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Alternative versus conventional treatment strategy in uncomplicated acute otitis media in children: a prospective, open, controlled parallel-group comparison

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Key words
childhood otitis media – antibiotics – clinical trial – phytotherapy – homeopathy

Abstract. Objectives: Evidence from clinical trials questions the benefit-risk ratio of first-line antibiotic treatment for uncomplicated acute otitis media in childhood. Alternative treatment strategies are very popular but have not been the subject of larger controlled clinical trials. This trial compares an alternative with a conventional treatment strategy for acute otitis media. Methods and patients: 390 children aged 1 – 10 years presenting with uncomplicated acute otitis media participated in a prospective, open, non-randomized, controlled, parallel-group study. According to self-assignment of investigators, children were treated either conventionally (free combinations of decongestant nose drops, mucolytics, analgesics and antibiotics) or alternatively with Otovowen® (fixed combination of plant-based tinctures and homeopathic potencies), supplemented by conventional medications when considered necessary. Results: Alternatively treated patients (n = 192) had significantly less severe otoscopic findings and clinical symptom ratings at baseline than children treated in conventional centers (n = 193). Patients cared for by conventional therapists took more antibiotics (80.5% vs. 14.4%; χ^2-test, $p < 0.001$) and analgesics (66.8% vs. 53.2%; χ^2-test, $p = 0.007$). Times to recovery were 5.3 ± 2.4 and 5.1 ± 2.2 days for alternative and conventional treatment, respectively. Odds ratios (OR) with a lower limit of 1-sided 97.5% confidence interval (CI) were 0.98 (0.76), 0.95 (0.73) and 0.88 (0.69) for results adjusted to baseline otoscopy, pain and symptom score, respectively (Cox-Mantel test). Absence from school or preschool nursery was 1.7 days in both groups; ORs (CI) were 1.00 (0.76), 0.96 (0.73) and 1.04 (0.80). Non-inferiority of alternative treatment (CI limit of OR above 0.696) was not proven for pain resolution (–5.2 vs. –5.8 score points); OR (CI) were 0.87 (0.68), 1.15 (0.87) and 0.74 (0.58). Alternative treatment was judged both by doctors (Mann-Whitney estimator with 2-sided 95% CI 0.41 (0.35 – 0.47)) and parents (0.42 (0.36 – 0.48)), to be significantly better tolerated than conventional treatment. Conclusions: In primary care management of uncomplicated acute otitis media in childhood, an alternative treatment strategy based on the natural medicine, Otovowen may substantially reduce the use of antibiotics without disadvantage to the clinical outcome.

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Introduction

Acute otitis media (AOM) is one of the commonest illnesses during childhood leading to primary care attendance in developed countries. In the USA, 12% of children visiting a primary care unit were diagnosed with AOM [Freid et al. 1998] and about 30% of British children under the age of 3 see their general practitioner for AOM each year [O'Neill 1999]. Although prognosis of uncomplicated AOM is good and about 80% of patients are restored without antibiotic treatment within 3 days [O'Neill 1999], in most Western countries more than 90% of children with AOM are still primarily treated with antibiotics [Froom et al. 1990].

However, evidence from systematic reviews provides little support for first-line antibiotic treatment for all children [Agency for Healthcare Quality and Research 2000, Froom et al. 1997, Glasziou et al. 2002, O'Neill 1999]. From these reviews, it can be concluded that antibiotics may have a small effect on days 2 – 7 of treatment in preventing clinical failure and in resolving pain. Depending on the review, between 7 and 20 children would have to be treated to achieve these effects [Agency for Healthcare Quality and Re-

search 2000, Glasziou et al. 2002, O'Neill 1999]. No effect was seen for antibiotic treatment with regard to prevention of complications (mastoiditis, meningitis) and recurrences, and no studies have been performed to investigate a benefit for children at high risk [Agency for Healthcare Quality and Research 2000, Froom et al. 1997, Glasziou et al. 2002]. On the other hand, a recent comparative study across several countries suggested a higher incidence rate of acute mastoiditis in the Netherlands of 3.8/100,000 person-years, where the antibiotic prescription rate for AOM is low, when compared to countries with very high prescription rates with incidence rates of 1.2 – 2/100,000 person-years [van Zuijlen et al. 2001].

