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Nonsevere Acute Otitis Media: A Clinical Trial Comparing Outcomes of Watchful Waiting Versus Immediate Antibiotic Treatment

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ABSTRACT. *Objective.* The widespread use of antibiotics for treatment of acute otitis media (AOM) has resulted in the emergence of multidrug-resistant pathogens that are difficult to treat. However, it has been shown that most children with nonsevere AOM recover without ABX. The objective of this study was to evaluate the safety, efficacy, acceptability, and costs of a non-ABX intervention for children with nonsevere AOM.

Methodology. Children 6 months to 12 years old with AOM were screened by using a novel AOM-severity screening index. Parents of children with nonsevere AOM received an educational intervention, and their children were randomized to receive either immediate antibiotics (ABX; amoxicillin plus symptom medication) or watchful waiting (WW; symptom medication only). The investigators, but not the parents, were blinded to enrollment status. Primary outcomes included parent satisfaction with AOM care, resolution of symptoms, AOM failure/recurrence, and nasopharyngeal carriage of *Streptococcus pneumoniae* strains resistant to ABX. Secondary outcomes included medication-related adverse events, serious adverse events, unanticipated AOM-related office and emergency department visits and telephone calls, the child's absence from day care or school resulting from AOM, the parent's absence from school or work because of their child's AOM, and costs of treatment. Subjects were defined as failing (days 0–12) or recurring (days 13–30) if they experienced a higher AOM-severity score on reexamination.

Results. A total of 223 subjects were recruited: 73% were nonwhite, 57% were <2 years old, 47% attended day

care, 82% had experienced prior AOM, and 83% had not been fully immunized with heptavalent pneumococcal vaccine. One hundred twelve were randomized to ABX, and 111 were randomized to WW. Ninety-four percent of the subjects were followed to the 30-day end point. Parent satisfaction with AOM care was not different between the 2 treatment groups at either day 12 or 30. Compared with WW, symptom scores on days 1 to 10 resolved faster in subjects treated with immediate ABX. At day 12, among the immediate-ABX group, 69% of tympanic membranes and 25% of tympanograms were normal, compared with 51% of normal tympanic membranes and 10% of normal tympanograms in the WW group. Parents of children in the ABX group gave their children fewer doses of pain medication than did parents of children in the WW group. Subjects in the ABX group experienced 16% fewer failures than subjects in the WW group. Of the children in the WW group, 66% completed the study without needing ABX. Immediate ABX resulted in eradication of *S pneumoniae* carriage in the majority of children, but *S pneumoniae* strains cultured from children in the ABX group at day 12 were more likely to be multidrug-resistant than strains from children in the WW group. More ABX-related adverse events were noted in the ABX group, compared with the WW group. No serious AOM-related adverse events were observed in either group. Office and emergency department visits, phone calls, and days of work/school missed were not different between groups. Prescriptions for ABX were reduced by 73% in the WW group compared with the ABX group. Costs of ABX averaged \$47.41 per subject in the ABX group and \$11.43 in the WW group.

Conclusions. Sixty-six percent of subjects in the WW group completed the study without ABX. Parent satisfaction was the same between groups regardless of treatment. Compared with WW, immediate ABX treatment was associated with decreased numbers of treatment failures and improved symptom control but increased ABX-related adverse events and a higher percent carriage of multidrug-resistant *S pneumoniae* strains in the nasopharynx at the day-12 visit. Key factors in implementing a WW strategy were (a) a method to classify AOM severity; (b) parent education; (c) management of AOM symptoms; (d) access to follow-up care; and (e) use of an

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effective ABX regimen, when needed. When these caveats are observed, WW may be an acceptable alternative to immediate ABX for some children with nonsevere AOM. *Pediatrics* 2005;115:1455–1465; otitis media/diagnosis, otitis media/therapy, otitis media/drug therapy, randomized, controlled trial, child, child/preschool.

ABBREVIATIONS. AOM, acute otitis media; ABX, antibiotic(s); WW, watchful waiting; OM-3, otitis media symptom questionnaire, 3 items; OS-8, otoscopy score, 8 grades of severity; AOM-Si, acute otitis media total severity index; ETG-5, ear treatment group symptom questionnaire, 5 items.

Acute otitis media (AOM) accounts for 60% of the antibiotics (ABX) written for children.¹ ABX treatment has contributed to the emergence of multidrug-resistant pathogens by permitting the selection of resistant strains and eliminating the normal flora that inhibits the growth of pathogens in the nasopharynx.^{2,3} Meta-analyses have concluded that children with nonsevere AOM may recover with watchful waiting (WW),^{4,5} but approximately half of the clinical trials cited in meta-analyses were not of good quality because they included children who did not meet the strict diagnostic criteria for AOM.⁶ Children experiencing otitis media with effusion would not be expected to benefit from ABX treatment. In general, the literature is lacking in studies comparing ABX treatment with placebo for AOM. Furthermore, experts have suggested that AOM treatment should be based on AOM severity,^{7,8} but there are no clinical trials using standardized methods for assessing AOM severity.

WW is practiced regularly in some countries; parents are taught to wait for 48 hours for symptoms to resolve before seeking treatment.⁹ This practice has resulted in a lower carriage of ABX-resistant bacteria. Closely related to a WW approach is the use of a contingency (“safety-net”) ABX prescription for nonsevere AOM. Parents receiving a contingency prescription are requested not to fill the prescription unless symptoms do not improve after 2 to 3 days of observation.

Studies using a contingency prescription have demonstrated the potential to reduce ABX prescriptions by 60% to 70%,^{10–12} but these studies have also been criticized for flaws in the design or inconsistent diagnostic criteria for subject enrollment.

The objective of the present study was to assess the safety, efficacy, acceptability, and costs to parents of immediate ABX treatment versus WW for children with nonsevere AOM.

METHODS

Setting, Subjects, and Diagnosis

Trained investigators screened children diagnosed with AOM at the University of Texas Medical Branch pediatric clinic. Parents gave verbal consent for screening and completed demographic, risk-factor, and symptom-severity questionnaires as approved by our institutional review board. If the child was eligible for enrollment in the study, parents signed written informed consent. To enroll, subjects were required to have (a) symptoms of ear infection, (b) otoscopic evidence of AOM, including middle-ear effusion, and (c) nonsevere AOM, as described below. Children were ineligible if they had a comorbidity requiring ABX, anatomic

defect of ear or nasopharynx, allergy to study medication, immunologic deficiency, major medical condition, and/or indwelling tympanostomy tube or draining otitis in the affected ear(s).

