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# Management of Acute Otitis Media: Efficacy of Naturopathic Eardrops vs Antibiotic Treatment

## Tratamiento de la Otitis Media: Eficacia de la Gotas Naturopáticas vs Tratamiento con Antibióticos

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## ABSTRACT

**Objective*:*** To compare the efficacy of naturopathic eardrops with amoxicillin in the management of ear pain associated with acute otitis media. **Design*:*** A randomized, double-blind design was used. **Patients and Methods**: Primary pediatric community clinics. Two hundred children aged 5 to 18 years with ear pain and clinical ear drum findings of acute otitis media were treated with naturopathic ear drops or oral amoxicillin. Ear pain was assessed over three days using a visual analog scale. The primary outcome measure was the reduction in mean score for pain, the secondary outcome measure was the presence of middle ear effusion on tympanometry during a 14-week follow-up. **Results*:*** Although a reduction in pain score was observed in both groups, it was significantly greater in the children treated with the naturopathic eardrops ($p<0.0001$). There was no statistically significant difference between the groups in the clinical resolution of acute otitis media or the presence of middle ear effusion (5% in both). **Conclusions*:*** The naturopathic eardrops solution used in the present study is at least as effective as amoxicillin in the treatment of middle ear effusion, and is significantly better for the management of ear pain associated with acute otitis media.

**Key Words**: Acute otitis media, Antibiotics, Ear pain.

## RESUMEN

**Objetivo**: Comparar la eficacia de las gotas óticas naturales con amoxicilina en el tratamiento del dolor ótico asociado con otitis media aguda. **Diseño**: Estudio aleatorio doble ciego. **Pacientes y Métodos**: Clínica pediátrica de Atención Primaria. 200 niños de 5 a 18 años de edad que presentaban dolor ótico y otitis media aguda fueron tratados con gotas óticas naturopáticas o amoxicilina oral. El dolor de oído fue valorado durante tres días utilizando una escala visual análoga. El primer desenlace clínico fue la reducción del dolor y el segundo desenlace fue la presencia de efusión en el oído medio a través de timpanometría durante 14 semanas de seguimiento. **Resultados**: Aunque fue observada una reducción del dolor en ambos grupos, la disminución fue más grande en los niños tratados con las gotas óticas naturopáticas ($p<0.0001$). Estadísticamente no existió diferencia significativa entre los grupos en cuanto a su evaluación clínica o bien en cuanto a la presencia de efusión en el oído medio (5% en ambos). **Conclusiones**: La solución de gotas naturopáticas usadas en el presente estudio es al menos tan efectiva como la amoxicilina en el tratamiento del dolor ótico con otitis media aguda.

**Palabras clave**: Otitis media agua, Antibióticos, Dolor ótico.

## Introduction

The reported incidence of acute otitis media (AOM) has increased 200% in the past two decades, making AOM one of the most common clinical conditions diagnosed by family physicians[1]. Ear pain, one of the major symptoms of the disorder [1,2], may result from receptor stimulation via stretch or pressure mechanisms or from the release of toxic products of inflammation [3,4]. Due to its subjective nature and relationship to many different variables, pain is usually best measured by self-report.Children, however, may find it difficult to verbally describe their pain experience, and probably do better with external scales. The Observational Scale of Behavioral Distress (Pain-O-Meter) has been found to serve as a good measure of pain in young children [5,6] with good -

agreement between its face and color scales [7]. The overall goals of treatment of AOM are the reduction of fever, elimination of ear pain and discomfort, prevention of secondary complications, and elimination of middle ear effusion (MEE) which may have detrimental effects on learning and performance [8]. The use of antibiotics to treat uncomplicated AOM is controversial, not only because of the risk of the emergence and spread of antimicrobial-resistant bacteria but also because the benefits have not been demonstrated [9,10]. In a recent review of ten trials eligible based on design and patient-relevant outcomes, Glasziou and collaborators [11], reported that antibiotics provide a small benefit and that most cases will resolve spontaneously. They also comment that this benefit must be weighed against the possible adverse reactions.