The benefit of antibiotics needs to be set against the potential risks of antibiotic treatment such as diarrhea, rashes and increasing the development of antimicrobial resistance. In the Netherlands, where already in 1986 only 31% of children were treated with antibiotics [Froom et al. 1990], the prevalence of Streptococcus pneumoniae strains showing decreased sensitivity to penicillin was found to be as low as 3% in a 1989 study compared with more than 10% in most other countries [van Klingeren et al. 1992].

As a result of a series of studies in the 1980s, the Dutch College of General Practitioners adopted a guideline for childhood AOM that recommends symptomatic treatment and a wait-and-see strategy [Appelman et al. 1990]. A similar approach had recently been investigated in a well-designed randomized, controlled trial by Little et al. [2001]. They reported that immediate administration of antibiotics resulted in only a slightly shorter time-to-recovery and less consumption of paracetamol when compared to the delayed use of antibiotics. They found no differences in absence from school and pain and distress ratings.

Complementary and alternative treatments are widely used in pediatric medical practice. In particular, uncomplicated infections of upper respiratory airways in children are frequently treated with herbal drugs and homeopathic agents [Breuner 2002, Schilcher 2002]. These medicines are also very popular with children and parents and are perceived as having an excellent tolerability profile. A large body of homeopathic literature on otitis media has been published over the last 100 years [Friese et al. 1997]. However, there is only little evidence so far from clinical trials that supports the effectiveness of homeopathic medicines in childhood AOM [Friese et al. 1997, Harrison et al. 1999, Jacobs et al. 2001, de Lange de Klerk et al. 2001].

In Germany, the natural medicine Otovowen, was one of the most frequently prescribed drugs for AOM in the first quarter of the year 2002 (26.7% of primary care pediatricians and 12.5% of ENT specialists) [IMS Health 2002]. For all 10 constituents of Otovowen, positive monographs from the Commission D of the former German Federal Health Office are available. Most of them are related to infections with fever, mucositis and specifically purulent otitis media (e.g. for Capsicum annuum). However, so far, no mechanistic or clinical studies have been carried out with Otovowen to verify favorable experience from the primary care field and to elucidate modes of action with sound scientific methodology.

The aim of this study was to compare the outcome of a conventional and an alternative treatment strategy, the latter based on the application of Otovowen, in childhood AOM in a real-life setting. It was hypothesized that alternative treatment is not inferior to conventional treatment with regard to time to recovery, pain resolution and absence from school or preschool nursery.

Methods and patients

Study design

Apart from simple comparisons of drugs or treatments, investigations of the outcome of different treatment strategies, particularly when education, beliefs and attitudes of doctors and patients are of significant importance for the success of treatment, double-blind, randomized study designs are less helpful. The aim of our study was not to simply compare drug effects, but to look at the overall outcome of patients cared for by alternatively and conventionally oriented doctors, who apply essentially different approaches of clinical medicine. Randomization of patients to alternative or conventional treatment within one center which is confessed to one or the

other approach is unsuitable. Therefore, we carried out a prospective open, nonrandomized, controlled parallel-group study with treatment directives kept to a minimum to mimic the conditions of everyday practice as closely as possible. Anticipated selection bias was intended as part of the hypotheses to be tested. The only significant instruction was that Otovowen was obligatory for alternatively treated patients, but not allowed for patients treated in conventional centers.

Patients were recruited from 22 pediatricians and 7 ENT specialists in the greater Munich area in Germany. Participating doctors had to declare themselves in advance as "alternative" (16 centers) or "conventional" therapists (13 centers). All patients of one center were treated either alternatively or conventionally depending on the self-assignment of their doctor. Pairs of alternative and conventional centers were matched regarding inner-city or rural location, size and specialty to minimize sociodemographic bias.

The study was performed in accordance with the principles of the Declaration of Helsinki on human rights in clinical research, and with European Union guidelines on Good Clinical Practice (GCP). Study centers and materials were monitored frequently by experienced and trained personnel.

Participants

Doctors were asked to prepare a prospective study log of all children consulting their practice with any diagnosis of otitis media, irrespective of eligibility for entry into the study. As in everyday practice in Germany, diagnosis was made on the basis of acute medical history, clinical symptoms and otoscopic findings (erythema, severe inflammation, bulging, perforation, loss of tympanic landmarks). Children from 1 – 10 years of age suffering from uncomplicated AOM (no tympanic perforation, no indication for myringotomy or adenotomy) who themselves or their parents were able to keep a diary were eligible for inclusion. Exclusion criteria were: concurrent homeopathic treatment, immunodeficiencies, treatment with immunosuppressants, concomitant diseases treated with antibiotics within 1 week preceding study entry.

