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Erdem I. Cantekin

Timothy W. McGuire

Terri L. Griffith
Santa Clara University, tgriffith@scu.edu

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Antimicrobial Therapy for Otitis Media With Effusion ('Secretory' Otitis Media)

Erdem I. Cantekin, PhD; Timothy W. McGuire, PhD; Terri L. Griffith, PhD

Objective.—To determine the effectiveness of antimicrobial treatment for otitis media with effusion ("secretory" otitis media) in children.

Data Source.—We report the reexamination of a previously published study by Mandel et al that evaluated the efficacy of a 2-week course of antimicrobials (amoxicillin trihydrate) with and without a 4-week course of an oral decongestant-antihistamine combination in a double-blind, placebo-controlled, randomized trial involving 518 infants and children with otitis media with effusion.

Data Synthesis.—At 4 weeks, amoxicillin efficacy as determined by a tympanometric criterion ($P=.121$) or by a measure of improvement in hearing ($P=.311$) was insignificant. Only by otoscopic judgment, which is shown to contain a systematic bias as used in this clinical trial, could an argument be made for a marginal efficacy of amoxicillin at the 4-week end point. Logistic regression analyses of the combined effects of treatment and prognostic factors showed no significant differences between placebo- and antibiotic-treated groups for unilateral effusions and for bilateral effusions. When subjects with unilateral and bilateral effusions were combined, the estimated efficacy of antibiotic treatment was 12.3% by otoscopy ($P=.014$) and 4.8% by tympanometry ($P=.171$). We also demonstrate the sensitivity of outcome to diagnostic measures used and provide statistical evidence questioning the validity of otoscopic observations in this study. Six weeks after the termination of amoxicillin therapy, the recurrence of effusion was two to six times higher in the amoxicillin-treated children than in those treated with placebo ($P=.001$), and resolution of effusion was not significantly different among antibiotic and placebo groups (13.6% and 11.3%, respectively; $P=.477$).

Conclusions.—Amoxicillin with and without decongestant-antihistamine combination is not effective for the treatment of persistent asymptomatic middle-ear effusions in infants and children.

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From the Department of Otolaryngology, University of Pittsburgh (Pa) School of Medicine, and Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh (Dr Cantekin); Graduate School of Industrial Administration, Carnegie-Mellon University, Pittsburgh (Dr McGuire); and College of Business and Public Administration, University of Arizona, Tucson (Dr Griffith).

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Reprint requests to Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, 125 DeSoto St, Pittsburgh, PA 15213 (Dr Cantekin).

IN CURRENT medical practice, nonsurgical treatment of otitis media with effusion ("secretory" otitis media) is limited to few choices.[1] Antibiotics with and without decongestant-antihistamine combination are the most commonly used medications. The lack of efficacy of an oral decongestant-antihistamine combination for treating this condition in children has been reported.[2] The present study was conducted at the Otitis Media Research Center (OMRC) in Children's Hospital of Pittsburgh, Pa, between July 1981 and October 1984 to determine the efficacy of antibiotics with and without decongestant-antihistamine combination for otitis media with effusion, using an experimental design and patient population similar to those in the previously reported decongestant-antihistamine trial. Two years after the termination of the trial, two separate manuscripts with opposite conclusions were submitted to the *New England Journal of Medicine* (*NEJM*) in June 1986. The first author of the present report was a co–principal investigator and a coauthor of the earlier drafts of the first manuscript (by Mandel et al) but had disagreed with its analysis and conclusions. The first manuscript (the official report of the OMRC), submitted by Mandel et al,[3] was accepted and subsequently published by the *NEJM*. Our manuscript, however, was returned without review according to the *NEJM*'s editorial decision of publishing only the articles submitted by principal investigators. (This statement is based on a written communication [January 6, 1987] from the editor of the *NEJM*, Arnold S. Relman, MD, to Robert L. Potter, JD. Dr Relman wrote: "The important question, therefore, is not whose interpretation is correct . . . but rather who has the right to publish . . ."!) Since 1986, the efforts of the University of Pittsburgh and Children's Hospital of Pittsburgh have been successful in cen-

For editorial comment see p 3333.

soring our manuscript from publication, as discussed in detail elsewhere.[4,5]

Since otitis media is a very common childhood disease, and since amoxicillin is the most frequently prescribed antibiotic for this condition, the results reported by Mandel et al are extremely important to the medical community and the public at large. Therefore, we believe it is important to report this reexamination of their results. Using the same data set, the analyses presented herein are substantially different in several major aspects from those presented by Mandel et al (eg, multiple outcome measures are examined, initial differences in prognostic factors among treatment groups are accounted for, recurrence patterns among treatment groups are analyzed). Therefore, we think this second publication is warranted.

Today's rationale for using antimicrobial therapy for otitis media is based on the following concepts and observations: (1) the commonly accepted but not proven hypothesis is that nonsuppurative, "secretory" otitis media with effusion is secondary to bacterial infection of the middle-ear space[6,7]; (2) the type and frequency of bacteria recovered from these effusions are similar to those of bacteria found in acute middle-ear infections[8-11]; (3) current medical practice for treating acute otitis media is a generous course of antimicrobials, although the efficacy of this treatment in resolving effusion was never established in a placebo-controlled, randomized, double-blind study,[12-15] and the wisdom of such medical management has been recently shown to be flawed[16-20]; and (4) some clinical trials report a varying range of efficacy of antimicrobials to treat otitis media with effusion.[21-30]

METHODS

Infants and children from 7 months to 12 years of age who were suspected of having otitis media with effusion were referred to this double-blind, placebo-controlled, randomized clinical trial from the Ambulatory Care Center of Children's Hospital and from private physicians in the community. After the enrollment of 518 children, the clinical trial was stopped without reaching the original target sample size of 1040 subjects because of an apparent significant difference in cure rates between the treatment groups. The study population, enrollment procedures, criteria for patient eligibility, random assignment, drug administration and compliance monitoring, follow-up observations, and issues related to other clinical procedures were described in detail by Mandel et al[3]; therefore, only a brief summary of the essentials is provided herein.