Herbal medications are becoming increasingly popular, and a growing number of herbal products are currently available for use in conjunction with or instead of conventional agents [12-14]. Our recently published study reported the effectiveness of naturopathic extracts in the management of ear pain associated with AOM [15]. Our results indicated that concomitant antibiotic treatment was apparently not contributory, but the lack of a comparison group treated with antibiotics alone precluded definitive conclusions. The present study was designed to clarify this issue.

## Patients and Methods

A double-blind randomized design was used. The study sample comprised 200 children aged 5 to 18 years who visited the ambulatory community clinics of the General Health Services, the major health management organization in Israel, with a complaint of ear pain associated with AOM. The diagnosis of AOM was based on the presence of ear pain; fever at least 35.5ºC; and a finding of middle ear effusion, in addition to at least one other indicator of acute inflammation, namely, marked redness or distinct fullness or bulging of the tympanic membrane.

The presence of middle-ear effusion was determined by the following findings: decreased or absent tympanic membrane motility on pneumatic otoscopy; "C" curve on the tympanogram; visible bubbles or air fluid level behind the tympanic membrane; or opacification of the tympanic membrane for reasons other than scarring. All tympanograms were performed by a specialized nurse in charge of this ancillary service, blinded to the initial diagnosis.

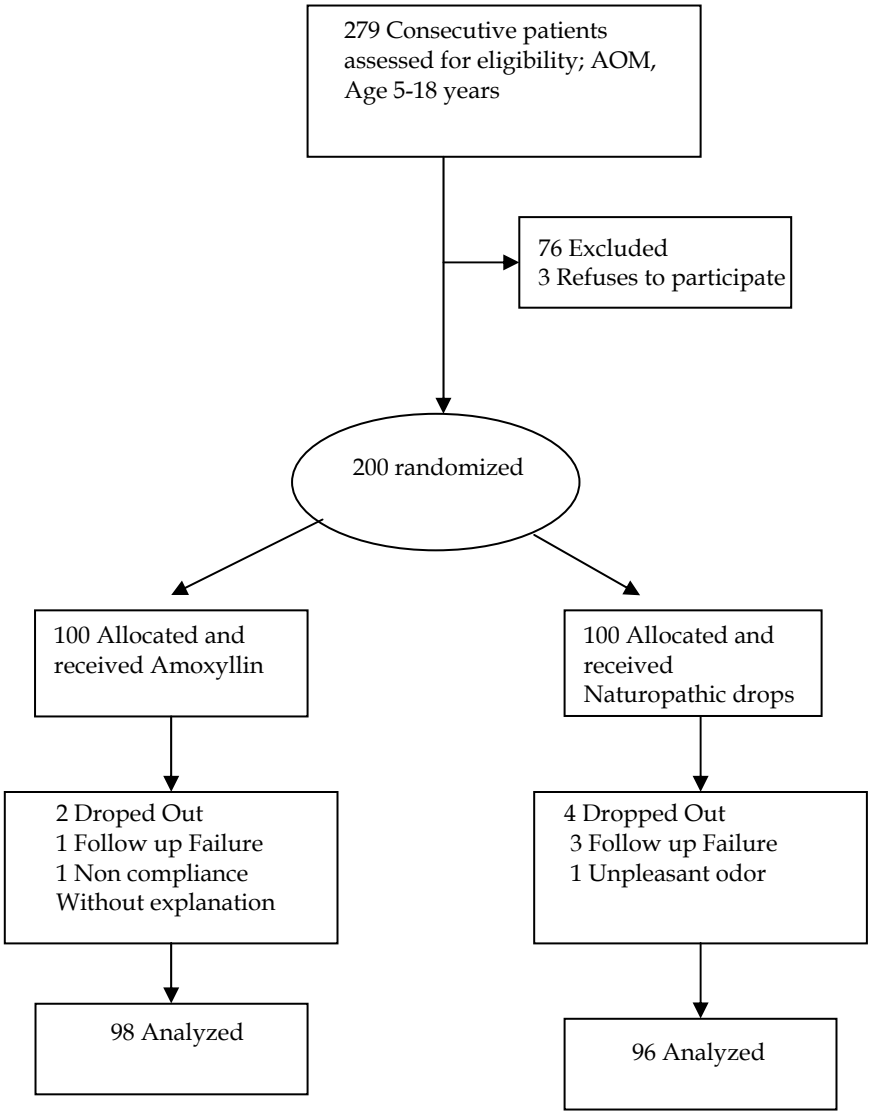
Exclusion criteria were as follows: receipt of any kind of eardrops or analgesic within 48 hours preceding the initial examination; known allergy to herbal medication, amethocaine, phenazone, glycerin, or acetaminophen; presence of otorrhea, ear drum perforation, or ventilation tubes; known immunodeficiency; otologic or craniofacial malformations, complications of treated or untreated ear disease (including AOM) in the past 2 weeks; inability to use a visual analog scale; and concomitant diseases (infection disease as upper respiratory tract illnesses and cough, diarrhea and vomiting, rash, infected skin lesions, eye discharge and conjunctivitis, etc.).

