Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials

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Background: Recommendations on withholding antibiotics in children with acute otitis media (AOM) have been inadequately implemented in clinical practice.

Objectives: We evaluated the role of prescribing antibiotics for AOM.

Methods: We performed a meta-analysis of randomized controlled trials (RCTs) that were retrieved from searches performed in the PubMed and Cochrane databases, and compared antibiotic treatment with placebo or watchful waiting (delayed antibiotic treatment if clinically indicated) for patients with AOM.

Results: We identified seven trials comparing antibiotic treatment with placebo (all double-blinded) and four trials comparing antibiotic treatment with watchful waiting (two investigator-blinded and two open-label) trials, all of which involved children (6 months to 12 years). Clinical success was more likely with antibiotics than comparator treatment in: placebo-controlled trials [seven RCTs, 1405 patients, risk ratio (RR) = 1.11, 95% confidence interval (CI) = 1.05–1.18]; watchful waiting trials (four RCTs, 915 patients, RR = 1.18, 95% CI = 1.07–1.32); and all trials combined (11 RCTs, 2320 patients, RR = 1.13, 95% CI = 1.08–1.19). Similarly, persistence of symptoms 2–4 days after treatment initiation was less likely with antibiotics in: placebo-controlled trials (four RCTs, 1014 patients, RR = 0.75, 95% CI = 0.64–0.88) and all trials combined (five RCTs, 1299 patients, RR = 0.68, 95% CI = 0.54–0.85). Diarrhoea was more likely with antibiotics (seven RCTs, 1807 patients, RR = 1.50, 95% CI = 1.16–1.95). No differences between the compared treatments were found regarding other effectiveness and safety outcomes.

Conclusions: Antibiotic treatment is associated with a more favourable clinical course in children with AOM, compared with placebo, and also compared with watchful waiting. However, safety issues and the rather small treatment effect difference render the consideration of additional factors necessary in relevant clinical decision making.

Keywords: upper respiratory tract infections, drug therapy, ear diseases, treatment outcome, delayed antibiotic treatment, wait-and-see strategy

Introduction

Acute otitis media (AOM) is a common community-acquired infection, particularly in young children. AOM is primarily caused by bacteria, such as Streptococcus pneumoniae, non-typeable Haemophilus influenzae and Moraxella catarrhalis; respiratory viruses may also play a role as co-pathogens.1–3

The clinical decision to treat or not to treat children with AOM with antibiotics is not always a clear-cut one.4 According to current relevant US guidelines, factors that should be taken into consideration in this clinical decision include age, the degree of certainty about the diagnosis and the severity of illness.5 For a considerable proportion of patients, antibiotic therapy may be initially withheld and instituted later in case the child fails to improve within 48–72 h.5 Additionally, relevant UK guidance suggests that immediate antibiotic therapy should be considered for children younger than 2 years with bilateral AOM or for children presenting with otorrhoea. For all other
patients with AOM, a no antibiotic or delayed antibiotic prescribing strategy is recommended. The implementation of the above-mentioned guidelines appears to have contributed to the observed decrease in the antibiotic prescriptions for children with AOM.

In this regard, we aimed to re-evaluate the effectiveness and safety of antibiotic treatment for AOM compared with placebo and particularly with watchful waiting, by performing a comprehensive meta-analysis of relevant randomized controlled trials (RCTs).

Methods

Data sources

The clinical trials to be included in our meta-analysis were retrieved from searches performed in PubMed and the Cochrane Library (up to 31 March 2009 for both databases), as well as by hand-searching the bibliographies of relevant articles. The PubMed search strategy was: ‘otitis AND (antibiotic OR antibiotics OR drug OR antimicrobial agents) AND (therapy OR treatment)’. The search criteria applied to the Cochrane Library were: ‘otitis AND (antibiotics OR placebo)’.