Interventions

Doctors in alternative centers prescribed the natural medicine Otovowen as the basic therapy for all children included in the study. They were free to additionally prescribe decongestant nose drops, mucolytics, analgesics or antibiotics when considered necessary.

Otovowen (Germany, Canada; identical with Otoplex, Orlando, USA; Weber and Weber, Inning, Germany) has been licensed in Germany for decades for inflammation and infection of the middle ear. 100 ml of Otovowen drops contain highly concentrated liquid plant extracts (i.e. tinctures) of Echinacea purpurea (7.5 ml), Sambucus nigra (2.25 ml), Sanguinaria canadensis (0.75 ml) and Chamomilla recutita (2.25 ml) as well as liquid homeopathic potencies (dilutions) of Aconitum napellus (D6), Capsicum annuum (D4), Hydrargyrum cyanatum (D6), Hydrastis canadensis (D4), iodine (D4) and Natrium tetraboracicum (D4). Ethanol is added to 53% (v/v).

Doctors in conventional centers could prescribe decongestant nose drops, mucolytics, analgesics and antibiotics without restrictions.

Outcome measures

Since the recovery time from uncomplicated AOM rarely exceeds 1 week, a control visit was scheduled after 2 – 5 days and the final visit took place a maximum of 2 weeks after inclusion. At baseline, control and final visits, doctors entered the otoscopic findings and pain-rating on a scale from 1 – 10, the presence or absence of typical clinical symptoms (fever, irritability, unusual crying or screaming, lack of drive, loss of appetite, unusual sleep behavior) and medications prescribed, in standardized case report forms. At control and final visits, doctors additionally documented if the patient had recovered or not and the duration of illness since entry into the study. Control and final visit recordings were performed simultaneously when the patient had already recovered by the control visit. Control and final visits could also be performed via telephone.

Patients or parents were asked to complete a daily diary for a global judgment of re-

covery (yes/no) and pain-ratings on a scale from 1 – 10, clinical symptoms, absence from school or preschool nursery and medications taken.

At the end of the study, doctors and parents were asked for a global judgment of efficacy and tolerability by means of a 6-point Likert scale (very good, good, moderate, slight, not much, not at all).

Since patients' or parents' ratings are closer to reality than investigator recordings, which frequently had to be done retrospectively or even via telephone, diary entries were used for primary analysis in this real-life study. Only in the case of missing information corresponding data recorded by the doctor were utilized in the analysis.

Duration of illness, pain-intensity and duration of absence from school or preschool nursery were chosen as equivalent primary outcome measures since they best represent measures of individual distress as well as familial and social burdens of the disease.

Doctors enquired in a neutral way about adverse drug reactions at each visit and recorded reported events in a standard form.

Statistical analysis

Since the real-life character of the study allowed optimally adjusted treatment for each individual patient, no ethical concerns were opposed to recruitment of a large number of participants without a strict sample size calculation. A total of 300 patients were planned to be included to ensure the detection of clinically relevant differences in efficacy and to prove non-inferiority within very narrow bounds.

Due to the lack of randomization and to the assignment of patients to a treatment by choice of a center, an increased risk of introducing operational bias had to be taken into account. Therefore, comparability of baseline data between groups was evaluated before finalizing the definitive statistical analysis plan. Baseline severity of illness was evaluated by means of otoscopic findings (sum score), clinical symptoms (sum score) and pain ratings (raw score). The otoscopy sum score was calculated by adding up score points for single findings (erythema 1, severe inflammation 2, bulging 2, perforation 3, loss of tympanic landmarks 3, bilateral presence of any finding 1). The sum score for clinical symptoms was calculated in a similar manner (fever 2, irritability 2, unusual crying or screaming 1, lack of drive 1, loss of appetite 1, unusual sleep behavior 1).