Table 1.—Comparison of Treatment Groups by Patient Characteristics*

	AB + DA	AB + PL	PL + PL	Total
Enrolled	178	168	172	518
Excluded†	23	13	22	58
Completed	155	155	150	460
Stratification variables				
Age				
7-23 mo	58	53	48	159
2-5 y	71	73	74	218
6-12 y	26	29	28	83
Duration of effusion, wk				
0-3	29	25	24	78
4-8	26	25	24	75
>8	48	52	52	152
Unknown	52	53	50	155
Previous antimicrobials for this episode				
Yes	54	56	52	162
No	101	99	98	298
Prognostic factors				
Laterality of effusion‡				
Unilateral	64	64	50	178
Bilateral	91	91	100	282
Middle-ear acoustic impedance§				
0-5.0	44	50	38	132
5.1-7.0	56	54	54	164
>7.0	51	48	58	157
Not measured	4	3	0	7
Hearing loss‖				
0-10	10	13	9	32
11-20	49	46	43	138
21-30	48	49	48	145
31-40	32	26	34	92
>40	9	10	8	27
Not measured	7	11	8	26
Other characteristics¶				
Sex				
M	101	102	100	303
F	57	58	56	171
Race				
White	112	113	114	339
Nonwhite	46	47	42	135
Socioeconomic status				
Upper or middle	85	81	89	255
Lower	63	69	61	193
Not recorded	10	10	6	26
Season at entry				
Winter	62	64	59	185
Spring	44	49	45	138
Summer	25	21	17	63
Fall	27	26	35	88
Upper-respiratory-tract infection at initial visit				
No	111	118	102	331
Yes	44	39	53	136
Unknown	3	3	1	7
History of middle-ear disease				
No	8	18	13	39
Yes	150	142	143	435
Allergy diagnosed				
No	156	155	150	461
Yes	2	4	6	12
Not recorded	0	1	0	1

*Treatment groups were amoxicillin with decongestant-antihistamine combination (AB + DA), amoxicillin with placebo (AB + PL), and placebo with placebo (PL + PL).

†Children missing one or more follow-up visits after entry were excluded.

‡When both ears contained effusion by both methods (tympanometry and otoscopy), the child was classified as having bilateral effusions.

§Minimum value of the two ears was used to represent child's middle-ear impedance measure in arbitrary units of tympanometry.

‖Maximum threshold in either ear for pure-tone average or speech awareness was used to represent child's hearing loss in decibels reference to normal hearing level (dB HL).

¶Based on the sample from reference 3 consisting of patients who were evaluated at the 4-week visit.

Table 2.—Outcome at 4 Weeks by Otoscopy, by Tympanometry, and by Change in Hearing According to Treatment Groups in 460 Children*

	AB + DA	AB + PL	PL + PL	Total
Otoscopy†				
Effusion	92	94	105	291
Acute otitis	11	12	20	43
Effusion free	52	49	25	126
	$\chi^2 = 14.89$, $df = 4$, $P = .005$			
Tympanometry‡				
Effusion	118	117	117	352
Acute otitis	11	12	20	43
Effusion free	26	25	13	64
	$\chi^2 = 8.29$, $df = 4$, $P = .081$			
Hearing§				
Same	97	85	83	265
Worse	5	3	5	13
Better	38	46	43	127
	$\chi^2 = 2.34$, $df = 4$, $P = .672$			

*Treatment groups were amoxicillin with decongestant-antihistamine combination (AB + DA), amoxicillin with placebo (AB + PL), and placebo with placebo (PL + PL).

†*Effusion-free subject* was defined as both ears being effusion free by otoscopy.

‡Subjects with tympanogram types 1, 2, 3, 4, 6, 9, or 10 for both ears were classified in the effusion-free group (based on 459 children with tympanometric data).

§For 405 children, improvement in hearing is based on maximum change in pure-tone average or speech awareness threshold from entry to 4-week visit; if threshold remained within ± 10 dB, hearing was considered unchanged (same), and 55 children did not have paired observations and thus were excluded.

The diagnosis of otitis media at entry and at each subsequent examination was based on the findings obtained by a "validated" otoscopist (sensitivity 94%, specificity 66%) and on the results of tympanometry (sensitivity 95%, specificity 70%).[31-36] Over 90% of the otoscopic observations were made by a single observer. Hearing acuity was also assessed by determining air-conduction and bone-conduction thresholds at four frequencies, as well as by measuring speech reception or awareness thresholds. These audiological testing procedures were described previously in detail.[37]

After entry evaluation, subjects were stratified according to age, duration of the effusion, and whether an antimicrobial drug had been administered for otitis media during the preceding 60 days. Within each subgroup, patients were randomly assigned in blocks of three, in double-blind fashion, to the amoxicillin and decongestant-antihistamine combination group, the amoxicillin and placebo group, and the placebo and placebo group. A liquid suspension of amoxicillin trihydrate (Amoxil, supplied by Beecham Laboratories, Bristol, Tenn) was administered in a dosage of 40 mg/kg per day in three divided doses for 2 weeks. The decongestant-antihistamine was a liquid preparation of pseudoephedrine hydrochloride and chlorpheniramine maleate (Novafed A syrup, supplied by Merrell-Dow Pharmaceuticals, Indianapolis, Ind), given at a dosage of 1.0 mg of pseudoephedrine hydrochloride and 0.09 mg of chlorpheniramine maleate per kilogram of body weight. The medication was administered four times daily for 4 weeks. The corresponding placebos for amoxicillin and for the decongestant-antihistamine were identical in appearance and similar in taste to the active medications. All medication was dispensed in double-blind fashion.