Study selection process

Two reviewers independently performed the literature search as well as the evaluation of retrieved articles. The latter were initially screened on the basis of title or abstract. Full text was obtained for the articles that were selected for further evaluation. A study was included in the meta-analysis if it constituted an RCT; evaluated patients of any age diagnosed with AOM; compared treatment with antibiotics versus either placebo or a watchful waiting strategy; and provided data relevant to the effectiveness or safety outcomes of this meta-analysis. We considered as watchful waiting a strategy of reserving antibiotic treatment for patients not showing an adequate clinical response. Trials that included patients with mixed types of upper respiratory tract illnesses were included in the meta-analysis if >75% of the patients had symptoms and signs of AOM. The latter consisted of a history of acute onset, along with symptoms and signs of middle ear inflammation and signs of middle ear effusion. Articles representing abstracts in scientific conferences or published in languages other than English, Spanish, French, German or Italian were excluded from the meta-analysis.

Data extraction

Data extracted from each of the included RCTs consisted of study design and methodology, characteristics and size of the included population, criteria used for AOM diagnosis along with exclusion criteria, characteristics of compared treatments and potential concomitant therapies, as well as specific data regarding the outcomes evaluated in this meta-analysis and the timing of relevant evaluations.

Outcomes of the meta-analysis

The primary effectiveness outcome of the meta-analysis was clinical success, defined as cure or improvement (complete or substantial resolution, respectively) of all symptoms and signs of AOM. For trials that only reported relevant data regarding specific symptoms or signs, we elected pain as a surrogate marker for clinical success. If data on the resolution of symptoms or signs were not reported, we defined clinical success as the absence of an unfavourable clinical course. The timing of determination of clinical success was during the course of therapy or a few days thereafter.

The secondary effectiveness outcomes of our meta-analysis included: cure, determined at the first post-treatment evaluation; short-term persistence of symptoms, defined as the presence of any AOM-related symptoms (or specifically pain if only data on specific symptoms were reported) within 2–4 days after the initiation of study treatments (we included data obtained at the earliest relevant assessment); bacteriological success, defined as the eradication of the initially isolated pathogens at the post-treatment evaluation; disease complications, which included eardrum perforation, as well as progression to severity requiring hospitalization, and intracranial or extracranial supplicative complications, and were determined during or shortly after treatment; development of persistent middle ear effusion, determined at the last follow-up assessment; and recurrence of AOM, defined as the reappearance of symptoms and signs of the disease in patients previously evaluated as cured, and determined at the last follow-up assessment. The safety outcomes of the meta-analysis consisted of adverse events, defined as total adverse events reported during the study period; along with specific common types of adverse events; and study withdrawals due to adverse events.

The effectiveness outcomes of the meta-analysis were assessed on the respective evaluable population, which included patients who satisfied the criteria for eligibility of evaluation for a specific outcome that were set in each RCT. If the number of the latter was not specified, we used the intention-to-treat patients (all patients randomized to receive study treatments) as the denominator. Only patient-related data, as opposed to data related to infected ears, were entered in the meta-analysis.

Subgroup and sensitivity analysis

The main analysis consisted of the separate evaluation of trials comparing antibiotic treatment with placebo and those comparing antibiotic treatment with watchful waiting. In a complementary analysis, we also evaluated all trials combined. In a sensitivity analysis, we evaluated clinical success in trials that used rigorous criteria for the diagnosis of AOM (specified as history of acute onset, along with the presence of symptoms and signs of middle ear inflammation, and signs of middle ear effusion), as well as in the remaining trials, and we tested for difference between the above subgroups of trials.

Quality assessment

The methodological quality of each of the included RCTs was assessed by the Jadad criteria. The Jadad criteria evaluate the presence of randomization, blinded design and information on study withdrawals, as well as the appropriateness of randomization and blinding procedures, if present. Specifically, one point is awarded for the presence of each of the former three parameters, whereas each of the latter two parameters is awarded the values of −1 (if deemed inappropriate) and +1 (if appropriate). In this regard, the maximum score that could be attributed to any specific trial was 5 points. A score higher than 2 points denoted adequate methodological quality.