For the process of patients' eligibility, randomization, allocation, and analysis, see figure 1 (Flow diagram of subject progress through the phases of the trial). Informed consent was obtained from one of the parents of all of the children eligible to participate. The study was approved by the Committee for Ethics in Human Subjects Research (Helsinki Committee).

*Sample size*

To calculate the necessary sample size for the study, we assumed that both treatments will be effective at least in the 90% of the cases [14]. Under this assumption, the needed sample size for each of the two groups, if we want to estimated the relative risk to within 10% of the true value (which is to believe is close to 1, that is no differences between the treatments) and a 95% confidence level, is 77 [16]. We added 30% to this number in the event of partial or missing data. Thus the final sample size was established as 100 for each group (total of 200 subjects).

**Figure I**




Flow diagram of subject progress through the phases of the trial. See text for details.

*Study design*

A single physician (M.S.) made the initial evaluation of all the patients, recorded all the initial data, decided the inclusion of subjects, proposed to them the inclusion in the trial, explained the research program including how to use the faces/color scale, and then recorded the first corresponding numerical response. Only children with a score of 3 or more at the time of diagnosis were included in the study and obtain the informed consent. After the decision of the inclusion this physician was blind to treatment assignment and trial follow up. After the enrollment, the nurse using a computer-numbered randomization assigned the children to receive either naturopathic remedy 5 drops 3 times daily and placebo syrup, 3 doses daily (group 1) or amoxicillin syrup 80 mg/kg/d (maximum 500 mg/dose) divided into 3 doses and placebo eardrops, in 3 doses daily. All ear drops were placed in identical bottles. Treatment was started by a nurse who received a specific training for the trial, in all the cases. The same nurse instructed again the patients and or the parents how to utilize the Pain-O-Meter (see instruments) and to register the data.

Parents and or children were assigned for a visit to the physician immediately at the end of the follow up. In order to assure a high quality registry, the nurse made phone call communications at the 3 days follow up time points, controlled the patient registry and managed a parallel registry. The naturopathic remedy tested (Otitis Naturopathic Eardrops, Nakar Pharmaceuticals, Israel) contains an abstract of the herbs Calendula officinalis flores (28%), Hypericum perforatum herba tota (30%), and Verbascum thapsus flores (25%) in olive oil in additin to Allium sativum in 0.05% in olive oil (10%), Lavandula officinalis (5%), and tocopherol acetate (2%). Other medications such different ear drops or analgesics (acetaminophen, ibuprofen, etc,) were not permitted during the study.