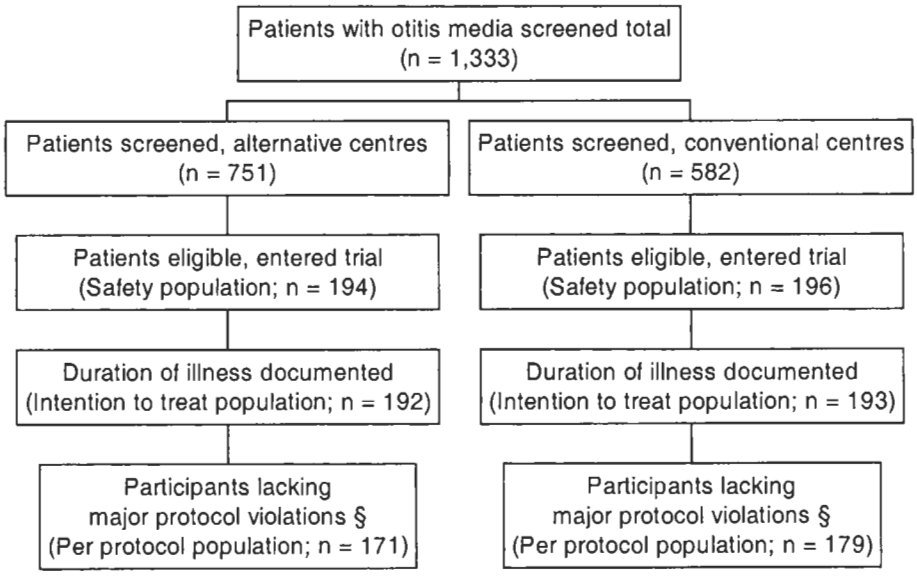
Non-equivalence of baseline variables was assumed when lower or upper limits of the 90% confidence interval of the Mann-Whitney estimator were outside the threshold for medium-sized inferiority (0.36) or superiority (0.64) according to non-parametric statistics applying Cohen's effect size [Cohen 1988, Lehmann 1998]. Table 1 shows that no significant differences between groups were seen regarding sociodemographic characteristics. However, patients treated conventionally had significantly more severe otoscopic findings and pain ratings at baseline.

In consequence, baseline otoscopy, pain and symptom scores were stratified by means of the 33% and 66% percentiles (low, medium and high scores), and each of the 3 primary outcome variables was analyzed by means of 3 parallel Cox-Mantel tests with Cochran-Mantel-Haenszel-pooling of strata (taking censored data into account), thereby adjusting results for baseline differences [Mantel 1963, 1966].

Following recommendations of the European guideline for clinical trials with analgesics, repeated pain-ratings were analyzed as the sum of pain-intensity differences [European Agency for the Evaluation of Medicinal Products 2001].

Primary analysis was carried out with the intention-to-treat sample (minimum requirement for inclusion: duration of illness can be obtained from the diary or doctor's records). It was hypothesized that alternative treatment strategy is not inferior to the conventional one with regard to time-to-recovery, pain resolution, and absence from school or preschool nursery. A confidence interval approach (type I error 2.5% 1-sided) was applied to test for non-inferiority, which is in accordance with the provisions of the International Conference of Harmonization (ICH) biostatistics guideline E9 [European Agency for the Evaluation of Medicinal Products 1998].

The lower equivalence margin of odds ratios for proof of non-inferiority was set to 0.696, representing the threshold for a small inferiority according to Cohen. If the limit of



§ Protocol violations leading to exclusion from per protocol analysis were: violation of in-/exclusion criteria (n=24); patient's wish to discontinue (n=4); erroneously treated with Otovowen® in the conventional group and vice versa; treatment with Vowen®-T (tablets closely similar to Otovowen®) in the alternative group (n=4); lacking information from doctor's records regarding duration of illness (n=2); erroneous discontinuation by doctor due to switch from Otovowen® to antibiotic treatment (n=1).

Figure 1. Flow of subject progress through the trial.

the one-sided 97.5% confidence interval of odds ratios is above 0.696, non-inferiority is proven within very narrow bounds [Cohen 1988, European Agency for the Evaluation of Medicinal Products 1998].

Sensitivity analyses were performed with the set of patients treated according to the protocol (per-protocol analysis). Data from patients showing major protocol violations were censored.

A supplementary analysis of the course of recovery from illness was carried out in a descriptive fashion by the method introduced by Kaplan and Meier [1958].