Statistical analysis

For outcomes expressed as dichotomous variables, pooled risk ratios (RRs) and respective 95% confidence intervals (CIs) regarding the analysed outcomes were estimated using a random effects model. Statistical heterogeneity among trials was assessed by the $I^2$-test; a value of 25%, 50% and 75% for the $I^2$-test was considered to
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Results

Selected RCTs

The flow diagram of the selection process of eligible articles for inclusion in the meta-analysis is presented in Figure S1 [available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. Briefly, among a total of 7418 and 736 articles initially retrieved from the PubMed and the Cochrane Library searches, respectively, we finally selected 11 individual RCTs as eligible for inclusion in the meta-analysis.14–24

Characteristics of the included RCTs

The main characteristics of the 11 RCTs included in the meta-analysis are presented in Table S1 [available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. All of the included RCTs involved children, whose age varied from 6 months to 12 years. Among the 11 RCTs, 7 compared antibiotic treatment with placebo,14–20 whereas the remaining 4 compared antibiotic treatment with a watchful waiting strategy (delayed antibiotic treatment for patients when this was clinically indicated).21–24 Regarding trials of the latter type, in two the decision to administer antibiotics was regulated by the study investigators, whereas, in the remaining two, antibiotic prescriptions were issued for all patients but the patients’ parents were instructed on whether and when to use them.21,23 All the included placebo-controlled RCTs had a double-blinded design.14–20 Regarding the four RCTs comparing antibiotic treatment with watchful waiting, two had a single-(investigator-)blinded design,21,22 one had an open-label design,23 and the remaining trial did not report about blinding.24 Regarding methodological quality, all of the included RCTs were assigned a Jadad score of >2 points, with the exception of one RCT that had a Jadad score of 2 points.24

Characteristics of treatment administered

Regarding the RCTs that used placebo as the comparator treatment, four of the seven used amoxicillin in the antibiotic treatment arm,14,15,17,19 while amoxicillin/clavulanate16 and penicillin V18 were used in one RCT each, and the remaining RCT had two antibiotic treatment arms, involving amoxicillin or phenoxymethyl penicillin combined with sulfoxazole.20

Regarding the RCTs that used a watchful waiting strategy as the comparator treatment, two of the four RCTs used amoxicillin in the immediate antibiotic treatment arm,22,23 another one used penicillin and amoxicillin in two respective antibiotic treatment arms,24 whereas, in the remaining relevant trial, the choice of antibiotics administered was left at the discretion of the clinicians participating in the study.21 In three of the four above-mentioned trials,21–23 the antibiotics used in the watchful waiting treatment arms were the same as those used in the immediate antibiotic treatment arms, while in the remaining trial relevant data were not specifically reported.24 The watchful waiting strategy used in these trials consisted of the institution of antibiotic treatment in the event of persistence or recurrence of the clinical manifestations of AOM. However, the exact methodology used was variable.

Among the 11 included RCTs, the duration of antibiotic therapy was 7 days in four trials,16–19 10 days in five trials,14,15,20–22 while in one trial antibiotics were administered for a variable duration of between 7 and 14 days (average 10 days).24 Specific data regarding this outcome were not provided for the remaining RCT.23 In all of the included RCTs, patients received concomitant symptomatic therapy, such as analgesics or decongestants.

Outcomes of the meta-analysis

In Table S2 [available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)], we present the data extracted from each of the included RCTs that were taken into consideration for the analyses of the outcomes we performed. The respective findings are presented below.

Effectiveness outcomes. Clinical success was more likely in patients treated with antibiotics versus comparator treatment in the subgroup analysis limited to placebo-controlled trials,14–20 in the subgroup analysis limited to watchful waiting trials21–24 and in the combined analysis including all trials.14–24 The specific relevant outcome data are shown in Figure 1. In the sensitivity analysis, no difference regarding clinical success was noted between the trials that used rigorous diagnostic inclusion criteria and the remaining trials (five RCTs, 1503 patients, RR = 1.14, 95% CI = 1.09–1.20,14,15,21–23 versus six RCTs, 817 patients, RR = 1.12, 95% CI = 1.06–1.18,16–20,24 respectively; P = 0.61 for the χ² test for subgroup differences). It should be mentioned that for two of the included trials we used resolution of pain as a surrogate marker of clinical success, as specific data for the latter outcome were not reported. These two trials, one of which compared antibiotics with placebo19 and the other with watchful waiting,21 did not show significant difference in the resolution of pain between the compared treatment arms.