AOM-Severity Scoring

Subjects were evaluated for AOM severity at enrollment, at scheduled follow-up on days 12 and 30, and whenever they returned for an interim visit because of treatment failure or recurrence. The AOM-severity assessment, described in detail below, was based on symptoms (OM-3 [otitis media symptom questionnaire, 3 items] score) and signs (otoscopy score, 8 grades of severity [OS-8]; body temperature; and middle-ear effusion scores). A total AOM total severity index (AOM-Si) was calculated as the sum of the scores: AOM-Si = parent questionnaire (OM-3) + otoscopy (OS-8) + body temperature + tympanogram. All enrolled children had symptoms (OM-3 \geq 4), an otoscopy score of \geq 3, and a total AOM-Si score of no more than 24 (the previously determined median score for pilot subjects). In case of bilateral AOM, subjects were enrolled based on the ear yielding the highest AOM-Si score.

Detailed Description of Symptom Questionnaire

Parents reported the severity of their child’s symptoms on a questionnaire (OM-3) listing 3 acute illness items adapted from a preexisting instrument^{13,14} as follows: “During the past 24 hours, has your child experienced any of the following due to ear infection (a) physical suffering such as ear pain, ear discomfort, high fever, or poor balance, (b) emotional distress such as irritability, frustration, sadness, restlessness, or poor appetite, and (c) limitation in activity such as playing, sleeping, doing things with friends/family, attending school or day care.” Parents marked each item on a 7-point scale: 1 indicates not present, not a problem, and 7 indicates an extreme problem. OM-3 total scores were calculated as the sum of the 3 items.

Detailed Assessment of Tympanic Membrane Signs

Visual assessment of the tympanic membrane was aided by removal of cerumen, use of fresh otoscope bulbs, and photographs of tympanic membranes obtained with a tele-otoscope as described previously.¹⁴ In brief, when the subject was sufficiently cooperative, photographs of the tympanic membrane were obtained by using a Storz tele-otoscope (Karl Storz Imaging, Goleta, CA) through a 3.0-mm reusable speculum held in place by a Welch Allyn otoscope head (Welch Allyn, Inc, Skaneateles Falls, NY). Photographs were printed in glossy format by using a Sony printer (Sony Electronics, Woodcliff Lake, NJ). Investigators had the benefit of reviewing photographs of 28% (376 of 1338) of the otoscopic examinations of tympanic membranes obtained during the study. Using otoscopic examination and photographs (when available), investigators graded the severity of inflammation of the tympanic membranes by using an 8-level otoscopic severity scale (OS-8)¹⁴: 0 indicates normal, or effusion only, without erythema; 1, erythema only, no effusion; 2, erythema, air-fluid level, no opacification, meniscus noted; 3, erythema, complete effusion, no opacification; 4, erythema, air bubble(s) observed, purulent (cloudy) fluid visualized through the tympanic membrane, no bulging; 5, erythema, complete effusion, complete opacification, no bulging; 6, erythema, bulging, opacification, rounded, doughnut appearance of tympanic membrane; 7, erythema, complete effusion and opacification with bulla formation. Grade 4 tympanic membranes were distinctly erythematous, and the middle ear was filled with purulent fluid, except for air bubble(s). Grade 4 membranes were sufficiently translucent so that the status (presence, absence, and cloudiness) of middle-ear fluid was directly observed through the membrane. All children with normal tympanograms (22%) were observed otoscopically to have distinctly erythematous tympanic membranes and purulent middle-ear effusion. No air was noted in the middle ears of children with grades 5, 6, and 7 tympanic membranes.

Examiner Training

Examiners were initially trained by reviewing and scoring photosets of tympanic membranes representing varying levels of AOM severity; after this, the investigators examined the ears of children with AOM until they reached an acceptable level of independent interobserver agreement ($\kappa > 0.6$). Seventy percent of

ears were examined by D.P.M., 24% by trained physician assistants, 6% by K.S., and <1% by T.C.

Validation of OS-8

In a study of practicing primary care pediatricians previously reported by our group¹⁴ and in an unpublished Web-based survey of members of the American Society of Pediatric Otolaryngology, pediatricians and pediatric otolaryngologists agreed with our ranking of OS-8 grades ($r = 0.84$ and 0.81 , respectively). Pediatricians consider OS-8 grades of ≥ 2 supportive of a diagnosis of AOM. The majority of pediatricians responded that they treat an asymptomatic child with AOM with ABX at a level of OS-8 ≥ 4 .

Detailed Assessment of Other Signs

Oral, rectal, or axillary body temperatures were measured, converted to axillary temperature in degrees centigrade, and assigned scores of 1 to 7 (1 indicates 35.5–36.0°C; 2, 36.1–36.6°C; 3, 36.7–37.2°C; 4, 37.3–37.7°C; 5, 37.8–38.3°C; 6, 38.4–38.8°C; 7, $\geq 38.9^\circ\text{C}$). Rectal and oral temperatures were converted to axillary temperatures by subtracting 1.2 and 0.6°C, respectively. Tympanograms were obtained on all subjects by using a Welch-Allyn TM262 Auto Tymp tympanometer and were scored from 1 to 7 according to criteria described by Le et al¹⁵: 1 indicates normal (compliance ≥ 0.2 mL and gradient ≤ 150 decapascals [daPa]); 4, partially abnormal (compliance ≥ 0.2 mL and gradient > 150 daPa or compliance < 0.2 mL and gradient ≤ 150 daPa); 7, abnormal (compliance < 0.2 mL and gradient > 150 daPa). As stated above, patients were eligible for enrollment with a normal tympanogram if purulent fluid was observed otoscopically or if the examiner observed decreased tympanic membrane mobility on pneumatic otoscopy.

Parent Education

Before enrollment, an investigator or research assistant used a hand-held flip chart to provide all parents with a 5- to 10-minute educational intervention describing (a) definition of ear infection, (b) causes of ear infections, (c) characteristics of nonsevere and severe AOM, (d) ABX resistance, (e) costs of ABX, (f) rate of symptom response to ABX, and (g) possible adverse outcomes associated with immediate ABX treatment versus WW, including the risk of mastoiditis.