*Instruments and Procedure*

Ear pain was assessed by the Pain-O-Meter [14]. One side of the instrument consists of a linear numbered scale, from 1 (no pain) to 10 (worst possible pain), and the reverse side contains a scale of 5 facial expressions ranging from a broad smile (no pain) to a sad and crying face (worst possible pain), and a corresponding color scale ranging from blue to dark red. The child is asked to describe his pain by placing a pointer on the appropriate face and color, and then the corresponding number on the numerical scale. The Pain-O-Meter used in this study was previously reported to be "simple to use and readily understood by the children", and showed a realistic distribution of scores with respect to other types of pain being measured [17]. After treatment allocation, each child then received one bottle of medication (naturopathic drops or amoxycillin syrup) and one bottle of placebo (either syrup or eardrops). The nurse administered the first treatment. The contents of the bottles were unknown to both the subjects and the nurse. The parents were instructed to administer the medication twice more that day (every 8 hours) and then 3 doses every 8 hours for another 2 days. Pain was measured at the following time points after diagnosis (TAD): at 15 and 30 minutes ($T_{A15}$, $T_{A30}$) after treatment with the help of the nurse; before the first dose in the morning ($T_{BO}$) and 15 and 30 minutes after the first dose ($T_{B15}$, $T_{B30}$) on day 2; and before the first dose in the morning and 15 and 30 minutes after the first dose on day 3 ($T_{C15}$, $T_{C30}$). In addition, the physician interviewed the parents by phone, 24 and 48 hours after these time points. Treatment was considered successful if the child or the parents reported a reduction in ear pain after 48 hours. If clinically significant otalgia persisted after 3 days, either alone or associated with fever or other signs and symptoms of infection, the child was reevaluated to determine the need for modifying treatment.

*Statistical analysis*

The $\chi^2$ and Fisher exact tests were used to compare categorical variables between the groups, and analysis of variance (ANOVA) and paired t-test were used for continuous variables. A multivariate stepwise linear regression model was fitted to the data using the change in the level of pain from pretreatment (TAO) to final pain assessment ($T_{C30}$) as the dependent variable and the following as independent variables: 1) group; 2) severity mild; 3) severity moderate; 4) severity severe; 5) temperature; 6) age (years); 7) medical history; 8) more than 1 child in household; 10) day-care attendance; 11) tobacco use at home; 12) major symptoms; 13) related symptoms; and 14) number of all other symptoms . Statistical significance was defined as $p < .05$. To evaluate the influence of the variable time (alone and interaction with the variable group) on the variance on the level of pain, we used repeated measurements analysis at three time points: before treatment, $T_{B30}$, $T_{C30}$.

**RESULTS**

Six children were dropped from the study, two from the amoxicillin group and four from naturopathic group because of noncompliance with the medication (one child complained of the smell of the eardrops), failure of the treating physician to reach the parent by telephone, or failure to complete the treatment regimen. All the 98 children in the amoxicillin group and the 96 children in the naturopathic group completed the follow up at 30 mi--

nutes of day 3. There were no between-group differences in any of the background variables, except for the number of children at home (Table 1). In both groups, there were more children with bilateral than with unilateral AOM. The children treated with naturopathic eardrops had a higher initial AOM severity score than those treated with amoxicillin (Table 1).

