluded) from subjects aged 2–24 months. Strep A, *Streptococcus pyogenes* group A; MEF, middle ear fluid.

[a] Assessed by the study physician after myringotomy with aspiration

in a cohort study performed 2 years earlier in the same geographic area using the same methods [6]. Compared with previous Finnish studies conducted in the late 1970s, the proportions of cases due to *H. influenzae* and *M. catarrhalis* have increased [4, 17]. Strep A was a rare finding. Mixed cultures were relatively common, especially when one of the identified pathogens was *M. catarrhalis*. Pneumococcal resistance to penicillin continued to be uncommon in the area.

S. pneumoniae was more often associated with severe symptoms and signs (especially fever and earache, but also spontaneous perforations) than were *H. influenzae* and *M. catarrhalis*. This is in agreement with earlier studies of Howie et al. [7] and Rodriguez and Schwartz [8]. In the latter study, *S. pneumoniae* AOM was associated with a red bulging tympanic membrane [8], whereas Howie et al. [7] were unable to find any difference in the tympanic membrane signs between *S. pneumoniae* AOM and *H. influenzae* AOM. In the present study, no tympanic membrane finding was clearly associated with a particular bacterial cause of AOM, although tympanic membrane bulging was most common for *S. pneumoniae* AOM. We were not able to fully assess the significance of redness of the tympanic membrane, because we only recorded the single most prominent finding in the appearance of the tympanic membrane (most commonly, yellow or opaque/cloudy appearance). In a smaller sample of our study, there was more intensive coding of the tympanic membrane findings, and an association between hemorrhagic redness and pneumococcal etiology was observed [18].

The probability of pneumococcal etiology was highest (PPV, 53%–57%) in AOM with severe tympanic membrane findings combined with fever measured at the clinic. Rodriguez and Schwartz [8] reported a similar combination (i.e., fever with severe tympanic membrane findings was predictive of *S. pneumoniae*); however, in their study, the PPVs were substantially higher.

The most distinct finding related to a single pathogen was the finding of signs of conjunctivitis (especially acute, red, pu-

Table 5. Predictive value of selected findings and their combinations for bacterial etiology of acute otitis media (AOM)–related events.

Clinical finding	Sensitivity	Specificity	PPV	NPV
Streptococcus pneumoniae (25% of all events)				
T_{rect} of ⩾38.0°C	39	80	39	80
Earache	43	71	33	79
Severe TM findings[a]	52	71	37	82
Earache and T_{rect} of ⩾38.0°C	18	94	49	78
Severe TM findings and T_{rect} of ⩾38.0°C	22	94	53	79
Severe TM findings, T_{rect} of ⩾38.0°C, and summer presentation	5	99	60	76
Severe TM findings, T_{rect} of ⩾38.0°C, unaffected eyes, and no current antibiotic treatment	19	95	57	78
Severe TM findings, T_{rect} of ⩾38.0°C, no eye symptoms, no current antibiotic treatment, and summer presentation	4	99	66	76
Moraxella catarrhalis (20% of all events)				
Cough	84	27	22	87
Lung rales present	23	83	26	81
Cough, no eye symptoms, bulging TM, no spontaneous perforation, no current antibiotic treatment, and bilateral AOM	16	91	31	81
Haemophilus influenzae (16% of all events)				
Purulent conjunctivitis	19	98	67	86
Purulent conjunctivitis and age of >1 year	11	99	70	85
Purulent conjunctivitis and history of previous AOM	13	99	69	85
Eye symptoms	54	83	38	90
Eye symptoms and history of previous AOM	41	90	44	89
None of the main pathogens,[b] analysis by events (39% of all events)				
Unilateral AOM event	63	56	47	71
Current antibiotic treatment	8	97	61	63
None of the main pathogens, analysis by ears (40% of all samples)				
Retracted TM	21	88	58	60
Sectorial MEF	36	77	54	62
Negative TPP (less than −100 daPa) on tympanometry	17	94	69	61
Sectorial MEF and retracted TM	8	97	65	59
Retracted TM and negative TPP	8	99	81	59
Sectorial MEF and negative TPP	10	97	71	59