Results

Between October 2001 and May 2002, a total of 1,333 patients were diagnosed with otitis media in participating centers, 390 (29.3%) of which entered the trial. Reasons for non-participation in alternative and conventional centers were patient's refusal n = 137 (25%) and n = 155 (40%), inability to keep the diary n = 71 (13%) and n = 77 (20%), patient too young/old n = 117 (21%) and n = 66 (17%), prescription of other therapy n = 112 (20%) and n = 31 (8%), other reasons n = 117 (21%) and n = 42 (11%) respectively. The other most frequent prescriptions in alternative centers were individualized homeopathic treatment and plant-based immunostimulants.

For 5 patients, data regarding duration of illness could be gathered neither from case records nor from diaries. Thus, 385 patients formed the intention-to-treat sample, and 350 patients lacking major protocol violations formed the per-protocol sample (Figure 1). Three patients each per treatment group did not recover within the 14-day observation period. Their data regarding duration of illness were censored. 378 of 390 diaries (97%) were returned and evaluated.

In baseline otoscopy, severe tympanic inflammation was recorded for 99% of patients, 65% exhibited tympanic bulging and 54% showed loss of tympanic landmarks, thereby reliably validating the diagnosis of AOM.

Table 1 shows that no significant differences between groups were seen regarding sociodemographic characteristics. However, patients treated conventionally had signifi-

Table 1. Comparability of baseline data and drug intake between alternative and conventional treatment groups (intention to treat population). Values are absolute (relative) frequencies or means ± standard deviations (ranges).

Variable (doctors' records)	Alternative treatment (n = 192)	Conventional treatment (n = 193)	Mann-Whitney estimator[1] (90% confidence interval)
Sex male	n = 95 (50%)	n = 105 (55%)	0.52 (0.47 – 0.57)
female	n = 96 (50%)	n = 85 (45%)	
Age (years)	4.4 ± 2.3 (0; 14)	4.3 ± 2.3 (1; 10)	**0.51 (0.46 – 0.56)**
Height (cm)	108 ± 16.6 (70; 179)	109 ± 17.5 (73; 154)	**0.50 (0.46 – 0.55)**
Weight (kg)	19 ± 7.8 (8.5; 78)	**19 ± 8.1 (7.7; 59)**	**0.54 (0.49 – 0.58)**
Otoscopy score	5.6 ± 2.2 (2; 12)	**6.6 ± 2.1 (2; 9)**	**0.37 (0.32 – 0.42)**
Pain score	5.5 ± 2.3 (1; 10)	**6.6 ± 2.0 (2; 10)**	**0.35 (0.30 – 0.40)**
Clinical symptoms score	5.3 ± 2.4 (0; 8)	**5.6 ± 2.0 (0; 8)**	0.48 (0.43 – 0.53)
Drugs taken (diary)	**Alternative treatment (n = 188)**	**Conventional treatment (n = 190)**	**p value (χ^2 test)**
Otovowen	**n = 187 (99.5%)**	n = 2 (1.1%)	p < 0.000
Antibiotics	**n = 27 (14.4%)**	n = 153 (80.5%)	p < 0.001
Analgesics	**n = 100 (53.2%)**	n = 127 (66.8%)	p = 0.007
Mucolytics	**n = 81 (43.1%)**	n = 70 (36.8%)	p = 0.215
Decongestant nose drops	**n = 129 (68.6%)**	n = 130 (68.4%)	p = 0.967

[1] = values suggesting inferiority or superiority (lower or upper limits of the 2-sided 90% confidence interval outside the thresholds for medium-sized inferiority (0.36) or superiority (0.64)) are set in bold.