The subjects were reexamined approximately 2 weeks after entry and at the end of 4 weeks. The presence or absence of middle-ear effusion was determined by otoscopy and by tympanometry. At 4 weeks, hearing acuity was reassessed in the same manner as at entry. All observers were blinded with regard to each subject's treatment group. In order to evaluate recurrences, patients whose middle-ear effusions had cleared during the 4-week study period were reexamined approximately 4 weeks after completion of the study.

Proportions were compared with the use of χ^2 statistics. We also used logistic regression analysis to estimate the effect of antimicrobial therapy while controlling for the differences in prognostic factors across treatment groups. Average power over the various outcome analyses employed was large enough to detect at the .05 level of significance a 10–percentage-point difference between the treatment groups with over 90% power.

RESULTS

Population Characteristics

Five hundred eighteen children with unilateral or bilateral otitis media were enrolled, of whom 460 were evaluated at both 2- and 4-week visits. The remaining 58 children did not return for either one or both of the follow-up visits and thus were excluded from the data analysis. The distribution of subjects within the three randomization strata—age, duration of effusion, and previous administration of antimicrobials—is shown in Table 1. Also, the distribution of prognostic factors and other demographic and clinical characteristics considered to have potential influence on outcome are depicted.

Outcome at 4 Weeks

On completion of the chemotherapy at 4 weeks, the middle-ear status was evaluated by otoscopy, tympanometry, and audiometric threshold. Table 2 shows that differences between the outcomes in antimicrobial-treated and placebo-treated groups were significant only when otoscopy was used as the diagnostic measure ($P = .005$). The differences between treatment groups were not significant when a tympanometric criterion for the clearance of middle-ear effusion was chosen ($P = .081$). Moreover, 32.8% of children in the placebo group showed improvement in hearing between entry and the 4-week visit, in contrast to 30.7% of children who had improved hearing in the two antibiotic-treated groups ($P = .672$). During this period, 43 children were diagnosed by otoscopy and by clinical signs and symptoms as having an episode of acute otitis media. The incidence of acute otitis media was greater in the placebo group than in the antibiotic groups (13.3% vs 7.1% and 7.7%, respectively; $P = .122$).

The results presented in Table 2 include 460 patients with bilateral otoscopic and/or bilateral tympanometric data during both visits at 2 and 4 weeks. Regardless of the initial laterality of effusion, only patients with bilateral effusion-free ears at the 4-week visit were classified in the no-disease category. A measure of improvement in hearing was available for children who had either pure-tone average or speech awareness thresholds at both entry and 4-week visits. Improvement was defined as a threshold at least 10 dB lower at 4 weeks than at entry. When bilateral pure-tone average data were available, the ear exhibiting maximum improvement was used to represent the improvement in the child's hearing.

By the study protocol, the principal outcome was the proportion of *children* without effusion at the 4-week visit as determined by a diagnostic algorithm based on otoscopic and tympanometric findings described previously.[32] The observed disparity between the objective (tympanometry, hearing) and subjective (otoscopy) measures as shown in Table 2 prompted us to conduct a sensitivity analysis. We examined the outcome at 4 weeks using the above-mentioned algorithm as well as six other measures to estimate the efficacy of amoxicillin at this time point. The sensitivity analysis in Table 3 reveals that the estimated efficacy of amoxicillin is relatively inconsequential—7.8% or less—and without statistical significance by all outcome measures that are not heavily influenced by otoscopy. Only for the pure otoscopy measure and for the algorithm are the estimated efficacies greater than 10% (16.0% and 11.7%; $P = .004$ and $P = .027$, respectively) if the outcome is not corrected for the preponderance of unfavorable prognostic factors for the placebo group. With correction, the efficacy is 9.1% ($P = .040$) using the algorithm.

In this analysis and the ensuing analyses of prognostic factors, we have omitted 43 cases for which acute otitis media was diagnosed during this 4-week period. Omission of those subjects was thought to be justified for the following reasons: (1) the purpose of this study

Table 3.—Sensitivity Analysis of Outcome at 4 Weeks*

Outcome Measure	Treatment Groups† AB+DA (n=144)	AB+PL (n=142)‡	PL+PL (n=130)	% Difference	Probability
Otoscopy	36.1§	34.3	19.2	16.0‖	.004¶
Algorithm#	26.4	24.6	13.9	11.7	.027
Tympanometry	18.1	17.6	10.0	7.8	.121
Otoscopy and tympanometry**	15.3	12.6	8.5	5.5	.225
Normal hearing††	23.0	20.9	18.0	3.9	.611
Hearing improvement‡‡	27.1	36.0	32.5	−1.0	.311
Combined criterion§§	11.5	9.0	6.6	3.7	.381

*Excluding 43 children who had developed acute otitis media during the 4-week period.
†Groups were amoxicillin with decongestant-antihistamine (AB+DA), amoxicillin with placebo (AB+PL), and placebo with placebo (PL+PL).
‡For otoscopy, an additional subject for whom tympanometric data are missing is included.
§Percentage of the treatment group that is effusion free or with normal or improved hearing or both.
‖Difference between the placebo group and the combined antibiotic groups.
¶Calculated by χ^2 statistics using three treatment groups and two outcome categories.
#Combination of otoscopy and tympanometry according to the algorithm described in the original study protocol (reference 32 with tympanogram type 12 with negative otoscopy as indicative of effusion using Bayesian estimates) and not employed by Mandel et al[3] in their analyses of outcome.
**Effusion free by both methods (tympanometry and otoscopy).
††Hearing loss in either ear not exceeding 10 dB HL; sample sizes were 139, 134, and 122, respectively.
‡‡As defined in Table 2; sample sizes were 129, 125, and 114, respectively.
§§Effusion free by both methods and hearing loss in either ear not exceeding 10 dB HL; same sample size as in footnote ††.