**Table I**

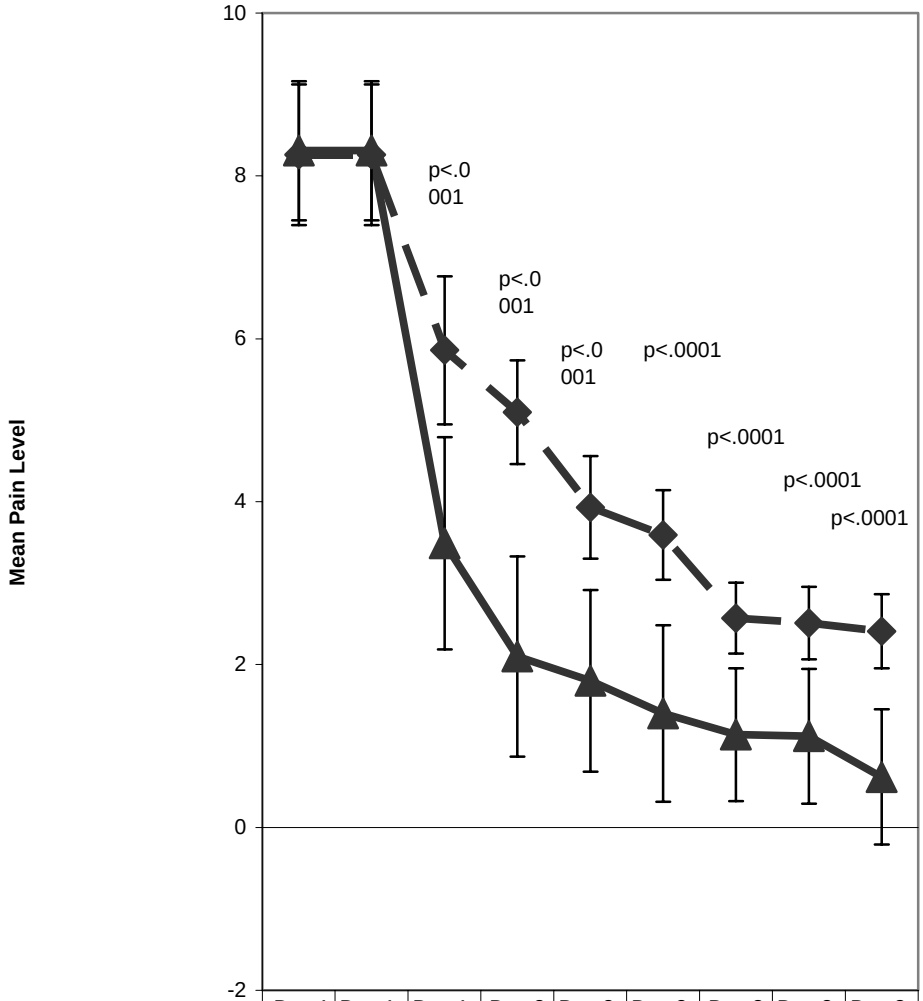
**Baseline sociodemographic characteristics, medical history, and otitis media symptoms by treatment group**

| Variable | Amoxycillin n=98 (%) | Naturopathic drops n=96 (%) | p |
|---|---|---|---|
| **Demographics** | | | |
| Age 5-12 years | 85 (86.7) | 82 (85.4) | NS |
| Age 13-18 years | 13 (13.3) | 14 (14.6) | NS |
| Male | 62 (63.3) | 61 (63.5) | NS |
| Female | 36 (36.7) | 35 (36.5) | NS |
| **Home environment** | 85 (86.7) | 87 (90.6) | NS |
| Two-parent home | 66 (67.3%) | 81 (84.4) | <.0001 |
| More than 1 child at home | 88 (89.7) | 86 (89.6) | NS |
| Day care attendance | 21 (21.4) | 19 (19.7) | NS |
| Smoking at home | | | |
| **Medical history** | 76 (77.5) | 82 (85.4) | NS |
| Good health usually | 14 (14.2) | 17 (17.7) | NS |
| History of allergy | 4 (4.1) | 3 (3.1) | NS |
| History of asthma | | | |
| **Bilateral infection** | 66 (67.3) | 78 (81.3) | <.0001 |
| **AOM-specific sign** | 64 (66.7) | 81 (82.7) | <.0001 |
| TM redness | 41 (41.8) | 45 (46.9) | NS |
| Facial pain | 51 (52) | 54 (56.3) | NS |
| Fullness or bulging TM | 28 (28.6) | 21 (21.9) | NS |
| Air-fluid level behind TM present | 41 (41.8) | 45 (46.9) | NS |
| Tympanogram & acoustic reflex | 78 (67.3) | 78 (81.3) | NS |
| Fever 37.5-38.4$^{o}$C | 20 (32.7) | 18 (18.8) | NS |
| Fever 38.5-41.0$^{o}$C | | | |
| **AOM severity score** | 22 (22.4) | 5 (5.2) | <.0001 |
| Mild | 37 (37.8) | 34 (35.4) | <.0001 |
| Moderate | 39 (39.8) | 57 (59.4) | <.0001 |
| Severe | | | |