Treatment

If randomized to the immediate-ABX group, subjects received oral amoxicillin: 90 mg/kg per day, 2 doses per day, maximum of 1500 mg/day, for 10 days.¹⁶ Subjects randomized to the WW group were not given immediate ABX. Subjects in the immediate-ABX group with AOM failure or recurrence received amoxicillin-clavulanate: 90 mg/kg per day of the amoxicillin component. Subjects in the WW group with AOM failure or recurrence received amoxicillin: 90 mg/kg per day. Subjects unable to take oral medication at follow-up received intramuscular ceftriaxone. All parents received a copy of the consent form, office-contact information, an electronic thermometer, saline nose drops and/or cerumen-removal drops (if needed), and ibuprofen and over-the-counter decongestant/antihistamine to be given as needed by the parent. Antihistamine was discontinued after subject number 194 because of research indicating that antihistamine given for AOM may prolong the duration of middle-ear effusion.¹⁷

Primary Outcomes

The study was designed to evaluate 4 primary outcomes: (a) parent satisfaction with AOM care; (b) resolution of AOM symptoms after treatment, including number of doses of symptom medication given; (c) AOM failure and recurrence; and (d) nasopharyngeal carriage of *Streptococcus pneumoniae* strains resistant to ABX.

Secondary Outcomes

The secondary outcomes were: (a) minor adverse events caused by medication, such as allergy, diarrhea, and candidal infection; (b) serious AOM-related adverse events such as invasive pneumococcal disease, mastoiditis, bacteremia, meningitis, perforation of the tympanic membrane, hospitalization, and emergency ear surgery; and (c) parent-child quality-of-life measures related to AOM,

such as unanticipated AOM-related visits to the office or emergency department, unanticipated AOM-related phone calls to the physician's office, number of days the child was absent from school or day care as a result of AOM, number of days the parent was absent from work or school as a result of AOM, and costs of treatment.

Measurement of Primary Outcomes

Parent Satisfaction

Parents completed an anonymous satisfaction questionnaire on follow-up days 12 and 30. Parents were asked to rate on a 4-point scale their feelings about treatment, including (a) medication side effects, (b) extra time spent at the doctor's office or emergency department because of the child's ear infection, (c) extra phone calls to the doctor's office because of the ear infection, (d) difficulty in giving the medicine the prescribed number of times, (e) the child's difficulty swallowing ABX or symptom medications, (f) concern about future ear infections that would be difficult to treat, (g) worries about the future cost of ABX medication, (h) parent absences from work or school because of the ear infection, (i) the child's absences from day care or school because of the ear infection, (j) trouble communicating with the research team, (k) effectiveness of symptom medication, (l) overall effectiveness of the treatment, and (m) overall satisfaction with the care provided.

Resolution of AOM Symptoms and Signs After Treatment

For the resolution of symptoms, each day from day 1 to 10 the parent was instructed to complete a diary documenting daily doses of symptom and ABX medication given. The parent also completed the ETG-5 (ear treatment group symptom questionnaire, 5 items).¹⁸ The symptoms rated by parents on the ETG-5 were fever (0 indicates $< 100.4^\circ\text{F}$; 4, 100.4 – 102.2°F ; 7, $> 102.2^\circ\text{F}$), ear ache (tugging) (0 indicates none; 4, occasional; 7, frequent), irritability (0 indicates none; 4, occasional; 7, frequent), feeding (0 indicates feeds well; 4, mild decrease in appetite; 7, very poor appetite), and sleeping (0 indicates normal sleep; 4, somewhat restless sleep; 7, very poor sleep). Symptoms were color-coded by score (0 indicates green; 4, yellow; 7, red). The ETG-5 score by parent diary was defined as the sum of scores of the 5 items (range: 0–35). Parents were encouraged to notify research personnel if symptoms remained in the yellow or red zones after initiation of treatment. For additional evaluation of symptoms, at the day-12 and day-30 visits, parents also completed a health status questionnaire by indicating whether, after treatment, their child was "much better," "better," "not changed," "worse," or "much worse." For additional evaluation of symptoms and signs, as already described, results of OM-3, OS-8, body temperature, tympanogram, and total AOM-Si scores were evaluated at days 12 and 30.

AOM Failure, Recurrence, and Cure

Subjects were defined as failing treatment (days 0–12) or recurring (day 13–30) when they returned to the office with acute ear symptoms (OM-3 ≥ 4), an abnormal tympanic membrane (OS-8 ≥ 3 plus middle-ear effusion), and an AOM-Si score higher than that at enrollment. Subjects without symptoms were not deemed to have AOM failure regardless of the appearance of their tympanic membranes, because the project required the subjects to have symptoms for a diagnosis of AOM. Subjects without a failure or recurrence episode before the day-30 visit were considered cured. Failure and/or recurrence were considered primary end points for each subject: subjects could be counted for only 1 failure or 1 recurrence but not both.

Carriage of *S pneumoniae* Strains Resistant to ABX

Nasopharyngeal specimens from all subjects at enrollment and day 10 were cultured for bacteria by using a wire swab and processed by using standard methods. Susceptibility of *S pneumoniae* isolates to 9 ABX (ceftriaxone, cefuroxime, clindamycin, erythromycin, levofloxacin, penicillin, trimethoprim sulfamethoxazole, and vancomycin) was tested following the National Committee for Clinical Laboratory Standards recommendations. Isolates with a minimum inhibitory concentration of 0.125 and 1.0 $\mu\text{g/mL}$ were considered intermediately susceptible to penicillin,

and those with a minimum inhibitory concentration of ≥ 2.0 $\mu\text{g}/\text{mL}$ were considered resistant to penicillin.

Measurement of Secondary Outcomes

(a) Minor adverse events caused by medication were recorded by the research personnel. (b) Serious AOM-related adverse events were documented. (c) For parent-child quality-of-life measures related to AOM, research personnel recorded all unanticipated AOM-related unplanned office and emergency department visits and phone calls. (d) To determine the costs of treatment, costs of ABX treatment for each intervention group were calculated.

Compliance

Parents returned bottles of ABX and symptom medication; medicine bottles were weighed and bottle weights were recorded at enrollment and day-12 visits.

Blinding

Many placebo-controlled studies have demonstrated the effectiveness of ABX in the treatment of AOM. Because the study was designed to evaluate parent satisfaction and quality-of-life outcomes in a real-life setting, parents were not blinded to treatment, but investigators were blinded. Research assistants dispensed medication and handled all data collection. Parents were asked not to reveal treatment group to the investigators, who were unblinded as necessary only to manage patient care issues. Otherwise, the investigators were blinded until all the data had been entered and summarized (see Table 1, Investigator blinding).

Follow-up

Routine follow-up appointments for data collection were scheduled for day 12 (range: 10–15) and day 30 (range: 28–33). Parent-initiated visits were scheduled on request by the parents for children who seemed to not be responding to treatment. Subjects' charts were reviewed subsequent to the day-30 visit to document additional outcome-related events that may have occurred during the 30-day follow-up. To assess *S pneumoniae* heptavalent vaccine status, charts were reviewed for dates of prior immunization. Immune status (no, partial, or full immunity) was defined according to the package insert (Prevnar, Wyeth Laboratories, Madison, NJ).