NOTE. Data are for 1522 AOM-related events for which middle ear fluid (MEF) samples were obtained through intact tympanic membrane (TM) from subjects aged 2–24 months that yielded pure isolates of *S. pneumoniae, M. catarrhalis,* or *H. influenzae*. NPV, negative predictive value; PPV, positive predictive value; TPP, tympanometric peak pressure; T_{rect}, rectal temperature.

[a] Bulging TM or spontaneous perforation in ⩾1 ear.

[b] Culture had negative results or yielded bacteria other than *S. pneumoniae, H. influenzae, M. catarrhalis,* or *Streptococcus pyogenes* group A.

rulent eyes) in patients with AOM caused by *H. influenzae*. This finding is concordant with earlier studies [3, 13].

For *M. catarrhalis*, no valuable diagnostic predictors were found. No general symptoms or signs were helpful for distinguishing AOM with negative MEF culture results from a bacterial culture–positive case, but tympanic membrane findings were of some value. This is concordant with the previous findings of Halsted et al. [19] and McCormick et al. [9]. In the latter study, a PPV of 74% and a negative predictive value (NPV) of 45% were reported for bulging tympanic membrane as a predictor that a bacterial pathogen would be identified in MEF samples. In the present study, the PPV and NPV were 78% and 48%, respectively (data not shown). Furthermore, negative pressure on tympanometry (tympanometric peak pressure, less than −100 daPa) combined with a retracted tympanic membrane indicated a high probability (PPV, 81%) that cultures for the main bacteria would be negative, which is in accordance with our earlier finding in another study [20].

The clinical usefulness of the findings was reduced by the low sensitivity of findings with a high specificity and PPV. How-

ever, by using a stepwise algorithm, the MEF culture result could be predicted correctly for one-half of the events. However, the algorithm picked up only one-half of the events; thus, only one-quarter of all events were predicted correctly.

Most symptoms and signs were equally common in the main etiologic categories, which largely reflects the underlying viral infection [21–23]. The overlap in the symptoms of the concurrent viral infection and AOM obviously makes it more difficult to distinguish between symptoms associated with different bacteria. Furthermore, individual children are likely to react differently to a case of AOM. It is quite plausible that differences in the individual inflammatory reaction to the viral and bacterial pathogens could cause more variation in the symptoms and signs of AOM than the different bacteria as such. Host immunity against the pathogens may also affect the clinical pattern of the disease. Furthermore, subjective differences in clinical assessment between observers increase variation in the data. Because of these factors, potential minor clinical differences in cases of AOM due to different causative organisms are easily obscured even in large series.

In conclusion, this intensive study on clinical patterns of AOM showed that, when isolated from MEF samples, *S. pneumoniae* was associated with more-severe symptoms and *H. influenzae* was associated with conjunctivitis. Although the differences from other bacterial causes of AOM were small, application of these results to clinical practice may be helpful in directing antimicrobial therapy to the most probable bacterial cause of the event. Also, consideration of withholding antimicrobial therapy is suggested if a negative bacterial culture result is expected on the basis of clinical signs.