Table 4.—Logistic Regression Analyses of Combined Effects of Antibiotic Treatment and Prognostic Factors on Patient Cure Rate by Initial Laterality of Effusion According to Otoscopic and Tympanometric Measurements

	Otoscopy			Tympanometry		
	Unilateral	Bilateral*	Total	Unilateral	Bilateral	Total
Antibiotic treatment	.060†	.108	.014	.100	.748	.171
Hearing loss	.400	.002	.001	.062	.014	.004
Middle-ear acoustic impedance	.100	.669	.463	.015	.534	.019
Laterality	. . .	. . .	.034	. . .	. . .	.933
Estimated antibiotic efficacy, %	18.3	10.1	12.3	6.8	1.5	4.8
Reduction in efficacy due to prognostic factors, %	2.7	1.3	3.7	6.6	2.2	3.0
Sample size‡	144	246	390§	144	245	389

*Initially, when both ears contained effusion by both methods (tympanometry and otoscopy), the child was classified as having bilateral effusions.
†P values for logistic regression are shown.
‡Sample sizes exclude 43 children who developed acute otitis media and 27 children with missing initial data on either hearing loss or acoustic impedance.
§For otoscopy, an additional subject for whom tympanometric data are missing is included.

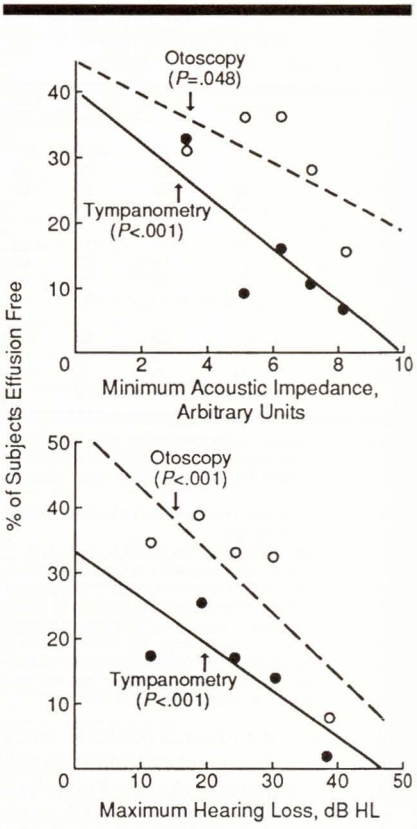

Fig 1.—Effect of prognostic factors on cure rate at 4-week visit by otoscopy and by tympanometry: initial middle-ear acoustic impedance (top) and initial hearing loss (bottom). Data points are the boxcar average values for one fifth of the sample without acute otitis cases and lines are the linear regression fits based on all observations (n=390), not just the five average values plotted.

was not to estimate the prophylactic efficacy of antimicrobial treatments, (2) acute otitis media is a common occurrence in this age group that is externally triggered and is not controllable within the study design, and (3) many of those children were treated with additional antimicrobials.

Prognostic and Diagnostic Factors in Relation to Outcome

Certain prognostic factors identified at the initial visit had significant effects on a child's status at the 4-week visit. Hearing loss and acoustic impedance of the middle ear were strongly associated with the outcome. The relationships between these two prognostic factors and cure rate found by otoscopy and tympanometry are illustrated in Fig 1. Large hearing loss or increased acoustic impedance due to mass loading of the middle cavity was significantly related to poor outcome.

Relationships between these prognostic factors and outcome at the 4-week visit were investigated to identify possible confounding factors. We believed that it might be important to control for the combined effect of differences in poor prognostic factors across treatment groups, because these factors have significant individual effects on outcome and because it happened by chance that in almost every case prognostic factors were worse for the placebo group than for the antibiotic-treated groups. For example, more children in the placebo group had bilateral effusions at entry than those in the other groups (66.7% vs 58.7%).

For the analysis presented in Table 4, both antibiotic-treated groups were combined, since these two groups showed similar results (see Tables 2 and 3). In this model the population was split into two ex ante identifiable subsamples: initial unilateral disease only and initial bilateral disease only. Curing two ears is fundamentally different from curing one ear. Since the observation unit is the patient, these two subpopulations exhibit significantly different cure rates. The differences between cure rates in the unilateral and bilateral disease are significant at the .001 level by otoscopy and the .01 level by tympanometry.

The logistic regression results, which include the effects of prognostic factors on the outcome, are summarized in Table 4. At the $P \leq .01$ level, none of the estimated effects for antibiotics are significant. When tympanometry is used as the diagnostic measure, the effects of antimicrobial treatment are insignificant ($P = .100, .748$, and $.171$) and have small estimated efficacies (6.8%, 1.5%, and 4.8%) for the unilateral, bilateral, and pooled samples, respectively. Even when the algorithm specified in the protocol is used as the diagnostic measure,

Table 5.—Subject Response Patterns Including 2-, 4-, and 8-Week Visits by Otoscopy and by Tympanometry According to Treatment Group in 460 Children*

	AB+DA	AB+PL	PL+PL	Total
Otoscopy				
Persistence	77	80	90	247
Recurrence	29	22	13	64
Acute otitis	13	16	21	50
Clearance	36	37	26	99
Differences in clearance: $\chi^2=2.33$, $df=2$, $P=.312$				
Differences in recurrence†: $\chi^2=6.44$, $df=2$, $P=.040$				
Tympanometry				
Persistence	103	98	109	310
Recurrence	21	17	3	41
Acute otitis	13	16	21	50
Clearance	18	24	17	59
Differences in clearance: $\chi^2=1.48$, $df=2$, $P=.477$				
Differences in recurrence†: $\chi^2=13.74$, $df=2$, $P=.001$				

*Persistence indicates otitis media with effusion during all visits; recurrence, presence of effusion after clearance at 2- or 4-week visit; and clearance, effusion free at last visit or visits without recurrence. By protocol, only patients without otitis media with effusion at the 4-week visit returned for the 8-week visit. Treatment groups were amoxicillin with decongestant-antihistamine combination (AB+DA), amoxicillin with placebo (AB+PL), and placebo with placebo (PL+PL).