Power Analysis

The study was designed originally with a power to detect differences in parents' satisfaction (a primary outcome) between the 2 treatment groups. For parent-satisfaction items, we predicted that if the difference between the means of the 2 groups were ≥ 0.4 times the SD, then 100 subjects in each group would provide sufficient power (0.81) to detect a difference at $\alpha = .05$. Regarding the nasopharyngeal culture data (a secondary outcome), we estimated that the percent of *S pneumoniae* isolates resistant to penicillin would be 37% at enrollment and 75% 12 days after ABX.³ Given 100 subjects in each group with $\alpha = .05$, we would have sufficient power (0.99) to detect a 38% percent difference in resistance and a power of 0.98 to detect a 27% increment in resistance to multiple ABX. We did not expect to detect differences in failure/recurrence, but if there were a clinically significant difference (10%) between immediate ABX and WW, we could demonstrate a statistically significant difference at power = 0.70 and $\alpha = .05$, given 100 subjects in each group.

Randomization

Five of every 10 participants were assigned randomly to the immediate-ABX group and the other 5 to the WW group. In this way the numbers of patients in the 2 groups could be closely maintained within any given time period. The randomization scheme was constructed by using the random-number generator function in SAS 8.2 (SAS Institute, Inc, Cary, NC).

Data Analysis

The 2-sample *t* test was used to compare the 2 intervention groups (immediate ABX and WW) for duration of breastfeeding, parent-satisfaction scores (13 items), OM-3 scores at enrollment and follow-up, and doses of pain medication given.

Diary Scores

ETG-5 scores over the first 10 days of treatment, by parent diary, a primary outcome, were analyzed by using analysis of variance for a 2-factor experiment with repeated measures on time (Proc Mixed in SAS 8.2). The 2 factors were treatment group and time (days 0–10).

Analysis by Age

We had not originally planned to stratify our failure/recurrence data (a primary outcome) by age. However, while our data were being analyzed, new guidelines for the treatment of AOM were published by a committee of the American Academy of Pediatrics and the American Academy of Family Practice.¹⁹ Because these guidelines suggest that clinicians may use different treatment options depending on age (<2 vs ≥ 2 years), we considered that it would be important to evaluate our failure/recurrence data based on age. Additional impetus for this decision was provided by our observation of a greater effect of immediate ABX on outcome than we had estimated from reviewing the literature. Therefore, the association between clinical outcome and the 2 intervention groups, controlling by age group (age <2 and ≥ 2 years), was tested by using the Cochran-Mantel-Haenszel statistic. Homogeneity of the associations of the 2 age groups was assessed by using a categorical data-modeling procedure (Proc Catmod in SAS 8.2) before using the Cochran-Mantel-Haenszel statistic.

Analysis of Categorical Variables

We used the Pearson χ^2 test to assess homogeneity of the 2 intervention groups for the following variables: demographic and risk factors; OS-8, tympanogram, and body temperature at enrollment, day 12, and day 30; parent perception of change in health status at days 12 and 30 (stratified by age, per considerations listed in the previous paragraph); ABX-resistance patterns of *S pneumoniae*; ABX-related minor adverse events; and parent/child quality-of-life outcomes (4 items). Fisher's exact test was used when the Pearson χ^2 test might not be valid because of small expected cell counts. All outcome data were analyzed on an intention-to-treat basis; all tests were assessed at the .05 level of significance.

Costs

Costs of ABX were calculated by using Galveston community pharmacy retail charges (as of June 2004) and data on the numbers of initial prescriptions (amoxicillin, 250 mg/5 mL, 150-mL bottle, \$7.99 per bottle, 2 bottles per subject, to achieve the 90 mg/kg twice-a-day dosage required) and failure/recurrence prescriptions (amoxicillin-clavulanate, 250/62.5 mg/5 mL, 150-mL bottle, \$87.79, plus 1 bottle of amoxicillin, 150 mL, to achieve the 90 mg/kg amoxicillin required) for each intervention group. These calculations were simplified by assuming that all children were at the median age (1.6 years) and weight (11.5 kg) and were able to take oral ABX for all failure/recurrence episodes.

RESULTS

Demographics and Participant Flow

Subjects were enrolled from May 1, 2000, until March 30, 2003. A total of 689 subjects were screened; 112 were enrolled to immediate ABX and 111 to WW (Fig 1). Subjects were distributed homogeneously between groups (Table 1). Eight percent (12 of 138) of the subjects cured (subjects who completed the study without a failure or recurrence) were inadvertently unblinded to the investigator because of comments by the parent while the investigator was assessing the subject. To manage patient care issues, 58% (42 of 73) of the subjects were unblinded to the investigator after a primary end point (failure, recurrence, or drop status) had been established but before the subject had completed the day-30 visit. For reasons of subject safety, 93% (27 of 29) of the subjects experiencing an adverse event were unblinded to the

TABLE 1. Demographic and Risk Factors at Enrollment, Investigator Blinding, and Compliance

	Immediate ABX (<i>n</i> = 112)	WW (<i>n</i> = 111)	<i>P</i>
Gender, <i>n</i> (%)			.59
Female	58 (52)	53 (48)	
Male	54 (48)	58 (52)	
Race/ethnicity, <i>n</i> (%)			.25
White/non-Hispanic	34 (30)	27 (24)	
Hispanic	42 (38)	37 (33)	
Asian/Pacific Islander	1 (1)	6 (5)	
Black	24 (21)	26 (24)	
Other	11 (10)	15 (14)	
Age, <i>y</i> , <i>n</i> (%)			.36
0.5 ≤ age <1 <i>y</i>	36 (32)	34 (31)	
1.0 ≤ age <2 <i>y</i>	32 (29)	24 (21)	
2.0 ≤ age <13 <i>y</i>	44 (39)	53 (48)	
Daycare attendance, <i>n</i> (%)			.98
Not attending	60 (54)	59 (53)	
1–20 h/wk	21 (19)	19 (17)	
21–40 h/wk	26 (23)	28 (25)	
>40 h/wk	5 (4)	5 (5)	
Tobacco-smoke exposure, <i>n</i> (%)			.38
Exposed	36 (32)	29 (26)	
Not exposed	76 (68)	82 (74)	
Breastfed, mo, <i>n</i> (%)			.99
Mean ± SD	2.6 (±3.7)	2.6 (±4.8)	
Number of prior AOM, <i>n</i> (%)			.72
0	24 (21)	15 (14)	
1–3	53 (47)	64 (58)	
4–6	22 (20)	21 (19)	
>6	13 (12)	10 (9)	
Heptavalent pneumococcal vaccine status, <i>n</i> (%)			.83
None	64 (57)	60 (54)	
Partial	31 (28)	31 (28)	
Full	17 (15)	20 (18)	
Most recent ABX use, <i>n</i> (%)			.70
≤30 d	35 (33)	29 (30)	
>30 d	72 (67)	67 (70)	
No data	5	15	
Most recent AOM episode, <i>n</i> (%)			.22
≤30 d	21 (19)	17 (18)	
>30 d	87 (81)	80 (82)	
No data	4	14	
Parent education, <i>n</i> (%)			.61
<8th grade	6 (5)	4 (4)	
>8th grade, no diploma	17 (15)	9 (8)	
High school diploma	36 (32)	36 (33)	
Some college	32 (29)	39 (35)	
College degree	15 (14)	16 (14)	
Post-graduate degree	6 (5)	6 (6)	
No data	0	1	
Investigator blinding (see “Methods”), <i>n</i> (%)			.53
Blinded	87 (78)	81 (73)	
Unblinded	25 (22)	29 (26)	
ABX compliance, no. of doses, <i>n</i> (%)			
Mean ± SD (<i>n</i> = 106; range: 3–22)	19 (±2)	NA	
OS-8 scores at enrollment, <i>n</i> (%)			.61
3	3 (3)	3 (3)	
4	39 (35)	33 (30)	
5	45 (40)	42 (38)	
6	24 (21)	29 (26)	
7	1 (1)	4 (3)	

