ARTICLE

Delayed Prescription May Reduce the Use of Antibiotics for Acute Otitis Media

A Prospective Observational Study in Primary Care

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Objectives: To evaluate the applicability and the effectiveness of practice guidelines based on a wait-and-see strategy for children with acute otitis media (AOM).

Population: Children from 1 to 14 years old having AOM who were referred to primary care pediatric practices.

Study Design: Prospective observational study.

Main Outcome Measure: Proportion of children having a diagnosis of AOM and eligible for symptomatic treatment who, at 72 hours from enrollment, recovered from their symptoms (fever and earache) without receiving antibiotic treatment.

Results: One hundred sixty-nine pediatricians participated in the study and enrolled 1672 children. One thousand two hundred seventy-seven children were included in the analysis. One hundred seventy-eight children received antibiotic treatment at first contact according to the practice guidelines criteria (presence of otorrhea or recurrent AOM). Of the 1099 children who were eligible for symptomatic treatment only, 743 (67.6%) recovered without antibiotic treatment at 3 days and 716 (65.1%) at 30 days. No complications were observed. Coexistence of a high fever (temperature ≥38.4°C) and red and bulging tympanic membrane as well as male sex were significantly associated with antibiotic use.

Conclusions: Practice guidelines based on a wait-and-see strategy for children with AOM are applicable and effective in primary care. This strategy was able to avoid the administration of antibiotic treatment in 2 of 3 children.

Arch Pediatr Adolesc Med. 2005;159:679-684

THE PRESCRIPTION OF ANTIbiotics is a major issue in medicine today[1]: increasing bacterial resistance to antimicrobial drugs should lead the medical profession to a more rational use of antibiotics,[2,3] but this is more easily preached than actually done. Acute otitis media (AOM) is one of the most common diseases to be treated with antimicrobials in the pediatric population, accounting for 25% to 50% of the oral antibiotics prescribed annually,[4,5] despite conflicting evidence on the magnitude of their efficacy in treating symptoms and preventing complications.[6,7] Evidence from systematic reviews suggests that the benefits of antibiotic treatment (ABT) are (1) limited since between 7 and 20 children must be treated with antibacterial agents for 1 child to derive benefit[8-11] and (2) counterbalanced by the adverse effects of ABT,[9] the higher costs of treatment, the increasing drug resistance at the community level,[12] and last, but not least, the missed opportunity of taking an educative approach that involves the family in informed decision making.[13]

A promising approach for reducing antibiotic use is delayed prescription. This approach ("wait-and-see") has been proposed by the Dutch College of General Practitioners[14] and recently adopted by the Cincinnati Pediatric Research Group in the United States.[15] The effectiveness of this approach was demonstrated in a randomized controlled trial carried out in England.[16]

In Italy, the Associazione Culturale Pediatri (ACP), a professional association of practicing pediatricians (PPs),[17] developed practice guidelines (PGs) for the treatment of AOM, which are similar to the PGs developed by the Dutch[18] in that they substantially restrict the indications for ABT. However, implementation of PGs based on their dissemination alone is usually ineffective. An effective strategy is to make PGs more user friendly and relevant by analyzing factors influencing physicians' behaviors.[19] Also, the direct in-

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Group Information: A list of the members of the Italian Study Group on Acute Otitis Media appears on page 683.

Table 1. Indications for Treatment of AOM According to the ACP PGs

Indications	Antibiotic Treatment
At onset: presence of otorrhea and/or history of recurrent otitis media	Amoxicillin, 75-90 mg/kg per day, in 3 doses for no fewer than 5 d
At onset: all other children aged >12 mo	Acetaminophen, 10-15 mg/kg per dose, 4 times a day plus nose washes with saline solution
At 48-72 h: persisting symptoms or otorrhea	Amoxicillin, 75-90 mg/kg per day, in 3 doses for no fewer than 5 d

Abbreviations: ACP, Associazione Culturale Pediatri; AOM, acute otitis media; PGs, practice guidelines.

volvement of the prescribers in evaluating the applicability and effectiveness of PGs in their own practice[20,21] is a key factor for their successful implementation. We designed and carried out a large collaborative study to evaluate the applicability and the effectiveness of the ACP PGs for AOM in the primary care setting.