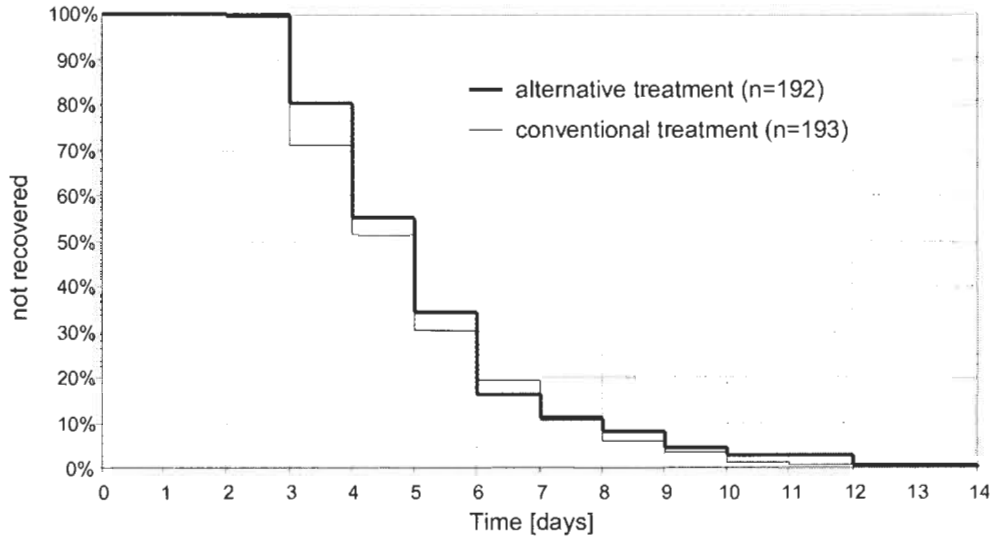


Figure 2. Estimated probability of recovery from uncomplicated acute otitis media within 14 days of observation from start of treatment (intention-to-treat population). Mean duration of illness estimated from Kaplan-Meier statistics was 5.31 days (4.98 – 5.64, 2-sided 95% confidence interval) for alternatively treated and 5.07 days (4.75 – 5.39) for conventionally treated participants.

cantly more severe otoscopic findings and pain ratings. As expected, patients for by conventional therapists were more frequently treated with antibiotics and analgesics. The administration of mucolytics and decongestant nose drops did not differ between groups (Table 1).

All but one participant in the alternative group took Otovowen. Mean duration of administration was 5.0 ± 2.9 days.

Table 2. Results from primary analysis of efficacy outcome measures. Descriptive statistics (intention-to-treat sample) comprise means ± standard deviations (ranges). Confirmatory statistics testing for non-inferiority of alternative treatment are adjusted for baseline differences (Cox-Mantel test with Cochran-Mantel-Haenszel pooling).

Outcome measure	Alternative treatment (n = 192)	Conventional treatment (n = 193)	Baseline adjustment	Odds ratio[1] (lower limit of 1-sided 97.5% confidence interval)	
				Intention-to-treat sample (n = 385)	Per-protocol sample (n = 350)
Duration of illness (days)	5.31 ± 2.36 (2; 15)	5.07 ± 2.22 (2; 14)	Otoscopy score	0.98 (0.76)	1.07 (0.81)
			Pain score	0.95 (0.73)	0.99 (0.75)
			Symptom score	**0.88 (0.69)**	**0.96 (0.74)**
Ear pain (sum of pain intensity differences)	–5.2 ± 2.5 (–9; 0)	–5.8 ± 2.4 (–9; 0)	Otoscopy score	0.87 (0.68)	0.88 (0.67)
			Pain score	1.15 (0.87)	1.13 (0.84)
			Symptom score	**0.74 (0.58)**	**0.75 (0.58)**
Absence from school, preschool nursery (days)	1.7 ± 1.9 (0; 11)	1.7 ± 1.8 (0; 8)	Otoscopy score	1.00 (0.76)	0.98 (0.73)
			Pain score	0.96 (0.73)	0.97 (0.73)
			Symptom score	1.04 (0.80)	1.02 (0.77)

[1] = odds ratios suggesting inferiority of alternative treatment (limit of the one-sided 97.5% confidence interval is below 0.696) are set in bold.