NA indicates not applicable.

investigator at the time of the event. Subject attrition and protocol violations are enumerated in Fig 1.

Parent Satisfaction

Total satisfaction scores for the immediate-ABX group compared with the WW group were not different at day 12 (44.4 vs 44.0, respectively) or day 30 (44.6 vs 44.6, respectively).

Change in ETG-5 Scores (by Diary)

Figure 2 displays differences in ETG-5 scores noted in the diaries. Subjects receiving immediate ABX resolved their symptoms faster than subjects randomized to WW (*P* = .004). Table 2 summarizes the health status results reported by parent questionnaire at days 12 and 30. In the group of children <2 years old, parents observed more improvement by

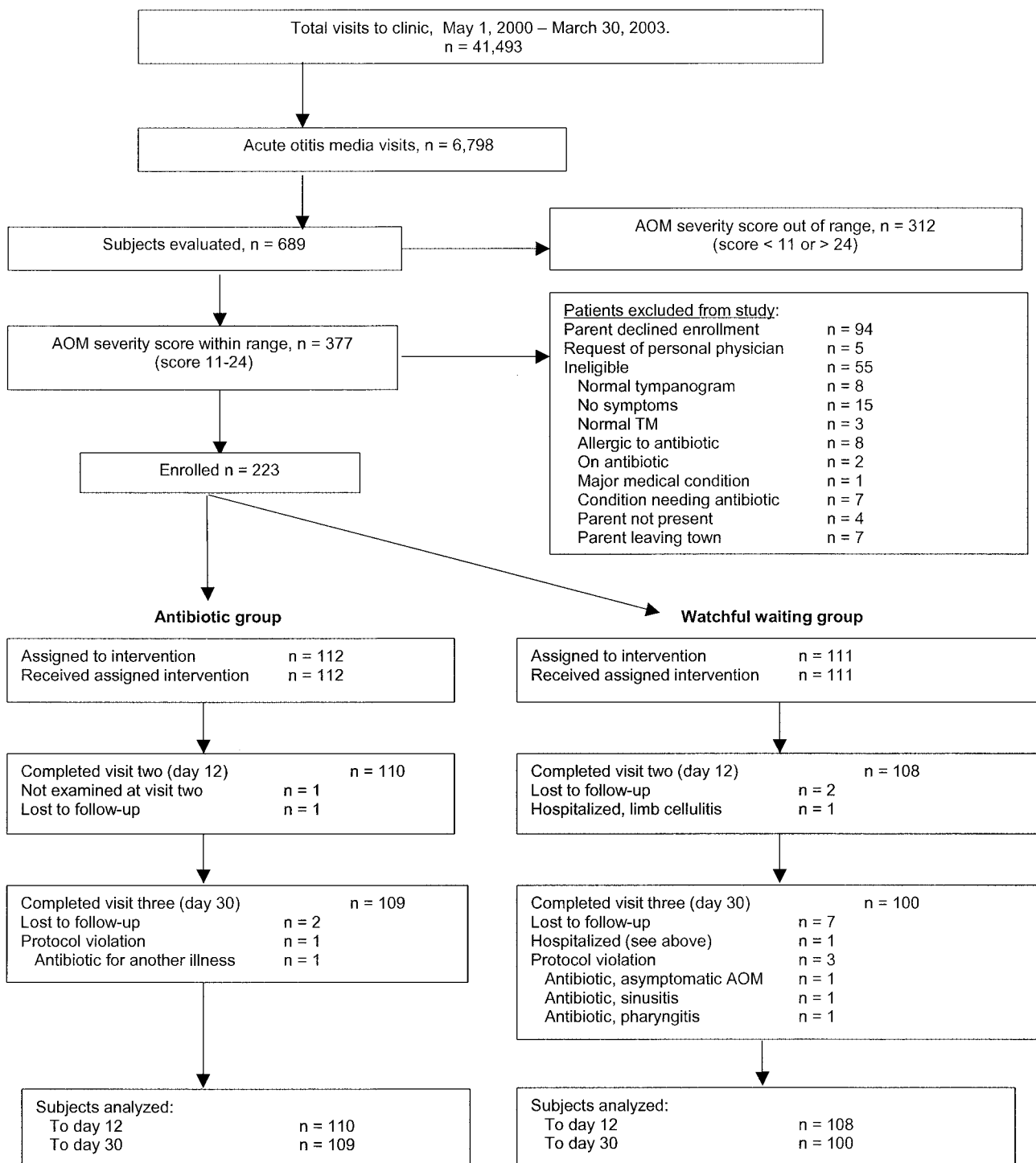


Fig 1. Participant flow.

day 12 if they received an immediate ABX (Table 2; $P = .0008$). Severity scores on days 0, 12, and 30 are summarized in Table 3. At day 12, otoscopic and tympanogram scores were lower in the immediate-ABX group than in the WW group (Table 3; $P = .02$ and 0.04, respectively). OM-3 and temperature scores were not different between treatment groups at days 12 or 30. Total AOM-Si scores for the immediate-ABX group were 20.1, 12.4, and 11.8 and for the WW group 20.1, 14.5, and 11.9 at enrollment, day 12, and day 30, respectively. Parents in the immediate-ABX

group gave their children, on average, 4.3 fewer doses of pain medication than parents in the WW group (Table 4; $P < .01$).