†Recurrence with respect to the total population.

the estimated efficacy was only 9.1% ($P=.040$). An effect can be demonstrated only when the unilateral and bilateral disease cases are pooled into a single combined sample and otoscopy is used as the diagnostic measure ($P=.014$). The estimated antimicrobial treatment efficacy is 12.3% in this case; the reduction in efficacy of 3.7 percentage points (from 16.0%; see Table 3) is the result of statistically standardizing for differences in prognostic factors.

Patient Response Pattern

In this study, subjects who were free of effusion at the 4-week end point by otoscopic diagnosis were reexamined approximately 4 weeks later. Taking advantage of this repeated measure in the study design, we evaluated patterns of patient response to antimicrobial therapy (which was terminated at 2 weeks) using 2-, 4-, and 8-week visits. The response patterns are summarized in Table 5. By otoscopic diagnosis, 23.5% of children treated with amoxicillin and 17.3% of children who had placebo were disease free during this 6-week interval ($P=.312$). Using the tympanometric criterion to define disease-free children, the antibiotic groups and the placebo group were very similar (13.6% vs 11.3%; $P=.477$). These findings do not support the hypothesis that antimicrobial treatment might have a beneficial but delayed effect. On the contrary, recurrence rates were two to six times larger in the antimicrobial-treated groups than in the placebo group by otoscopy ($P=.040$) and by tympanometry ($P=.001$), respectively, as shown in Table 5. If the recurrence rates are calculated conditional on children who were effusion free at the 2- or 4-week visit, then the recurrence rates by tympanometry were 47.5% for the combined antimicrobial-treated group and 15.0% for the placebo group ($P<.01$).

Period of Observation, Compliance, and Side Effects

The actual interval between entry into the trial and evaluation at 4 weeks—the period of observation—and compliance with medication requirements are discussed in detail in the report by Mandel et al.[3] These two parameters were not related to outcome, and the differences with respect to compliance and period of observation were insignificant among the treatment groups.

Commonly reported side effects by parents were mild sedation or irritation, with occasional incidence of diarrhea and rash. In the antibiotic-treated groups, these side effects were reported in 15% of the children who were also treated with decongestant-antihistamine combination and in 9% of those children treated with amoxicillin alone. In the placebo-treated group, side effects were reported for 6% of the children.

COMMENT

Comparison With Study by Mandel et al, 1987

The present report, based on reexamination of the database of the clinical trial reported by Mandel et al,[3] reveals opposite conclusions, ie, lack of efficacy of amoxicillin for treatment of otitis media with effusion in children. The purported efficacy of amoxicillin could not be demonstrated by our analysis of the same data. Our presentation of the data from this clinical trial contradicts as well as augments the information disseminated by the report by Mandel et al in several aspects.

Mandel et al base their primary results and conclusions on the proportion of children determined to be effusion free at 4 weeks by the combination of otoscopic and tympanometric findings using an algorithm cited in the "Methods" section of their study.[33] The algorithm Mandel et al employed is, however, not the algorithm described in the original study protocol[32,33]; it is not validated based on some "gold" standard such as myringotomy[34]; and it is an algorithm in which over 90% of the decisions are based on the subjective measure of otoscopy alone.[34]

We attempted to replicate the primary end-point findings of Mandel et al using the method they describe to assess middle-ear status; however, we were unable to do so. In the *NEJM* article (Table 2), Mandel et al show 118 children as "cured" at the 4-week visit. Applying conservatively the algorithm they claimed they have used, we found only 88 "cured" children at the 4-week visit. (For example, in 12 cases, when the algorithm required the acoustic reflex measurement to determine the outcome, those measures for reflex were missing. This is a condition where otoscopy was recorded to find the ear effusion free, with a tympanogram type 12 associated with a .91 probability of effusion for the same ear. These 12 cases were counted as "cured" by Mandel et al, notwithstanding the high probability of effusion by tympanometry. In 16 other cases with positive tympanometry and negative otoscopy, middle-ear status deteriorated from the initial visit to the 4-week visit, but those patients were also counted as "cured" by Mandel et al.) If the statistical analysis of Mandel et al in the *NEJM* article is applied to 88 "cured" children, amoxicillin's efficacy is reduced from 16.1% to 10.5%, and the significance of the P value diminishes from $P<.001$ to $P=.05$.

Our results using otoscopy alone are in agreement with the conclusions of Mandel et al. Our sensitivity analysis shown in Table 3 demonstrates that only with otoscopy can an argument be made about a statistically significant antibiotic efficacy. Other combinations to measure outcome, including the original study protocol algorithm, show either marginal or insignificant differences. Further examination of the outcome at 4 weeks via logistic regression analysis reveals that prognostic factors have a significant effect on the results (Table 4); correcting statistically for these differences in prognostic factors reduces estimated efficacy by 1.3 to 6.6 percentage points. The role of initial hearing loss and acoustic impedance on the outcome, not examined by Mandel et al, shows that the differences in cure rate between antibiotic and placebo groups are further reduced when those prognostic factors are included. After this adjustment, even with otoscopic results, the estimated antibiotic efficacy is reduced from 16.0% to 12.3%.

In addition to the 4-week outcome, we also have included an analysis of patient response patterns based on all data from 2-, 4-, and 8-week visits (Table 5). This section also addresses the recurrence issue and concludes that children treated with amoxicillin had more recurrences than children who received placebo within a 6-week period after termination of the antimicrobial therapy. The report by Mandel et al does not expose the fact that there is a recurrence problem with amoxicillin-treated children that is greater than the recurrence found in placebo-treated children. Mandel et al also fail to mention that,

even with otoscopic measure, there were no statistically significant differences among the treatment groups with respect to children who remained effusion free at the 8-week visit.