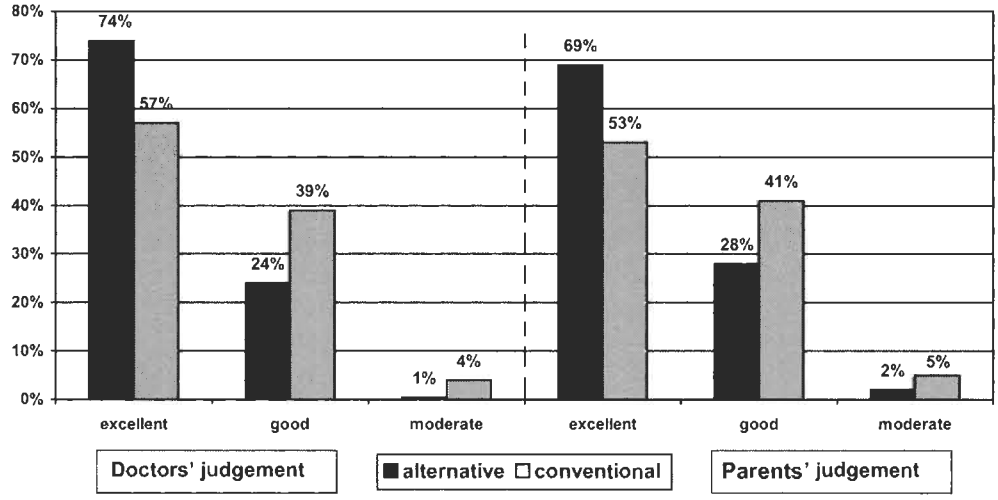


Figure 3. Global judgment of tolerability by doctors and parents by means of a 6-point Likert scale (safety population, n = 390). Ratings "slight", "not much" and "not at all" are not displayed for very low frequencies (doctors: "not much", n = 2, parents: "not much", n = 1, "not at all", n = 1, all treated alternatively), but statistical testing was performed with results from all 6 rating categories. Alternative treatment was judged to be significantly better tolerated than conventional treatment by both doctors ($p < 0.001$, two-sided Mann-Whitney U test, 0.41 (0.35 – 0.47), Mann-Whitney estimator with two-sided 95% confidence interval) and parents ($p = 0.002$, 0.42 (0.36 – 0.48)).

Time course of recovery did not differ between groups ($p = 0.34$, log rank test). Mean duration of illness estimated using Kaplan-Meier statistics was 5.31 days (4.98 – 5.64, 2-sided 95% confidence interval) for alternatively treated and 5.07 days (4.75 – 5.39) for conventionally treated participants (Figure 2).

Taking into account, adjustment for baseline differences in severity of illness non-inferiority of alternative treatment regarding duration of illness was proven within very narrow bounds. When adjusted for baseline symptom scores, the odds ratio for duration of illness did not quite reach the threshold for significance in the intention-to-treat sample (Table 2).

In both groups, mean absence from preschool nursery or school was 1.7 days. Adjustment for baseline differences revealed no

significant advantage for one or the other treatment strategy (Table 2).

For pain resolution, a slight tendency for inferiority of the alternative treatment strategy must be noted. Alternative treatment was slightly inferior when adjusted for baseline otoscopy and symptom scores, but slightly superior when adjusted for higher baseline pain scores in conventionally treated patients (Table 2).

Results from per-protocol analysis agreed with those from the intention-to-treat analysis.

Descriptive evaluation of the course of otoscopic findings and of clinical symptoms revealed no significant differences between groups.

Parents as well as doctors globally judged both treatments to be highly effective, with no significant differences between groups. Alternative treatment was rated to be "excellent" or "good" in 88% and 87% of cases, conventional treatment reached similar figures with 88% and 83%.

Figure 3, however, shows that alternative treatment was judged by both doctors and by parents to be better tolerated than conventional treatment.

One adverse drug reaction was reported. A 4-year-old child in the conventional group experienced a rash under amoxicillin treatment and recovered quickly after a switch to roxithromycin.

Discussion

To our knowledge, this is the largest controlled study to compare an alternative with a conventional treatment strategy in acute otitis media in childhood. The real-life setting does not solely compare an alternative medicine to a conventional one, but also incorporates into the experiment the education, attitudes and expectations of doctors and patients (or their parents) towards conventional and alternative treatments. As expected, the results of our trial demonstrate that antibiotics are prescribed more frequently by conventional therapists (80.5% vs. 14.4%). This validates retrospectively the original prospective self-assignments by investigators into their treatment groups. The data further suggest that treatment in alternative centers had comparable efficacy to treatment in conventional centers, but is better tolerated.

No clinically relevant differences regarding time-to-recovery and absence from school or preschool nursery were seen between treatment strategies. Pain management seemed to be slightly more effective with the conventional treatment, when adjusted for more severe otoscopic findings and clinical symptoms of conventionally treated patients at baseline. However, after adjustment for baseline pain values, which were also higher in the conventional group, the conventional treatment showed slight inferiority. Furthermore, time course of relative decrease in pain intensity was almost identical in both groups.

More frequent use of antibiotics and analgesics in the conventional group may explain minor differences in pain score favoring this group. More effective pain resolution from days 2 – 7 of illness was suggested for antibiotics in previously reported placebo-controlled trials [Agency for Healthcare Quality and Research 2000, Glasziou et al. 2002].