No difference was found regarding cure between patients treated with antibiotics and those treated with comparator treatment in the subgroup analysis limited to placebo-controlled trials (two RCTs, 306 patients, RR = 1.05, 95% CI = 0.61–1.82)15,20 as well as in the combined analysis including all trials (three RCTs, 448 patients, RR = 1.15, 95% CI = 0.71–1.85).15,20,24 Specific data regarding this outcome were reported in one of the four included watchful waiting trials.24

Short-term persistence of symptoms was less likely in patients treated with antibiotics versus comparator treatment in the subgroup analysis limited to placebo-controlled trials14–16,18 and in the combined analysis including all trials.14–16,18,23 Specific data regarding this outcome were reported in one of the four included watchful waiting trials.23 The specific relevant outcome data are shown in Figure 2.

No difference was found regarding eardrum perforations between patients treated with antibiotics and those treated with placebo (two RCTs, 381 patients, RR = 0.57, 95% CI = 0.25–1.33).17,18 Relevant data were not reported in the included watchful waiting trials. No difference was also found regarding hospitalizations between patients treated with antibiotics and those treated with comparator treatment in the combined analysis including all trials (two RCTs, 463 patients, RR = 0.36, 95%
Specific data regarding this outcome were reported in one placebo-controlled and one watchful waiting trial.\(^{22}\)

No difference was found regarding the development of middle ear effusion between patients treated with antibiotics and those treated with placebo (three RCTs, 872 patients, RR = 0.95, 95% CI = 0.74–1.20).\(^{14,15,17}\) Specific data regarding this outcome were not provided from the included watchful waiting trials. No difference was found regarding recurrences between patients treated with antibiotics and those treated with comparator treatment in the subgroup analysis limited to watchful waiting trials (two RCTs, 351 patients, RR = 1.32, 95% CI = 0.83–2.08)\(^{22,24}\) or in the combined analysis including all trials (three RCTs, 822 patients, RR = 1.07, 95% CI = 0.80–1.42).\(^{14,22,24}\) Specific data regarding this outcome were reported in one of the seven included placebo-controlled trials.\(^{14}\)

**Safety outcomes.** No difference was found regarding the occurrence of diarrhoea between patients treated with antibiotics and those treated with placebo.\(^{14,15,17,18}\) Diarrhoea was more likely in patients treated with immediate antibiotics versus those treated with a watchful waiting strategy.\(^{21,23,24}\) Overall, diarrhoea was more likely in patients treated with antibiotics versus comparator treatments in the combined analysis including all trials, both placebo-controlled and watchful waiting.\(^{14,15,17,18,21,23,24}\) The specific relevant outcome data are shown in Figure 3.

No difference was found regarding the occurrence of rash between patients treated with antibiotics and those treated with comparator treatment in the subgroup analysis limited to placebo-controlled trials,\(^{14,15,17,18}\) in the subgroup analysis limited to watchful waiting trials\(^{23,24}\) and in the combined analysis including all trials.\(^{14,15,17,18,23,24}\) The specific relevant outcome data are shown in Figure 4.

No difference was found regarding study withdrawals between patients treated with antibiotics and those treated with comparator treatment in the subgroup analysis limited to placebo-controlled trials (five RCTs, 1259 patients, RR = 1.24, 95% CI = 0.34–4.56)\(^{14–18}\) or in the combined analysis including all trials (eight RCTs, 1939 patients, RR = 1.24, 95% CI = 0.34–4.56).\(^{14–18,22–24}\) No study withdrawals were reported in three of the four included watchful waiting trials.\(^{22–24}\)

**Discussion**

The main finding of our meta-analysis is that clinical success in children with AOM, during or shortly after treatment, is more likely to be noted in those treated with antibiotics compared...
with those treated with placebo. Moreover, antibiotic treatment is associated with a lower likelihood of persistence of AOM-related symptoms within 2–4 days after the initiation of treatment. However, diarrhoea was more frequently observed in the antibiotic group. No difference between the compared groups was found in the remaining comparisons performed.