Comparison With Other OMRC Studies

Following the early termination of this clinical trial with only one half of the target sample size, the OMRC between 1984 and 1987 conducted the second phase of this study using the same design but with four treatment arms. The OMRC kept the placebo and amoxicillin groups but added two additional antibiotic groups, Pediazole (erythromycin, ethylsuccinate-sulfisoxazole) and cefaclor, for the second clinical trial. Once again, the OMRC terminated the clinical trial without reaching the target sample size, when the OMRC discovered that the placebo group and the three antibiotic-treated groups had virtually the same cure rates at the 4-week end point.[38] With a sample size of 310 subjects, cure rates were 26.7%, 29.9%, 25.0%, and 33.3% for placebo-, amoxicillin-, Pediazole-, and cefaclor-treated groups, respectively.[39]

At the time of the publication of the study by Mandel et al in the *NEJM* in February 1987, the OMRC was in possession of those second-phase data, and those data indicate that amoxicillin was *not* effective and that two other antibiotics, Pediazole and cefaclor, also were *not* effective according to the method of analysis the OMRC had chosen to use.[38,39] Nevertheless, the OMRC published the report by Mandel et al in the *NEJM*, knowing that the second-phase data did not support but contradicted the conclusions of the report by Mandel et al. The results of the second phase have never been published.

A curious result in the report by Mandel et al is the 4-week cure rate (14.1%) for the placebo control group. It was significantly less than those encountered in an earlier study of the OMRC (decongestant-antihistamine) and in the second phase of the antibiotic trial (24.0% and 26.7%, respectively; $P = .022$). Between 1981 and 1987, the OMRC completed three randomized, placebo-controlled clinical trials evaluating the efficacy of decongestant-antihistamines and antibiotics for otitis media with effusion with 4-week sample sizes of 553, 474, and 310, respectively. Those trials had nine treatment groups with the following 4-week cure rates: 24.0%, 14.1%, and 26.7% (for the three placebo groups); and 24.5%, 28.8%, 31.6%, 29.9%, 25.0%, and 33.3% (for the six active treatment groups). Among those nine groups, only the placebo group in the report by Mandel et al is strikingly different ($P = .018$).

This anomalous cure rate in the placebo group, however, is not discussed by Mandel et al. We speculate that it is the result of a preponderance of poor prognostic factors in that placebo group (more bilateral disease, larger hearing losses, higher acoustic impedance values). Such a maldistribution of prognostic factors can result from either improper randomization or other problems related to group assignments. Mandel et al neither try to explain nor statistically correct for this problem.

Between January 1984 and May 1985, the OMRC conducted another clinical trial to evaluate the relative effectiveness of a new antibiotic, Augmentin (amoxicillin trihydrate–clavulanate combination), in comparison to amoxicillin for otitis media with effusion. This clinical trial also was patterned after the report of Mandel et al but without a placebo control group. The study subjects were enrolled and evaluated by two private pediatric practice groups outside Children's Hospital of Pittsburgh on a fee-for-subject basis arrangement. This trial was supported by the manufacturer of the new antibiotic.

The findings of this clinical trial involving 108 children were published by the OMRC in 1988, with Chan et al[28] concluding that both antibiotics (Augmentin and amoxicillin) were equally effective. According to Chan et al, the cure rate for amoxicillin-treated subjects at the 4-week end point was 51.5%. This result was significantly better than the 28.8% cure rate reported for the amoxicillin-treated group by Mandel et al, who used the identical method of analysis. Chan et al inexplicably fail to mention this significant difference ($P = .005$) between the two amoxicillin-treated groups. When the 4-week end point in the study by Chan et al is evaluated using tympanometric results, however, the studies by Chan et al and Mandel et al yield almost identical cure rates (19.2% vs 17.6%). This discrepancy between the subjective measurements (otoscopy) and objective measurements (tympanometry) illustrates nicely the dangers in relying on subjective measurements to define the outcome of non–placebo-controlled clinical trials. The otoscopists in the study by Chan et al knew that both groups were receiving antibiotics and managed to see "cures" almost twice as frequently as the otoscopists in the study by Mandel et al and almost three times as frequently as tympanometric cure rates.

Bias in Otoscopy

One of the most puzzling aspects of the present findings was the difference in results by otoscopy and by tympanometry. In a study published by Maw and Herod,[40] no such significant difference appears. In the present study, however, twice as many children were judged to be effusion free at the 4-week visit by otoscopy as by tympanometry (27.4% vs 13.9%; $P < .001$).

The difference in cure rates between the treatment groups (efficacy) is shown in Table 3 for various outcome measures (sensitivity analysis). Efficacies as determined by otoscopy and by tympanometry were 16.0% and 7.8%, respectively. When the entry imbalance of prognostic factors is corrected for, those figures are further reduced to 12.3% and 4.8% (Table 4). The overlap in efficacy between otoscopy and tympanometry was 5.5% (Table 3, row 4 and column 4), resulting in 18.3% and 5.5% upper and lower bounds. These values are reduced to 13.3% and 3.8% when corrections for prognostic factors are included.

We hypothesized that the disparity between otoscopic and tympanometric results could be explained in part by the fact that the otoscopist observed both ears before recording the results. This knowledge, we hypothesized, might well bias the otoscopist in the direction of judging both ears the same. The tympanometry, of course, could not have that bias.