METHODS

STUDY PARTICIPANTS

Of the 35 local ACP chapters, 13 were able to include the study in their research program, for a total of 169 PPs, that is, more than 90% of the chapters' members. The 13 groups were representative of the whole country, with 5 groups (75 PPs) from northern Italy, 3 from central Italy (35 PPs), and 5 from southern Italy (59 PPs). Italy's National Health System ensures pediatric care free at the point of provision to all children. Each PP provides care to a maximum of 880 children aged from 0 to 14 years.[17]

STUDY PROTOCOL

The study protocol was finalized after an initial draft, developed by an ad hoc working group including PPs and epidemiologists. The study protocol was circulated among and ultimately approved by all participating groups. Approval by an ethics committee (Verona Health Authority) based on European Union norms of Good Clinical Practice[22] and World Medical Association's Declaration on Ethics of Biomedical research[23] was obtained.

According to the study protocol, within a 2-month period (February 1-March 31, 2001) each PP was to enroll up to a maximum of 11 consecutive children aged from 1 to 14 years diagnosed as having AOM who presented within 24 to 36 hours from onset of symptoms. The following definition of AOM was adopted[16]: the presence of fever (temperature of >38°C rectal or 37.5°C axillar as reported by parents) and/or earache and/or irritability plus 1 or more of the following findings: marked redness, bulging, dullness, and perforation of the tympanic membrane. Since the study was aimed at evaluating pragmatic effectiveness, definition criteria were identified that were similar to the conditions of practice in Italy and in other countries (such as the United Kingdom)[16] where diagnosis of AOM is made on the basis of symptoms and characteristics of the tympanic membrane.

To explore whether a specific combination of signs and symptoms was predictive of antibiotic use, the following definition of "severe AOM" was adopted: coexistence of fever (a temperature of ≥38.4°C) and a red and bulging tympanic membrane. This definition was based on a study showing an association between these features and *Streptococcus pneumoniae* infection.[24]

The following exclusion criteria were adopted: age younger than 1 year, earlier antibiotic administration, severe concomitant acute disease (asthma, bronchitis, bronchopneumonia), Down syndrome, cystic fibrosis, immunodeficiency, and craniofacial malformations. Informed consent was obtained from the parents of all enrolled children.

Antibiotic treatment (amoxicillin, 75-90 mg/kg per day in 3 doses for no fewer than 5 days) was indicated in the presence of otorrhea or a history of recurrent AOM (defined as ≥3 attacks in 6 months or ≥4 in 12 months). In all other cases, children were given symptomatic treatment only (acetaminophen, 10-15 mg/kg per dose, 4 times a day, and nose washes with a saline solution) (**Table 1**). Amoxicillin was chosen based on evidence from controlled clinical trials and also considering its safety and cost.[7,25,26]

The protocol developed for our study (Table 1) differed from the Dutch experience[18] in that the period of observation was 48 to 72 hours, instead of 72 hours. Another main difference with respect to the Dutch approach was the indication for ABT in children with a history of recurrent AOM or with otorrhea.[27] These modifications were suggested by the PPs to better reflect everyday practice.

FOLLOW-UP

Follow-up was ensured to all cases by a telephone call at 48 to 72 hours after first contact. In children who at the time of enrollment were prescribed symptomatic treatment, antibiotics were given only if fever or earache persisted and in any case after a direct physical examination. A follow-up visit 30 days after first contact was also arranged. Episodes of AOM during the follow-up period were defined as relapses if occurring within the first 10 days after the resolution of symptoms of the first episode and as recurrent episodes if occurring later. The exact timing and motivations for prescribing antibiotics beyond the indications provided by the protocol, as well as compliance with treatment, were recorded.

OUTCOME MEASURES

The main outcome measure was the proportion of children having a diagnosis of AOM and eligible for symptomatic treatment who, at 72 hours from enrollment, recovered from their symptoms (fever and earache) without receiving ABT. A secondary outcome measure was the proportion of children having a diagnosis of AOM who were eligible for symptomatic treatment only, who, at the follow-up visit at 30 days, had not received ABT. An additional outcome measure was the proportion of children receiving ABT to whom amoxicillin was prescribed.

QUALITY CONTROL AND DATA ANALYSIS

A record card was completed by all participating pediatricians. A quality score, based on completeness of information and consistency with the inclusion criteria, was assigned to all cards by a reviewer (F.M.). Incomplete and inconsistent record cards were excluded from the analysis. Outcome measures were analyzed for enrollment variables (sex and age, mother's educational level, exposure to passive smoking, otoscopy features, and previous episodes of AOM) using the χ^2 test. To identify factors associated with a poor outcome and as a consequence patients who may be more likely to benefit from antibiotic use, a multivariate analysis (logistic regression, forward stepwise method) was performed using the SPSS 9.0

statistical software (SPSS Inc, Chicago, Ill). Results are presented as odds ratio (OR) and 95% confidence interval (CI).