The clinical significance of the above findings merits further interpretation. The margin of benefit of antibiotics over placebo in achieving a favourable clinical course does not appear to be large. Whether such an effect size can justify a universal policy in favour of or against prescribing antibiotics for children with AOM is a multifaceted issue.

The rapidity of resolution of symptoms is an important quality of life outcome measure for diseases that tend to have a self-limiting nature, such as AOM. Continuing AOM-related symptoms, such as pain, fever and irritability, are also a source of parents’ anxiety and distress. Moreover, parents may need to take time off work to provide special care for the sick child. For older children, prolongation of the course of AOM may relate to increased number of days lost from school. In our meta-analysis, antibiotics were superior to placebo with regard to short-term resolution of symptoms, so they may have a value in improving the quality of life of patients or caregivers. A study that used a decision analysis approach to assess the above-mentioned issues and, additionally, economic costs, estimated that deferring antibiotic therapy for children meeting the current US guidelines criteria would result in 0.3–4 lost quality of life-adjusted days.

The above beneficial effects of antibiotics in terms of clinical effectiveness, translated into improved quality of life, may be counterbalanced by the development of treatment-related adverse events. Specifically, diarrhoea was found to be more likely in patients treated with antibiotics compared with those who were not initially treated with antibiotics. Similar findings have also been shown for acute sinusitis, which shares many features with AOM.

Another consideration regarding the value of antibiotics for AOM is their role in preventing disease complications. Although severe complications of AOM, such as mastoiditis and meningitis, are still being observed at a low, albeit not negligible, rate in community cases, they were rarely observed in our meta-analysis. Moreover, the incidence of acute mastoiditis appears to be higher in countries that have followed a restrictive antibiotic prescribing policy for AOM, compared with countries with high relevant antibiotic prescription rates.

An important question regarding the treatment of AOM is whether a strategy of reserving antibiotics for the children who appear to be in need for such treatment after a relatively short watchful waiting period is equally effective as a strategy of immediate institution of antibiotics to all candidate patients. In our meta-analysis, the difference in clinical effectiveness between a strategy of early administration of antibiotics versus a watchful waiting strategy did not appear smaller than that observed in trials comparing antibiotics with placebo. The above observation may indicate that the benefit of antibiotics in improving the outcome of AOM is greater if they are administered early.
Figure 3. Diarrhoea in children with AOM who were treated with antibiotics compared with either placebo or according to a watchful waiting strategy. The vertical line indicates no difference between the compared treatment groups. RRs (95% CI) are shown by diamond shapes; 95% CIs are shown by horizontal lines. Squares indicate point estimates; the size of the squares indicates the weight that each individual study has in the meta-analysis. M-H, Mantel–Haenszel random effects model.

Figure 4. Rash in children with AOM who were treated with antibiotics compared with either placebo or according to a watchful waiting strategy. The vertical line indicates no difference between the compared treatment groups. RRs (95% CI) are shown by diamond shapes; 95% CIs are shown by horizontal lines. Squares indicate point estimates; the size of the squares indicates the weight that each individual study has in the meta-analysis. M-H, Mantel–Haenszel random effects model.
in the course of the infection, when the host defence responses have not been fully activated.\textsuperscript{35} Notably, early administration of antibiotics has been associated with substantial clinical benefits and has become the standard of practice in severe infections, such as community-acquired and nosocomial pneumonia or bacteraemia.\textsuperscript{36–38}

From a public health perspective, limiting antibiotic use for AOM would contribute to the battle against antimicrobial drug resistance. This is important since it has been shown that resistance rates of major respiratory pathogens isolated from children attending day care centres are considerable.\textsuperscript{39} At a patient level, unnecessary use of antibiotics contributes to colonization with resistant pathogens,\textsuperscript{40} which may cause subsequent infections.\textsuperscript{41} Resistant pathogens might also spread to close contacts of the affected children.\textsuperscript{42,43}

The potential methodological limitations of our meta-analysis should be taken into consideration in assessing its findings. First, similarly to many other studies of this type, appreciable heterogeneity exists regarding the inclusion diagnostic criteria, along with the types of outcomes evaluated, and the methods and timing of the assessment of the outcomes among the included RCTs. It has been shown that such differences may appreciably influence findings in studies of AOM.\textsuperscript{44} Yet, we found no significant difference between the findings of trials using rigorous diagnostic inclusion criteria and the remaining trials.