The probability of effusion associated with a given tympanogram is well known from prior work.[34] If otoscopy measures were unbiased, one would expect the proportion of ears that are judged to have effusion by otoscopy not to be different from the known tympanometric probability of effusion. In other words, for a given tympanogram type, the difference between the proportions of ears found to have effusion by otoscopy and by tympanometric probability of effusion should be zero on the average. The top frame in Fig 2 shows this difference in probability (vertical axis) plotted against the tympanometric probability of effusion (horizontal axis) for two conditions: (1) other ear without effusion (solid circles) and (2) other ear with effusion (open circles). In the absence of bias, both of these plots should fluctuate randomly around a line of zero difference. However, for every tympanogram type, the probability that the otoscopist would find effusion in one ear was greatly influenced by the otoscopic findings of the other ear. Figure 2 (top frame, solid circles) shows that where the otoscopist found no effusion in one ear, the otoscopist scored the second ear at a lower probability of effusion than the unbiased probability associated with the given tympanogram type for that other

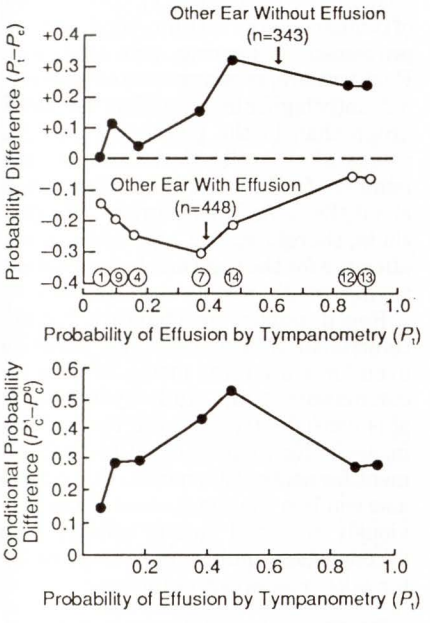

Fig 2.—Top, Probability of effusion associated with a given tympanogram type (P_t) and difference between this tympanometric probability and conditional probability of effusion by otoscopy ($P_t - P_c$) at 4-week visit. Open circles are conditional probability differences from tympanometric probabilities given that the "other" ear has effusion (P_c^1); filled circles are for the "other" ear being without effusion (P_c^0). Numbers in circles indicate tympanogram types. Data are plotted for tympanogram types with more than 10 observations. Bottom, The relationship between P_t and the difference in conditional probabilities by otoscopy when the "other" ear is with and without effusion ($P_c^1 - P_c^0$).

Table 6.—Effects of Observer Expectations on Otoscopic Decision Making

Dependence	Coherence Between Tympanometry and Otoscopy*		
	Agreement	Disagreement	Coherence
Time			
Initial	441	4	0.991
2 wk	356	89	0.800
4 wk	358	87	0.804
		$\chi^2 = 90.65$, $df = 2$, $P < .001$	
Treatment†			
AB + DA	118	33	0.792
AB + PL	112	37	0.752
PL + PL	128	17	0.883
		$\chi^2 = 8.80$, $df = 2$, $P = .012$	
Laterality‡			
Both ears with effusion	219	35	0.862
Both ears without effusion	49	13	0.790
1 ear with effusion	90	39	0.697
		$\chi^2 = 14.82$, $df = 2$, $P < .001$	

*Based on 445 children with matching data for otoscopy and tympanometry.
†Results at 4-week visit by treatment groups: AB + DA (amoxicillin with decongestant-antihistamine combination), AB + PL (amoxicillin with placebo), and PL + PL (placebo with placebo).
‡Laterality by tympanometric results at 4-week visit.

ear warranted. Similarly, where the otoscopist had scored the first ear with effusion, the otoscopist scored the other ear at a higher probability of effusion than the tympanogram warranted (open circles). The two-sidedness of this result is strong evidence that there is indeed a bias in otoscopy arising from the otoscopist's simultaneous knowledge of the status of both ears ($P < .001$).

We also tested to see if otoscopy was influenced by tympanogram type. Although in the design of the experiment it was intended that the otoscopist be blind to the tympanogram type, in fact in practice the otoscopist frequently knew the outcome of tympanometry before recording the otoscopic findings. The bottom frame in Fig 2 shows that the magnitude of otoscopic bias (see preceding paragraph) varies with tympanogram type, being larger for ambiguous tympanograms (such as types 7 and 14, with effusion probabilities of 0.38 and 0.47, respectively) and smaller for tympanograms of greater certainty (such as types 1, 4, 9, 12, and 13). This effect is significant ($P = .008$).

We have thus demonstrated that there is a systematic bias in otoscopy arising from at least two factors: (1) the otoscopist's simultaneous knowledge of the condition of both ears before recording and (2) the otoscopist's knowledge of the tympanogram type.

We also investigated the relationship between the curing of ears vs the curing of patients with bilateral disease. Efficacies (difference between the placebo and the antibiotic groups) for ears alone were very similar by otoscopy and tympanometry (9.9% vs 7.2%, respectively). Significant differences in efficacies between otoscopy and tympanometry appeared when the patient was the experimental unit (11.4% vs 3.7%). For otoscopy, the efficacy for patients is 11.4%, which is 15% larger than the 9.9% efficacy for ears. This is a most curious and unlikely result. If there were a perfect correlation between curing ears and curing patients (every patient with bilateral disease in whom one ear was cured was also a patient in whom both ears were cured), then the efficacy of curing ears and the efficacy of curing patients would be the same. One would expect, however, that the efficacy for curing ears is always higher than that for curing patients (because of the presence of patients with bilateral disease who had clearance in only one ear). It is not logically possible to have the patient efficacy rate higher than that for ears alone. For tympanometry, the patient efficacy rate is 3.7%, which is lower than the ear efficacy of 7.2%. There is, therefore, sound reason to be suspicious of the otoscopic data produced by this experiment.

Observer Expectations Biasing Otoscopy

We also investigated the possible confounding effects of other observer expectations on the outcome. Since the tympanometric method is essentially a machine-made recording, we assumed that it would not be influenced by observer expectations. Also, the tympanogram patterns used in the diagnostic decision making were externally validated. Using the coherence (agreement or disagreement) between the two methods of diagnosis as the measure, we tested three elementary hypotheses concerning observer expectations: (1) middle-ear effusions resolve after some time; (2) medically treated children will do better than untreated children; and (3) if the observer sees one effusion-free ear first, chances of finding a contralateral effusion-free ear are higher.