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

A total of 1672 cases of AOM were reported by 169 PPs. Although the enrollment period was 2 months, the time needed to enroll the first 11 consecutive patients was much shorter, with more than 75% of the cases enrolled within the first 15 working days. Of these 1672 cases, 395 were not considered in the analysis for the following reasons: (1) at first contact more than 36 hours had passed from the onset of symptoms (n=165); (2) information on the time of onset was lacking (n=134); (3) failure to meet the diagnostic criteria for AOM (n=42); (4) presence of exclusion criteria (n=43); and (5) concomitant illness that required ABT regardless of the presence of AOM (n=11). One thousand two hundred seventy-seven children were included in the analysis. The general characteristics and the clinical and otoscopic features of this population are listed in **Table 2**. No relevant differences in the general characteristics as well as in the clinical and otoscopic features were observed in children younger than 3 years and in the 395 patients excluded from the analysis, with respect to the general population.

Table 2. General Characteristics and Clinical and Otoscopic Features of 1277 Children With AOM

General Characteristics	Value
Age, mean (range), y	4.8 (1.0-13.9)
Male sex, %	51
Mother's educational level, %	
Primary	40
Secondary and/or university	60
Family history of AOM, %	31
No. of previous episodes of AOM (mean No. in the previous 12 mo), %	60 (1.5)
Antibiotic treatment for AOM in the previous month, %	11
Clinical features, %	
Fever (mean temperature), °C	52 (38.3)
Children with temperature ≥38.4°C	47
Earache	96
Irritability	48
Rhinitis	59
Cough	36
Otorrhea	11
Otoscopic features, %	
Redness	84
Bulging	52
Luminous reflex, %	
Absent	54
Opaque	30
Perforation	12
Bubble or water/air levels, %	2
Concomitant presence of fever with a temperature of ≥38.4°C and redness and bulging tympanic membrane, %	11

Abbreviation: AOM, acute otitis media.

TREATMENT

SYMPTOMATIC TREATMENT

Acetaminophen was prescribed in 93% of the cases and nose washes with a saline solution was prescribed in 73% of the cases. Three hundred thirty-two children (26%) received an additional symptomatic treatment (anesthetic eardrops, vasoconstrictor nose drops, and oral antihistamines); 125 children (9.8%) were given a different nonsteroidal anti-inflammatory drug. In 86 cases, the nonsteroidal anti-inflammatory drug was given together with the acetaminophen.

ANTIBIOTIC TREATMENT

Of the 1277 children meeting the enrollment criteria for the study, 178 (13.9%) met the requisites for ABT according to the PGs, that is, they had otorrhea (n=112, 8.8%), a history of recurrent AOM (n=52, 4.1%), or both (n=14, 1.1%) while 1099 children (86.1%) were eligible for symptomatic treatment alone (**Figure**). Of these, 84 patients (7.6%) received ABT at first contact; 82, antibiotics within 48 hours; and 190, between 48 and 72 hours. At 30 days, an additional 27 patients had received ABT for a relapse; 42 had received ABT for a new episode of AOM. Overall, of 1099 children eligible for symptomatic treatment alone, a total of 356 patients did receive ABT within the first 72 hours; 27 suffered from a relapse and were given ABT later, for a total of 383, leaving a total of 716 (65.1%) of 1099 children who recovered without receiving ABT.

The percentage of success at 72 hours and at 30 days does not differ if children younger than 3 years are considered (65% and 62%, respectively). Nor does it differ if data regarding the 395 patients who were excluded from the analysis because of incomplete records or noncompliance with the study protocol are included (66% and 63%, respectively).

There were no complications, including the 1 child who was admitted to hospital owing to concurrent disease (pneumonia). Two hundred eighty-nine (81.2%) of 356 children who were treated with an antibiotic were prescribed amoxicillin, in accord with the ACP PGs. In the remaining cases a second- or third-generation cephalosporin (cefaclor, cefalexine) or a macrolide (clarithromycin, azithromycin) was administered. The reasons given for not using amoxicillin were previous unsuccessful experiences with amoxicillin or the patient had an allergic reaction to penicillin.