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References

1. Lahikainen E. Clinico-bacteriologic studies on acute otitis media. Acta Otolaryngol **1953**; (Suppl 107):1–82.
2. Grönroos JA, Kortekangas AE, Ojala L, Vuori M. The aetiology of acute middle ear infection. Acta Otolaryngol **1964**; 58:149–58.
3. Coffey JD Jr. Otitis media in the practice of pediatrics: bacteriological and clinical observations. Pediatrics **1966**; 38:25–32.
4. Luotonen J, Herva E, Karma P, Timonen M, Leinonen M, Makela PH. The bacteriology of acute otitis media in children with special reference to *Streptococcus pneumoniae* as studied by bacteriological and antigen detection methods. Scand J Infect Dis **1981**; 13:177–83.
5. Bluestone CD, Stephenson JS, Martin LM. Ten-year review of otitis media pathogens. Pediatr Infect Dis J **1992**; 11:S7–11.
6. Kilpi T, Herva E, Kaijalainen T, Syrjänen R, Takala AK. Bacteriology of acute otitis media in a cohort of Finnish children followed for the first two years of life. Pediatr Infect Dis J **2001**; 20:654–62.
7. Howie VM, Ploussard JH, Lester RL Jr. Otitis media: a clinical and bacteriological correlation. Pediatrics **1970**; 45:29–35.
8. Rodriguez WJ, Schwartz RH. *Streptococcus pneumoniae* causes otitis media with higher fever and more redness of tympanic membranes than *Haemophilus influenzae* or *Moraxella catarrhalis.* Pediatr Infect Dis J **1999**; 18:942–4.
9. McCormick DP, Lim-Melia E, Saeed K, Baldwin CD, Chonmaitree T. Otitis media: can clinical findings predict bacterial or viral etiology? Pediatr Infect Dis J **2000**; 19:256–8.
10. Harley EH, Sdralis T, Berkowitz RG. Acute mastoiditis in children: a 12-year retrospective study. Otolaryngol Head Neck Surg **1997**; 116:26–30.
11. Goldstein NA, Casselbrant ML, Bluestone CD, Kurs-Lasky M. Intratemporal complications of acute otitis media in infants and children [see comments]. Otolaryngol Head Neck Surg **1998**; 119:444–54.
12. Petersen CG, Ovesen T, Pedersen CB. Acute mastoidectomy in a Danish county from 1977 to 1996 with focus on the bacteriology. Int J Pediatr Otorhinolaryngol **1998**; 45:21–9.
13. Bodor FF. Conjunctivitis-otitis syndrome. Pediatrics **1982**; 69:695–8.
14. Coffey JD Jr, Martin AD, Booth HN. *Neisseria catarrhalis* in exudate otitis media. Arch Otolaryngol **1967**; 86:403–6.
15. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med **2001**; 344:403–9.
16. Palmu A, Puhakka H, Rahko T, Takala AK. Diagnostic value of tympanometry in infants in clinical practice. Int J Pediatr Otorhinolaryngol **1999**; 49:207–13.
17. Karma P, Pukander J, Sipila M, et al. Prevention of otitis media in children by pneumococcal vaccination. Am J Otolaryngol **1985**; 6:173–84.
18. Palmu A, Kotikoski M, Kaijalainen T, Puhakka H. Bacterial etiology of acute myringitis in children less than two years of age. Pediatr Infect Dis J **2001**; 20:607–11.
19. Halsted C, Lepow ML, Balassanian N, Emmerich J, Wolinsky E. Otitis media: clinical observations, microbiology, and evaluation of therapy. Am J Dis Child **1968**; 115:542–51.
20. Palmu A, Syrjanen R, Kilpi T, et al. Negative pressure tympanograms in children less than 2 years of age-different bacterial findings in otitis media by tympanometric results. Int J Pediatr Otorhinolaryngol **2001**; 61:61–9.
21. Niemelä M, Uhari M, Jounio-Ervasti K, Luotonen J, Alho OP, Vierimaa E. Lack of specific symptomatology in children with acute otitis media. Pediatr Infect Dis J **1994**; 13:765–8.
22. Heikkinen T, Ruuskanen O. Signs and symptoms predicting acute otitis media. Arch Pediatr Adolesc Med **1995**; 149:26–9.
23. Kontiokari T, Koivunen P, Niemela M, Pokka T, Uhari M. Symptoms of acute otitis media. Pediatr Infect Dis J **1998**; 17:676–9.