AOM Failure, Recurrence, and Cure

The distribution of the clinical outcomes (failure, recurrence, and cure) adjusted for age (<2 vs ≥2 years old) was significantly different between the immediate-ABX and WW groups (Table 5; $P = .001$). This difference was mainly because of the large and consistent differences in failure rates. Combining all

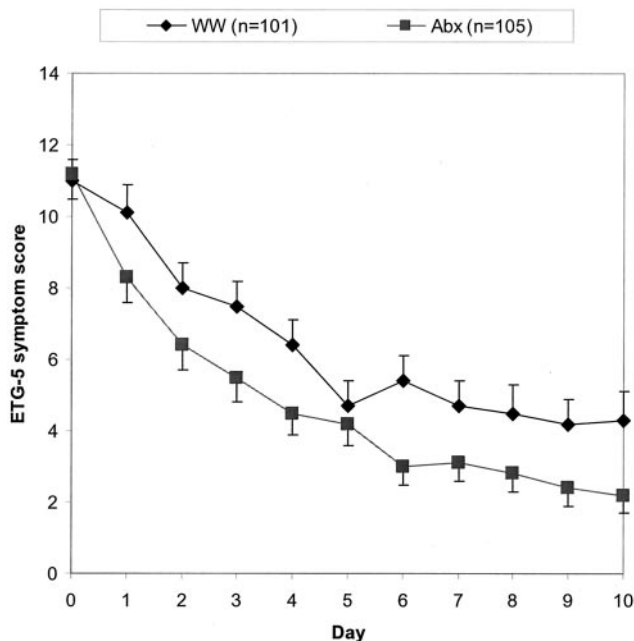


Fig 2. ETG-5 scores (with standard error bars) according to group (immediate ABX versus WW), recorded by parents in the patient diaries on days 0 to 10 based on fever, earache, irritability, decreased appetite, and sleep; the maximum score possible was 35 (see "Methods").

ages, the failure rates of the immediate-ABX and WW groups were 5% (5 of 109) and 21% (21 of 100), respectively. The association between clinical outcome and intervention group was not significantly different from one age group to the other ($P = .13$). Failure or recurrence was more common in subjects who had received ABX within 30 days before enrollment, regardless of the intervention group ($P = .001$). In the immediate-ABX group, 36% (12 of 33) had AOM failure or recurrence if they had received recent ABX, and 17% (12 of 71) had AOM failure or recurrence if they had not received recent ABX. In the WW group, 52% (14 of 27) had AOM failure or recurrence if they had received recent ABX, whereas 25% (15 of 61) had AOM failure or recurrence if they had not received recent ABX.

Carriage of *S pneumoniae* Strains Resistant to ABX

Results are summarized in Table 6.

Minor Adverse Events Caused by Medication

Results are summarized in Table 4.

Serious AOM-Related Adverse Events

No serious AOM-related adverse events were observed. Two subjects experienced non-AOM-related adverse events requiring hospitalization: 1 developed limb cellulitis, and the other was hospitalized for a febrile convulsion during an episode of roseola.

Parent-Child Quality-of-Life Measures Related to AOM

Treatment groups did not differ significantly in the number of unanticipated office and emergency department visits, phone calls to the doctor, and days of work/school missed by the parent (Table 4).

Cost of Treatment

The number of visits and days of work lost by the parents were not significantly different between groups. Therefore, only the cost of ABX was calculated (only including subjects who completed the study). The immediate-ABX group required 109 initial prescriptions for amoxicillin and 28 prescriptions of high-dose amoxicillin clavulanate for failure/recurrence episodes (total: \$5167.26 [\$47.41 per subject]). Subjects in the WW group required 34 prescriptions of amoxicillin and 4 prescriptions of high-dose amoxicillin clavulanate for failure/recurrence episodes (total: \$1143.24 [\$11.43 per subject]).

DISCUSSION

The 16% difference in failures between treatment and WW for nonsevere AOM is clinically significant and larger than the 4% difference we had expected from our review of the literature.⁴ Our result highlights the importance of detecting clinically meaningful differences by using strict enrollment criteria, careful clinical evaluation at follow-up, and an effective antimicrobial agent and dosage. We attempted to carefully describe the clinical status of the children enrolled by including a detailed assessment of the appearance of the tympanic membrane to provide a stepping stone for future researchers to explore this topic. As has been shown previously,³ our study demonstrates that ABX treatment decreases carriage of *S pneumoniae* but significantly increases the percent of drug-resistant bacteria carried by the host.

Standard procedure for describing the outcome of ABX clinical trials for AOM requires the reporting of failure, recurrence, and total failure/recurrence rates. Failure in clinical trials is defined as occurring during ABX treatment, up until 1 or 2 days posttreatment. Recurrence is usually defined as occurring after completion of the initial course of ABX. Subjects are usually followed for recurrence until at least 30 days postenrollment. Recurrences may occur because of relapse (the same organism recurs after cessation of treatment) or acquisition of a new infection. New infections are especially common in young children who have experienced a recent AOM, often because they are exposed to respiratory viruses in day care settings during the respiratory season, when AOM is most often diagnosed and clinical trials enroll the majority of their subjects. Because recurrences may be common and may represent new infections, on-treatment failure-rate data are the most important to consider when judging the effectiveness of a treatment for AOM, especially without the benefit of middle-ear fluid culture.

Our overall day-0 to -12 failure rate of 12% (26 of 209) and recurrence rate of 16% (33 of 209) is somewhat lower than rates published previously in recent studies.²⁰⁻³¹ When results from these studies are combined, the overall failure rate is 15% (536 of 3487), and recurrences occurred at a rate of 23% (611 of 2683), for a total combined 30-day failure/recurrence rate of 38%. This translates to an overall cure rate of 62% at 30 days. These published data compare with our cure rates of 77% in the immediate-ABX

TABLE 2. Parent Perception of Change in Status at Days 12 and 30 According to Age and Group