Variability was also observed regarding the antibiotic dosages used in the included trials, raising concerns regarding the adequacy of antibiotic dosing.\textsuperscript{17,19} Additionally, the clinical course of AOM was evaluated with the use of different methods such as questionnaires or diaries filled out by parents in four trials\textsuperscript{14,15,18,22} and over-the-phone diagnosis in one trial.\textsuperscript{21} Moreover, in the watchful waiting trials of AOM that were included in our meta-analysis, their open-label or single-blinded design may have allowed bias to interfere with the evaluation of the outcomes. This may be implied by the fact that the effect of antibiotics in causing diarrhoea appeared exacerbated compared with the subgroup analysis including only placebo-controlled trials. Finally, it should be mentioned that antibiotic resistance may be observed in a substantial proportion of AOM cases in today’s clinical setting.\textsuperscript{45,46} thus compromising the utility of antibiotics.

Furthermore, we did not perform an intention-to-treat analysis, since such data were reported in only 5 of the 11 included trials, with regard to the primary effectiveness outcome of our meta-analysis.\textsuperscript{14,15,17,22,24} In these five trials, data on the intention-to-treat population corresponded to those of the clinically evaluable population that we included in our meta-analysis.\textsuperscript{15,17,22,24} In the remaining seven trials, the clinically evaluable population constituted 84%–96% of the intention-to-treat population.\textsuperscript{14,16,18–21,23} Therefore, data on the former type of population could be considered as a good approximation of the missing data on the latter.

Pooling the placebo-controlled with the watchful waiting trials may also raise some methodological concerns. We considered this combined analysis as a complementary one, mainly contributing in the derivation of non-definitive conclusions regarding secondary outcomes for which few of the trials included in the meta-analysis reported specific data. Regarding the primary effectiveness outcome that we selected for our meta-analysis, namely clinical success, it was determined by various criteria in the included RCTs and evaluated at different time points. In addition, this outcome, although not as specific, is more comprehensive compared with the evaluation of the course of specific symptoms only, which was commonly performed in prior meta-analyses in AOM. Specifically, another meta-analysis that used the severity and duration of pain as one of the primary endpoints showed that antibiotic treatment confers no benefit over placebo in this regard within the first 24 h, whereas it is associated with a small absolute reduction in pain after the first 2 days.\textsuperscript{10}

In our meta-analysis, we included trials that involved children of various age groups. Yet, scarcity of data on the outcome of children of different age strata precluded us from assessing the utility of antibiotics over placebo or watchful waiting with regard to this factor. It is well recognized, though, that children younger than 2 years old, and particularly those younger than 6 months, are more prone to untoward events associated with AOM.\textsuperscript{47,48} Similarly, a recent meta-analysis concluded that antibiotic treatment is more beneficial for children younger than 2 years old and for children with bilateral AOM.\textsuperscript{49}

Our meta-analysis, compared with recent ones,\textsuperscript{10,49} has included additional trials, which provides greater confidence regarding the variance of its findings. Still, the main novelty of our meta-analysis lies in the evaluation of the watchful waiting strategy in comparison with the immediate antibiotic treatment strategy.

In conclusion, our meta-analysis showed that antibiotics have greater clinical effectiveness compared with placebo for the treatment of AOM in children. This benefit of antibiotics was maintained when immediate antibiotic treatment was compared with watchful waiting. The margin of benefit conferred by antibiotic treatment does not appear to be large. Several other factors, such as the rapidity of resolution of symptoms, along with the frequency and nature of treatment-related adverse events, the potential for occurrence of disease complications and the community- and patient-related risks associated with antimicrobial drug resistance development should be further considered in the evaluation of different therapeutic strategies for AOM. Clinicians should bear in mind the above issues and also consider patient-related factors, referring to disease severity and the presence of adverse prognostic factors, in the relevant clinical decision-making process.

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Supplementary data
Figure S1 and Tables S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References
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