REASONS FOR USING ABT

Antibiotic treatment beyond the PGs criteria was motivated by the severity of the clinical picture (47 of 84 children who were given ABT at first contact) and by persisting symptoms (241 of 272 children who were given ABT after first contact and before 72 hours) (Figure). In 44 cases parents explicitly requested ABT either because they were concerned about the condition of the child or because of contingent situations that made a wait-

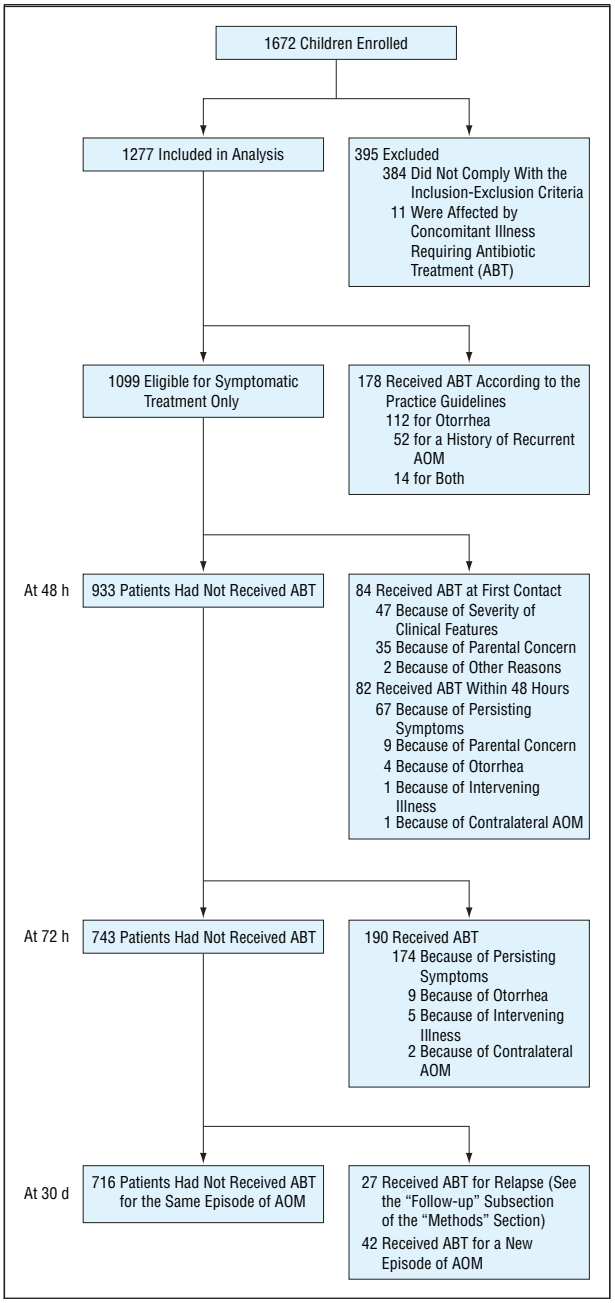

Figure. Flowsheet of study on acute otitis media (AOM) in children.

and-see approach infeasible (eg, planned travel). In 13 cases antibiotics were prescribed for the appearance of otorrhea, in 6 cases for intervening illness, and in 2 cases the decision was made by the hospital emergency department where children were directly brought by their family.

FACTORS ASSOCIATED WITH USE OF ABT

Among the 1099 cases eligible for the wait-and-see approach, 121 (11%) had simultaneous presence of fever with a temperature of ≥38.4°C plus a red and bulging tympanic membrane. Among children showing this combination of signs and symptoms, 67 (55%) of 121 children were prescribed the antibiotic at first contact or within the first 72 hours compared with 284 (29%) of 978 children in the remaining group, the difference being statistically significant (relative risk, 1.91; 95% CI, 1.58-2.30). Univariate analysis indicated that, besides the clinical score, the other variable that had a statistically significant influence on the choice of whether to use the antibiotic was the male sex of the patient (relative risk, 1.24; 95% CI, 1.04-1.49). In the multivariate analysis the adjusted odds ratio for a picture of severe AOM and male sex were 3.47 (95% CI, 2.19-5.50) and 1.53 (95% CI, 1.11-2.1), respectively (**Table 3**).

Table 3. Variables Associated With Antibiotic Use in 1099 Children 1 to 14 Years with AOM Eligible for Symptomatic Treatment Alone

Variables Included in the Multivariate Analysis	OR (95% CI)
Simultaneous presence of fever with a temperature ≥38.4°C and a red and bulging tympanic membrane	3.47 (2.19-5.5)
Male sex	1.53 (1.11-2.10)
Child aged ≤3 y	1.4 (0.97-2.03)
Mother's educational level primary or secondary alone	0.96 (0.69-1.34)
Mother smoking	1.18 (0.76-1.83)
Father smoking	1.01 (0.70-1.45)
Family history of AOM	0.89 (0.62-1.26)
Antibiotic treatment for AOM in the previous month	1.18 (0.69-2.02)
≥3 Previous episodes of AOM	0.90 (0.62-1.3)
Attendance at nursery school (only for preschool-aged children)	1.12 (0.74-1.69)

Abbreviations: AOM, acute otitis media; CI, confidence interval; OR, odds ratio.