	Day 12		<i>P</i>	Day 30		<i>P</i>
	Immediate ABX, <i>n</i> (%)	WW, <i>n</i> (%)		Immediate ABX, <i>n</i> (%)	WW, <i>n</i> (%)	
Age <2 y			<.01			.75
Much better	41 (64)	15 (28)		42 (65)	28 (57)	
Better	16 (25)	25 (46)		14 (21)	15 (31)	
Not changed	5 (8)	10 (19)		7 (11)	5 (10)	
Worse	2 (3)	4 (7)		2 (3)	1 (2)	
Much worse	0 (0)	0 (0)		0 (0)	0 (0)	
Total	64 (100)	54 (100)		65 (100)	49 (100)	
Age ≥2 y			.25			.29
Much better	29 (67)	26 (49)		26 (62)	38 (76)	
Better	12 (28)	21(40)		13 (31)	9 (18)	
No changed	2 (5)	4 (8)		2 (5)	3 (6)	
Worse	0 (0)	2 (3)		1 (2)	0 (0)	
Much worse	0 (0)	0 (0)		0 (0)	0 (0)	
Total	43 (100)	53 (100)		42 (100)	50 (100)	

TABLE 3. Number of Subjects at Each Level of AOM Severity: Days 0, 12, and 30

	Day 0			Day 12			Day 30		
	Immediate ABX (<i>n</i> = 112)	WW (<i>n</i> = 111)	<i>P</i>	Immediate ABX (<i>n</i> = 110)	WW (<i>n</i> = 108)	<i>P</i>	Immediate ABX (<i>n</i> = 108)	WW (<i>n</i> = 99)	<i>P</i>
Symptoms (OM-3)			.68			.24			.76
Mean ± SD	8.3 ± 2.7	8.1 ± 2.5		4.7 ± 2.9	5.2 ± 3.1		4.5 ± 2.6	4.3 ± 2.5	
Otoscopy (OS-8), <i>n</i> (%)			.21			.02			.27
0,1	0	0		75 (69)	55 (51)		83 (77)	71 (72)	
2-5	87 (78)	78 (70)		25 (23)	43 (40)		18 (17)	15 (15)	
6,7	25 (22)	33 (30)		9 (8)	10 (9)		7 (6)	13 (13)	
Total	112 (100)	111 (100)		109	108		108	99	
Temperature, <i>n</i> (%)			.63			.41			.53
35.5-36.0°C	56 (50)	54 (49)		74 (67)	64 (59)		69 (64)	70 (71)	
36.1-36.6°C	40 (36)	36 (32)		26 (24)	34 (32)		30 (28)	21 (21)	
36.7-38.9°C	16 (14)	21 (19)		10 (9)	10 (9)		9 (8)	8 (8)	
Total	112 (100)	111 (100)	110 (100)	108 (100)	108 (100)	99 (100)			
Tympanogram, <i>n</i> (%)			.20			.04			.98
1	22 (19)	27 (24)		27 (25)	21 (19)		30 (28)	28 (28)	
4	20 (18)	11 (10)		24 (22)	12 (11)		23 (21)	22 (22)	
7	70 (63)	73 (66)		59 (53)	75 (70)		55 (51)	49 (50)	
Total	112 (100)	111 (100)	110 (100)	108 (100)	108 (100)	99 (100)			

group and 66% in the WW group. The differences between our results and published studies may be explained by the different enrollment criteria used, because the published studies permitted enrollment of subjects with more severe otitis.

Recently published guidelines¹⁹ indicate that in children ≥2 years old with uncomplicated nonsevere AOM, clinicians may observe the WW option, using symptom management only. We originally did not intend to make comparisons by age. However, because few data were available to support this age-specific guideline, we present our data on failure/recurrence and change in health status, stratified by age (Tables 2 and 5). In reviewing these results stratified by age, when considering failure, recurrence, and cure, the association was not significantly different by age (Table 5). Regarding cure, immediate ABX treatment provided superior early results, but recurrences were observed, resulting in nearly identical outcomes between the immediate-ABX and WW groups by day 30 (77% vs 76% cure, respectively). Regarding parent perception of change in status (Table 2), no differences were noted between the immediate-ABX and WW groups for the group of subjects ≥2 years old (*P* = .25 vs 0.29, respectively), but

significant differences were noted for subjects <2 years old (*P* < .01 vs *P* = .75, respectively).

Despite the inclusion of subjects with risk factors (<2 years old, day care exposure, history of prior AOM, recent ABX for AOM, lack of full heptavalent pneumococcal immunization, low rate of breastfeeding, and exposure to tobacco smoke), 66% (66 of 100) of all subjects randomized to WW completed the study without ABX. ABX prescriptions were reduced by 73% and costs of ABX were reduced by 76% in the WW group compared with the immediate-ABX group.

Regardless of treatment group, the clinical otoscopic status of subjects' ears was not different at day 30, and parents expressed equal satisfaction with care at days 12 and 30. To mimic a real-world setting, parents were not blinded, because using a placebo would not have allowed the parent to experience the full impact of a WW approach. Our goal was not to assess the effectiveness of ABX, which had clearly been demonstrated in many placebo-controlled clinical trials, but to assess the impact of parent education combined with shared decision-making. Nonetheless, a limitation of this parent-unblinded study design is that parent satisfaction may have been in-

TABLE 4. Adverse Events and Parent/Child Quality-of-Life Outcomes

	Immediate ABX (n = 111)	WW (n = 108)	P
ABX-related adverse event, n (%)			
Yes	13 (12)	5 (5)	.06
No	98 (88)	103 (95)	
Extra office visit, AOM-related, n (%)			.15
Yes	14 (13)	22 (20)	
No	97 (87)	86 (80)	
Emergency department visit, AOM-related, n (%)			.21
Yes	1 (1)	4 (4)	
No	110 (99)	104 (96)	
Extra phone calls, AOM-related, n (%)			.91
Yes	26 (23)	26 (24)	
No	85 (77)	82 (76)	
Parent missed work or school, n (%)			.53
Yes	14 (13)	10 (9)	
No	60 (54)	66 (61)	
Parent does not work or go to school, n (%)	37 (33)	32 (30)	
Doses of pain medicine			<.01
Subjects reporting, n	105	102	
Mean ± SD	3.4 ± 4.0	7.7 ± 7.5	

No outcome data were recorded for 1 subject in the immediate-ABX group and 3 subjects in the WW group who were lost to follow-up. Outcome data were included only until the drop date for subjects dropped after 1 follow-up visit (2 subjects in the immediate-ABX group and 8 subjects in the WW group).

TABLE 5. Clinical Outcome According to Treatment and Age Groups

	Failure (Day 0–12)	Recurrence (Day 13–33)	Cure	Total
<2 y				
Immediate ABX, n (%)	4 (6)	11 (17)	50 (77)	65
WW, n (%)	12 (24)	10 (20)	28 (56)	50
Total	16	21	78	115
≥2 y				
Immediate ABX, n (%)	1 (2)	9 (21)	34 (77)	44
WW, n (%)	9 (18)	3 (6)	38 (76)	50
Total	10	12	72	94

The association between clinical outcome and intervention group adjusted for age group was statistically significant ($P = .001$), mainly because of large and consistent differences in failure rates. This association was not significantly different from one age group to the other ($P = .13$). Three subjects dropped out of the immediate-ABX group, and 11 dropped out of the WW group. Within the 30-day follow-up, 7 subjects (all <2 years old) required multiple courses of ABX (3 in the immediate-ABX group and 4 in the WW group).