Note: All values are n(%). TM – tympanic membrane

The severity of the pain experienced by the patients was graded on a scale of 1 to 10. Mean pain score was evaluated from the score on the morning of each of the three days of the study, before treatment. A 70% or more reduction in pain was noted in both groups. (Fig. II)

**Figure II**




| | Day 1 before Treat | Day 1-15 mints | Day 1-30 mints | Day 2 before Treat | Day 2-15 mints | Day 2-30 mints | Day 3 before Treat | Day 3-15 mints | Day 3-30 mints |
|---|---|---|---|---|---|---|---|---|---|
| Amoxycillin | 8.26 | 8.26 | 5.86 | 5.1 | 3.93 | 3.59 | 2.57 | 2.51 | 2.41 |
| Naturopathic | 8.31 | 8.31 | 3.49 | 2.1 | 1.8 | 1.4 | 1.14 | 1.12 | 0.62 |

Level of pain (score 0 to 10) in naturopathic and amoxicillin groups by time of treatment.

Although the reduction was greater in the naturopathic than the amoxicillin group. Mean ear pain score at diagnosis was 8.31 (CI: 7.96-8.66) in the naturopathic group and 8.26 (CI: 7.91-8.53) in the amoxicillin group; corresponding scores on day 3 were 0.62 (reduction of 92.5%, 95% CI 0.43-0.38), and 2.41 (reduction of 70.8%; 95% CI: 2.05-2.76). This difference was statistically significant (p<.001).

To clarify the reasons for the difference in pain reduction between the groups, a multivariate stepwise linear regression analysis was performed. The variables *severity of symptoms at diagnosis* (TAO) and *group* (treatment) were found to have a significant effect on the reduction in pain between pretreatment to last follow-up at 30 -

minutes of day 3 (Table II), after controlling for age, temperature, medical history, day-care attendance and tobacco use at home (rejected due to lack of significance), and other symptoms (cough, rhinorrhea, sore throat, headache, postnasal drip, facial pain, lymphadenopathy, malaise and sleeping problems) which could explain the influence of pain from sites other than the ear.

**Table II**

**Stepwise linear regression model for change in pain level (score from 0 to 10) between moxicillin t to last follow-up**

| Independent variables | Beta | Significance | $R^2$ |
|---|---|---|---|
| Intercept | 5.829 | 0.0001 | - |
| Group (2) | 1.913 | 0.0001 | 0.145 |
| Severity: Mild (3) | Rejected (1) | Rejected (1) | - |
| Severity: Moderate (4) | 1.021 | 0.001 | 0.055 |
| Severity: Severe (5) | 1.364 | 0.0001 | 0.059 |
| moxicillin (6) | Rejected (1) | Rejected (1) | - |
| Age (years) | Rejected (1) | Rejected (1) | - |
| Medical History (7) | Rejected (1) | Rejected (1) | - |
| More than 1 child at home (8) | Rejected (1) | Rejected (1) | - |
| Day care attendance (9) | Rejected (1) | Rejected (1) | - |
| Smoking at home (10) | Rejected (1) | Rejected (1) | - |
| Major symptoms | Rejected (1) | Rejected (1) | - |
| Related symptoms | Rejected (1) | Rejected (1) | - |
| All other symptoms | 0.254 | 0.0040 | 0.035 |

$R^2$ of variables in the last step = 0.239, $R^2$ of variables not on the last step = 0.038. Total $R^2$ = 0.458

**Notes**:
(1) Variables rejected from the model due to lack of significance ($p<0.05$)
(2) Group (dummy variable): Naturopathic drops = 1; antibiotics = 0
(3) Severity mild (dummy variable): mild = 1, moderate + severe = 0
(4) Severity moderate (dummy variable): moderate = 1; mild+severe = 0
(5) Severity severe (dummy variable): severe = 1; mild+moderate = 0
(6) Temperature ≥ 38.5° C = 1; 37.5 – 38.4° C = 0
(7) Medical history (dummy variable): good health = 1; persistent illnesses = 0
(8) More than 1 child at home (dummy variable): one child = 1; more than 1 child = 0
(9) Day care attendance (dummy variable): in day care = 1; at home = 0
(10) Smoking at home (dummy variable): no smoking = 1; smoking = 0

Analysis of the variance in pain level using repeated measurements showed that the variable time (3 days) was significant ($p<.001$), as was the *group* and *time* interaction. No adverse effects of either medication were documented, and there were no secondary complications, such as sinusitis, mastoiditis, or meningitis. Eight of the children (8.1%) who received antibiotics reported mild gastrointestinal symptoms that did not require discontinuation of treatment (95% CI: 0.4-2.1).