COMMENT

We carried out a prospective observational study to assess the applicability on a large scale of PGs for AOM in children based on a wait-and-see approach.[8-11] This approach was applied at first contact in more than 90% of the eligible cases and ultimately avoided the use of ABT in 2 of 3 children. Among those treated with antibiotics most cases (8 of 10) were prescribed amoxicillin although amoxicillin is normally prescribed in less than half of the cases of AOM in Italy[5] and other European countries.[28] In our study, about 20% of children did not show improvement within 48 to 72 hours from first contact, which is consistent with the result of a recent meta-analysis by Takata et al,[10] in which 19% of children untreated with antibiotic did not show improvement 1 to 7 days after onset of symptoms.

Based on our findings as well as on other studies on criteria for antibacterial treatment of AOM,[15,29] we believe that it would be difficult to achieve a further reduction in antibiotic use. In a Dutch study on pediatric AOM that was also designed to investigate the reasons for failed compliance with PGs, the percentage of children treated with antibiotics at first contact was 19%.[30] The lower percentage reported in our study (8.2%) can be explained by the fact that the follow-up visit was planned within a

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shorter period and by the exclusion of children younger than 1 year.

The presentation characterized by a high fever plus a red and bulging tympanic membrane was present in about 10% of our patients. In these cases the use of an antibiotic was more frequent owing to the PPs' perception of a greater severity. Bearing in mind that sex does not affect the course of AOM, the greater use of ABT in male patients is difficult to explain, unless one considers gender-biased concerns in parents.

None of our children suffered from any serious complication, such as mastoiditis, during the observation period. The debate about whether a wait-and-see attitude in cases of AOM leads to a higher incidence of mastoiditis was recently reopened by the publication of 2 articles with conflicting results.[31,32]

The study presents a few limitations. The failure of some PPs to comply with the inclusion criteria or to correctly complete the recording form led to 395 cases being excluded from our analysis. We assessed the comparability of these cases with those included and we found no statistical and clinical differences between the 2 groups in terms of baseline characteristics and percentage of success with the wait-and-see approach.

In our study, the diagnosis of AOM was based on clinical symptoms and abnormality of the tympanic mem-

brane. This was based on what is normally done in clinical practice and followed the indications from studies carried out in primary care settings.[16] The diagnostic criteria used do not exclude that children affected by otitis media with effusion were included in the study. Some authors believe that a true diagnosis of AOM can only be made when a pneumatic otoscope is used.[7] However, a pneumatic otoscope is not routinely used in Europe, at least at the primary care level. Furthermore, overdiagnosis of AOM and unnecessary antimicrobial use are common everywhere,[33,34] so that a wait-and-see approach is useful also to avoid unnecessary antibiotic use in cases in which diagnosis is uncertain, such as in otitis media with effusion.

The study did exclude an assessment of the severity of earache that the American Academy of Pediatrics' guidelines[7] suggest as adjunctive criterion for antibiotic use nor did our study include an assessment of parents' satisfaction that was shown to be good in previous studies.[15]

We cannot be sure that all participating pediatricians enrolled only and exclusively the first 11 consecutive patients, but the fact that most PPs completed the enrollment within the first 15 working days limits the possible dimension of a selection bias, particularly if we consider that a PP in Italy examines an average of 6 patients with AOM per working week[5] and that this figure can be much smaller for younger professionals with much less than 880 children in their care. The high number of PPs participating in the study, their countrywide distribution, and the characteristics of the children studied, which do reflect those of the general population,[35] make the findings of our study largely representative of everyday pediatric practice, at least in Italy.

Although the success of the wait-and-see strategy adopted may not be sufficient to make the ACP PGs on AOM a common practice in Italy, we think that the likelihood of their widespread application will be greatly increased, particularly because of the peer-to-peer nature of the experience. The study strengthened our belief that involving practicing physicians in a large observational study represents an effective implementation strategy for PGs.

Accepted for Publication: February 13, 2004.
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Additional Information: Approval by an Ethics Committee (Verona Health Authority) based on European Union norms of Good Clinical Practice and World Medical Association Declaration on Ethics of Biomedical research was obtained to conduct this study.

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