The findings of this investigation are shown in Table 6. All the above three factors demonstrated significantly different coherence values between the two methods, suggesting a strong observer expectation effect. The time effect on observer expectations is illustrated in the first panel. At entry to the study, the two methods were almost in total agreement (coherence, 99%); however, by 2 weeks, agreement was only 80% ($P < .001$). The second panel shows the effect of treatment assignment on observer expectations. At 4 weeks, coherence for the placebo-treated group was 88%, which was significantly higher than coherence values for the two antibiotic-treated groups ($P = .012$). Although the observers were blinded to treatment assignments, some unknown factors such as reported side effects or conversations with parents might have induced clues about the assignment, thus influencing the observer. The presence of a single disease-free ear is more likely to produce an otoscopic decision of a disease-free child. The third panel in Table 6 shows that in unilateral effusion (by tym-

panometry) the coherence between the two measures was 70%, which was significantly different from the coherence when subjects had either bilateral effusions or bilateral effusion-free ears ($P = .001$).

Another problem associated with otoscopic findings is the cure rate difference between placebo- and antibiotic-treated groups in unilateral disease that exceeds the possible physiologic upper bound. The most plausible mode of action of antimicrobials in resolving secretory otitis media is the sterilization of effusion from pathogenic bacteria. Although it is not documented, if sterilization and clearance are related, then it may be possible to estimate the maximum efficacy of amoxicillin and to determine the upper bound for cure-rate differences between placebo-treated and antimicrobial-treated groups.

It was reported that *Haemophilus influenzae* and *Streptococcus pneumoniae*, the two amoxicillin-sensitive pathogenic bacteria, were isolated in 16% of the effusions from ears with secretory otitis media.[11] Also, it has been shown that amoxicillin is 83% efficient in eradicating these two species of microorganism in acute otitis media.[13] Using these two figures, the upper bound or the maximum differences between the two treatment groups would be about 13% when *ears* are used as the experimental unit if the sterilization concept is the only operative mechanism.

According to tympanometric findings, the *ear-based* cure-rate differences among the placebo and amoxicillin groups were 7.2% for bilateral disease and 13.5% for unilateral disease, which is within the limits of the hypothesis of pathogenic bacteria eradication. However, by otoscopic results, the differences were 9.5% for bilateral disease and 15.7% for unilateral disease. Therefore, otoscopic findings for children with unilateral disease who were treated with amoxicillin are beyond this upper bound and not possible to explain by this hypothesis—sterilization of the effusion.

These observations support our argument that the tympanometric results are more valid than the otoscopic findings and that otoscopy as employed in this study has a systematic bias. Furthermore, the arguments and evidence provided above suggest that estimates of antibiotic efficacy by otoscopy for the bilateral effusions cannot be valid, and estimates for the unilateral disease are an unlikely physiologic possibility. Therefore, averaging of the otoscopic and tympanometric measures is unlikely to contribute to our understanding of the efficacy of antibiotics. It is our judgment that science is better served by the exclusion of the present otoscopic results.

Comparison With Other Studies

The children treated with amoxicillin in the present study had less frequent resolution of effusion at 4 weeks than the values reported by other uncontrolled clinical trials evaluating the efficacy of various antimicrobials for otitis media with effusion.[21-26] With the exception of the OMRC clinical trials, comparison of the present findings with other studies will be difficult since the diagnostic accuracy, measures for outcome, patient selection criteria, study design, choice of antibiotics, and duration of treatment were all different between the studies. Furthermore, none of the previous studies used a placebo-controlled, double-blind, randomized study design with a large cohort of subjects to balance the distribution of prognostic factors. Five of the six previous reports demonstrating significant benefit of antimicrobial treatment (cure rate range, 45% to 65%) did not include a placebo control group, and the only study with a placebo group used a nasal decongestant treatment as placebo and was limited to 51 subjects.[21] As demonstrated in Tables 3 and 4, even in a large randomized study like the present one, the combined effects of treatment, diagnostic accuracy, and prognostic factors must be analyzed very carefully before reaching efficacy conclusions.

In two recent placebo-controlled clinical trials, it was claimed that antibiotics are effective in the treatment of childhood secretory otitis media. Thomsen et al[29] concluded in 1989 that a 1-month course of Augmentin (amoxicillin with clavulanate) is effective for the treatment of otitis media. One of us (E.I.C.) has already published a critical examination of this article,[41] questioning the conclusion of Thomsen et al on Augmentin efficacy for otitis media with effusion. Otten and Grote[30] reported in 1990 that a 10-day amoxicillin therapy is efficacious for otitis media with effusion in children with concurrent chronic rhinosinusitis. However, their published (refereed) article shows that after 6 weeks of follow-up the amoxicillin- and placebo-treated groups had cure rates of 5.3% and 7.9%, respectively. This is a curious result considering the efficacy conclusions of the authors.

CONCLUSIONS

Of the seven different measures of outcome, otoscopy, notwithstanding the questions about its validity, was the only measure that showed significant differences favoring the antibiotic-treated group at the 4-week visit. Outcome, as measured by the remaining six methods including tympanometry, combination of tympanometry with otoscopy, and improvement in hearing, was equivocal. Furthermore, recurrence rates were significantly higher in the antibiotic-treated group than in the placebo group. Six weeks after antibiotic treatment, the number of children without effusion was about the same in each group. We conclude, therefore, that amoxicillin is not effective for the treatment of persistent asymptomatic middle-ear effusions.

Recent publications indicate that antimicrobial treatment is not effective even for acute otitis media.[14-19] Our reexamination of the study by Mandel et al is consistent with those recent findings—ineffectiveness of antibiotic treatment for acute otitis media. Our results also confirm the conclusions of the previously reported lack of efficacy of a decongestant-antihistamine combination for otitis media with effusion.[2]

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