Evaluation of middle ear effusion by tympanoscopy at 1, 6-8, and 12-14 weeks after treatment was completed yielded positive findings in 45% of the naturopathic group and 55% of the amoxicillin group at 1 week, and in 10%and 9%, respectively, at 6-8 weeks. By 14 weeks, 5% of the children in both groups still had middle ear effusion. None of the differences between the groups at any of these time points was significant. The two groups were also similar for functional status and relapse rate.

## Discussion

Ear pain associated with AOM may originate from the periosteum of the mastoid or mucoperiosteum. The response to pain may vary, depending on its source and the mechanism of relief. Although the reduction in pain –

was satisfactory in all our patients according to the study criteria (≥70%), it was greater in the children treated with naturopathic than in the children receiving amoxicillin: the difference on days 2 and 3 was statistically significant. The passage of time itself was probably a factor, too, in both groups, as noted in a previous report [15]. It is possible that the antibiotics achieved poorer amelioration of the otalgia because they upset the protective mechanism of the mucociliary clearance system of the middle ear, leading to dysfunction of the eustachian tube, a known risk factor for the development of otitis media with effusion [13].

Middle ear effusion often follows an episode of AOM [1,9,10]. We did not find a statistically significant difference in the outcome of middle ear effusion between the groups. Antibiotics are a prevalent treatment of AOM with middle ear effusion despite growing evidence that they have little benefit in the prevention or reduction of the risk of mastoiditis and meningitis and bacteremia [18]. Several authors reported that spontaneous resolution can be expected in 80-90% of children by the third month after diagnosis [19,20].

The indiscriminate use of antibiotics may lead to increased drug resistance of pathogens, particularly *Streptococcus pneumonia*, the organism most commonly isolated from middle ear exudate and responsible for 40% of all episodes of AOM [10]. An increasing resistance to multiple antibiotics, including the cephalosporins and non-beta-lactam drugs, has been observed as well [9,10].

To help delay the development of antimicrobial resistance in both, the individual and the community [21,22], physicians in the Netherlands and Switzerland treat patients with mild or moderate AOM symptomatically. In Norway, antibiotics are reportedly presented by physicians only in children with recurrent episodes of otitis media [23-25]. In other countries, some investigators recommend shorter courses of antibiotics and others advocate initially withholding antimicrobial therapy, especially in older children [21,22]. On the other hand, it was recommended antimicrobial treatment if no improvement is observed at follow-up [26].

The bacterial and immunologic abilities of plant extracts are well documented in the treatment of middle ear infection [14,15], and the naturopathic solution used here has been shown to have *in vitro* bacteriostatic and bacteriocidal activity against common pathogens [27]. Some authors suggest that herbal extracts may meet the requirements of medication that may be routinely used in the pediatric population [28,29]. Herbal extracts have been shown to stimulate the immune system [30], to serve as antioxidants [31], and to have anti-inflammatory effects [32]. They are of natural origin and are well absorbed with good tissue penetration. They also work via local enhancement of anti-inflammatory and immunological activity [30,31]. In addition, herbal extracts are well tolerated, have a long half-life, and are easy to administer. There are no documented major adverse effects [14,33].

In conclusion, the naturopathic eardrop formulation used here, appears to be at least as effective as amoxicillin for the resolution of middle ear effusion and significantly better for the management of ear pain associated with AOM. Its use reduces the need for systemic antibiotic treatment without an increased risk of secondary complications. We suggest that in children older than 5 years, initial antibiotic treatment at the diagnosis of AOM may be withheld and replaced with naturopathic drops.

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