Since adverse drug reactions and not adverse events were to be recorded in this study, the notification of only one such report, a rash related to amoxicillin intake, is not surprising. Patients and doctors favored the alternative treatment as being the better tolerated. However, since the treatments were neither randomized nor blinded, these results to some extent may be anticipated through observer bias. Nevertheless, in our opinion a degree of importance should be applied to patients' subjective ratings of satisfaction, especially in minor but highly symptomatic conditions, such as uncomplicated AOM.

Critics may question the validity of the trial, since assignment of patients to treatment strategies was not done randomly. However, the question to be answered by this trial did not allow the utilization of randomization procedures. Results from non-randomized clinical trials can provide useful pointers to potential treatment differences [McKee et al. 1999]. Applying control of operational bias and using appropriate statistical methods can be a basis for acceptance of results from non-randomized studies [Abel and Koch 1998, McKee et al. 1999].

We employed several measures to control for operational bias, such as recruitment of a large sample, matching of centers, keeping of

a screening log and frequent monitoring of activities according to Good Clinical Practice guidelines. The success of the latter can be seen in the return rate for diaries of 97%, which is an exceptionally high figure for studies of this kind. Appropriate statistical analyses were applied to allow for baseline differences in severity of illness.

Duration of symptoms before entry into the trial were not assessed, but the large sample size and baseline-adjusted analysis provide compensation for this shortcoming. Due to the real-life design of the study, diagnostic procedures were not strictly prescribed and thus mimicked everyday practice. Every patient underwent otoscopic examination, at least at baseline. Documentation of pain intensity and clinical symptoms in case report forms helped to verify of the diagnosis.

Efficacy of treatment strategies to prevent complications or recurrences cannot be evaluated from this trial since the observation period was limited to 2 weeks.

No definitive statement can be made regarding the specific contribution of Otovowen and of other medicines to the results. The aim of the trial was not to compare Otovowen alone with antibiotics alone, and the study design does not allow ultimate conclusions. To date, no medication provides clear evidence of efficacy in childhood AOM. Only minimal-to-moderate benefits regarding pain resolution at 2 – 7 days, 7 – 14 days clinical resolution rate (about 90% of patients recover within 1 week without antibiotics) and reduction of contralateral AOM are attributed to antibiotic treatment [Agency for Healthcare Quality and Research 2000, Froom et al. 1997, Glasziou et al. 2002, O'Neill 1999]. Even for decongestant nose drops, no clear recommendation can be given from the data available [Flynn et al. 2002]. Studies investigating homeopathic treatment provide some evidence for a beneficial effect [Friese et al. 1997, Harrison et al. 1999, Jacobs et al. 2001, de Lange de Klerk et al. 2001]. The natural course of the illness and placebo effects probably provide a substantial contribution to recoveries observed in clinical studies. Taken together, it cannot be ruled out confidently that alternative treatment was as ineffective as conventional treatment, since no control group observing the spontaneous course of illness was incorporated in this study, which would have been ethically impossible.

Since patients with complicated AOM were not allowed to enter our trial, we do not know whether conventional treatment would have been the more effective in these individuals. However, patients with emerging complications could also be treated with antibiotics in the alternative centers, which is mirrored by the 14% antibiotic intake in this group. Thus, alternative treatment resulted in a reduction in antibiotic prescriptions on at least a comparable scale to a wait-and-see strategy of 31% in the Netherlands and 24% in a large controlled trial [Froom et al. 1990, Little et al. 2001] with no disadvantage in outcome.

In conclusion, in everyday practice, an alternative treatment strategy based on the administration of the natural medicine Otovowen was as efficacious but better tolerated than a conventional strategy that primarily applied antibiotics in uncomplicated acute otitis media in childhood. Besides symptomatic treatment with analgesics, mucolytics and decongestant nose drops, Otovowen may be useful as an alternative first-line treatment at least in this uncomplicated disease, thereby satisfying parental wishes for a "directly-acting" therapy and supporting the wait-and-see strategy. As a consequence, the use of antibiotics may be reduced – especially in cases where they are not required – without disadvantage in clinical outcome. Primary antibiotic treatment may be best limited to the treatment of complications, and considerations of defensive medicine should assume less prominence in decision-making.

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