TABLE 6. ABX-Resistance Patterns of *S pneumoniae* Strains Isolated From the Nasopharynx of Subjects at Enrollment and Day 12

	Enrollment		P	Day 12		P
	Immediate ABX	WW		Immediate ABX	WW	
Number of ABX to which <i>S pneumoniae</i> was resistant*						
0	18 (35)	21 (40)	.58	0 (0)	13 (30)	<.02
1–3	20 (38)	15 (29)		8 (44)	18 (42)	
4–6	14 (27)	16 (31)		10 (56)	12 (28)	
Penicillin resistance, <i>S pneumoniae</i>			1.00			<.04
Sensitive	25 (48)	25 (48)		2 (11)	17 (40)	
Intermediate/resistant	20 (39)	18 (35)		10 (56)	16 (37)	
Resistant	7 (13)	9 (17)		6 (33)	10 (30)	

* Included are only the subjects from whom *S pneumoniae* strains were isolated. The ABX tested were ceftriaxone, cefuroxime, clindamycin, erythromycin, levofloxacin, penicillin, trimethoprim sulfamethoxazole, and vancomycin.

fluenced by the parents' personal beliefs and preconceptions about the advantages or disadvantages of ABX treatment.

As with any treatment regimen for AOM, a number of trade-offs should be considered; treatment

decisions can be adjusted depending on what is most important to the child and parents. Some parents may prefer immediate treatment with ABX, especially if their child is uncomfortable and the parent is not whether sure symptom management will be ef-

fective. On the other hand, the option of WW may be attractive to some parents with the intent of (a) eliminating the cost, inconvenience, and adverse effects of ABX treatment, (b) avoiding the colonization and proliferation of a multidrug-resistant organism, and (c) avoiding the suppression of normal nasopharyngeal flora that have been shown to inhibit the growth of pathogens.³²⁻³⁵

Our assessment of AOM severity was based on 4 factors (parental perception of severity, otoscopic examination, body temperature, and tympanogram); total scores gave equal weight to symptoms (parent perception) and signs (remaining items). In retrospect, we could have obtained the same results by using a streamlined scoring system that omitted body temperature and tympanogram. Most children with AOM are afebrile at the time of diagnosis as a result of antipyretic medication. Furthermore, practicing clinicians rarely use the tympanogram to make a diagnosis of AOM. With a streamlined 2-factor severity-scoring system (OM-3 and OS-8, weighted equally), we would have identified 87% of the non-severe cases that were identified by the more-cumbersome 4-factor AOM-Si. We recently reported the development of a "faces" AOM-severity scale for use by parents to assess their child's AOM symptoms. This scale is even easier to use in clinical practice and provides comparable results to the verbally based OM-3, which requires verbal skills and familiarity with a multiple-choice format.³⁶

For safety, our study required routine follow-up 12 days postenrollment. Our protocol required ABX treatment for subjects experiencing any documented increase in total severity at follow-up, including many subjects who still scored in the nonsevere category. Children seen soon after a nonsevere episode of AOM will often have persistent nonsevere findings such as mild erythema of the tympanic membrane and persistent middle-ear effusion. Although we feel that children with nonsevere findings at follow-up do not necessarily need to be retreated with ABX, clearly more data will need to be obtained to answer this important question. As well, studies should be designed to determine the optimal time for follow-up to assess for middle-ear effusion and/or hearing loss.

Safety issues will need to be considered whenever children traditionally treated with ABX are provided with a WW option. The incidence of mastoiditis, a frequent complication of AOM in the pre-ABX era, has decreased since ABX were introduced. The incidence of mastoiditis in children with AOM is relatively low, compared with the incidence of other AOM-related adverse events such as tympanic membrane perforation. Among 4860 consecutive Dutch patients with AOM who did not receive ABX at initial presentation, there was 1 new case of mastoiditis and no cases of bacterial meningitis.³⁷ In the Netherlands, Norway, and Denmark, in which ABX-prescribing rates for AOM are 31% to 76%, the incidence of mastoiditis was 4 cases per 100 000 children per year over 5 years.³⁸ In Canada and the United States, in which 95% of children with AOM received ABX, the incidence of mastoiditis was 2 cases per

100 000 children per year. These data are difficult to interpret, because different methodologies were used to calculate these incidences. However, the results suggest that restricted use of ABX for AOM may have resulted in 2 additional cases of mastoiditis per 100 000 children.

Children with bacterial meningitis have the same rates of positive blood cultures regardless of whether they are treated with preadmission ABX.³⁹ Although meningitis and AOM occur together in ~2 of 1000 children, it has not been demonstrated that routine use of ABX treatment for nonsevere AOM is more effective than selective use for prevention of mastoiditis or meningitis.

We did not observe AOM-related serious adverse events in either the ABX or WW groups, but we did not have sufficient power to document an altered risk of such events. We provided each parent/guardian with education describing the complications and incidence of mastoiditis before enrollment (see "Methods"). We recommend using this approach when discussing the WW option with parents of children with nonsevere AOM.

Parents of children <2 years old randomized to immediate ABX were more likely to perceive their child as "much better" or "better" at day 12, compared with parents of children randomized to WW. Also, compared with subjects who had not received recent ABX, subjects who had received ABX within 30 days before enrollment were more than twice as likely to fail treatment, regardless of whether they were given immediate ABX or followed with a WW approach. The failure rate for children in the WW group who had recently received ABX was 52% (14 of 27).

CONCLUSIONS

Our results suggest that some children with nonsevere AOM may be observed with WW as long as they maintain nonsevere status and are kept comfortable with appropriate symptom management. Under these conditions, WW seems to be an alternative that is acceptable to parents, reduces the number and cost of ABX prescriptions, and reduces the percent of multidrug-resistant bacteria colonizing the nasopharynx of children after an episode of AOM. Key factors in implementing a WW strategy were (a) a method to classify AOM severity, (b) parent education regarding the risks and benefits of treatment, (c) management of AOM symptoms, (d) access to follow-up care, and (e) use of an effective ABX regimen if needed.

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Nonsevere Acute Otitis Media: A Clinical Trial Comparing Outcomes of Watchful Waiting Versus Immediate Antibiotic Treatment
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