



Review article

The importance of being specific—a meta-analysis evaluating the effect of antibiotics in acute otitis media



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ABSTRACT

Background: Whether acute otitis media (AOM) should be the cause for antibiotic treatment has been a matter of debate during the last decades. Treatment guidelines are based on less than twenty trials that have found the effect of antibiotics on symptomatic outcomes in AOM, such as pain, to be very modest. Two recent trials found a more substantial effect of antibiotics when they looked at treatment failure as the outcome. That the effect varies with the chosen outcome may not only be because the true effect is different but also because different outcomes are more or less specific for the disease in question.

Objective: The purpose of this study was to perform a meta-analysis to calculate a composite risk ratio for treatment failure in AOM and also to investigate whether the specificity of treatment failure as an outcome differs from that of symptomatic outcomes, such as pain.

Methods: Trials evaluating the effect of antibiotics in AOM and reporting the number of treatment failures were identified and a fixed-effects meta-analysis was performed. In addition, the literature was searched for articles providing direct or indirect figures on the specificity of different outcomes in AOM trials. A hypothetical study was designed to show how differences in sensitivity/specificity of inclusion/outcome criteria affect the results of a trial.

Results: The meta-analysis yielded a composite risk ratio of 0.4 (95% CI 0.35–0.48), $p < 0.001$ for the effect of antibiotics on treatment failure. Based on data from the literature, the specificity of treatment failure was estimated to 92–100%. The hypothetical study showed how a non-specific outcome biases the effect estimate towards the null, whereas other kinds of misclassification only decrease precision.

Conclusion: Future trials should focus on improving diagnostic criteria to increase precision but primarily, they should focus on choosing a specific outcome in order not to get a biased effect estimate.

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Contents

1. Introduction	1222
2. Materials and methods	1222
2.1. Definitions	1222
2.2. Types of studies, interventions and participants	1222
2.3. Search methods	1222
2.4. Data extraction and management	1222
2.5. Statistical analysis	1223
3. Results	1223
3.1. Literature search	1223
3.2. Treatment failure meta-analysis	1224
3.3. Calculations using retrieved figures of specificity	1225
3.4. Hypothetical study	1225

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4. Discussion	1226
5. Conclusion	1226
Acknowledgement	1226
References	1226

1. Introduction

Acute otitis media (AOM) is the most common bacterial infection in childhood and also the most common reason for prescribing antibiotics to children [1]. The clinical picture is very varied and extends from self-limiting infections to life-threatening complications. Before the introduction of antibiotics, AOM-related complications were an important cause of child mortality but today, the complication rate has decreased to parts of thousands [2], antibiotics probably only being one of several reasons for this. From the 1950s, antibiotics became standard practice for AOM with the main purpose of protecting against complications. However, due to growing antimicrobial resistance, the standard use of antibiotics in a disease with an often benign course has been questioned and during the last 20 years, most countries in the Western world have developed guidelines that prescribe initial withholding of antibiotics in various cases of AOM. These guidelines are based on the less than twenty existing trials that have evaluated the effect of antibiotics in AOM in children and found it to be very modest [3–19].

However, AOM is a clinical diagnosis that is often difficult to make, physicians being uncertain of the diagnosis 40% of the time [1,20–22]. It has been argued that care should be taken when making inferences from the trials evaluating the effect of antibiotics in AOM since the diagnostic quality in many of them is poor and since exclusion of important patient groups creates bias [23]. A problem that has not earlier been discussed is the choice of outcome in these studies. A treatment may have a different effect on different outcomes but the outcomes may also be more or less specific for the condition you aim to treat. Due to the rarity of the ultimate outcome – complication – AOM trials have often used symptomatic outcomes such as pain or fever. These measures are present in many conditions besides AOM [21]. A recently published Cochrane review on antibiotics and AOM [24] reported varying relative risks for various outcomes; e.g. pain at 2–3 days (RR=0.7), development of contralateral AOM (RR=0.5) and development of tympanic membrane perforation (RR=0.4).

In 2011, two randomised placebo-controlled trials described a much larger effect of antibiotics in AOM than has previously been reported [7,17]. Both these trials used strict diagnostic criteria and both used treatment failure, which requires diagnostic findings as well as symptoms, as the outcome rather than purely symptomatic outcomes such as pain or fever. Antibiotics may well have a greater effect on treatment failure than on pain or fever but an additional explanation for these differing results could be that treatment failure as an outcome is more specific for AOM than are strictly symptomatic outcomes.

In this paper, figures from published trials are used to obtain a pooled risk ratio for treatment failure as an outcome. The literature is then reviewed to obtain figures directly or indirectly on the specificity of outcomes used in AOM trials to see if this information agrees with the retrieved risk ratios and to see if a “backward count” will yield risk ratios similar to those obtained in meta-analyses. A hypothetical study is presented with the aim of showing how changes in measurement accuracy of inclusion criteria as well as outcome criteria affect results.

2. Materials and methods

2.1. Definitions

AOM was defined as a purulent infection of the middle ear in a child with acute symptoms. In the sensitivity/specificity calculations, the gold standard for diagnosis was defined as growth of AOM pathogens in an effusion obtained at myringotomy.

Treatment failure was defined as persisting symptoms and clinical signs of AOM during the course of treatment, causing a change of treatment strategy from placebo/watchful waiting to antibiotics or from one antibiotic to one with a broader spectrum.

2.2. Types of studies, interventions and participants

Trials evaluating the effect of antibiotics in AOM in children (age 0–16 years) either by comparison with placebo or with watchful waiting/delayed prescription were considered for inclusion in the meta-analysis. If such trials reported the number of treatment failures in each group, they were eligible for this exercise.

In order to obtain figures on specificity for different outcomes used in AOM trials, studies of children with AOM where the investigators had either reported such figures directly or performed myringotomies twice (at diagnosis and during treatment – so called “double tap studies” – were identified. If the latter type of trial reported figures on symptoms or treatment failures in correlation to myringotomy results, they were used to calculate the specificity of these outcomes.

2.3. Search methods

In addition to the trials identified in a recently published Cochrane review [24], an identical search strategy was used to search Medline and Embase for trials published after the “search deadline” (November 2012) for the Cochrane review.

In order to identify studies presenting figures on specificity for pain, fever or treatment failure, Medline and Embase were searched for: (1) acute AND ‘otitis’/exp AND media AND [humans]/lim AND sensitivity OR specificity AND ‘pain’/exp OR ‘fever’/exp OR ‘treatment’ AND failure AND diagnos* (2) acute AND ‘otitis’/exp AND media AND [humans]/lim AND sensitivity OR specificity AND sym?tom (3) acute AND ‘otitis’/exp AND media AND [humans]/lim AND sign* AND sym?tom* AND ‘diagnosis’/exp OR ‘otoscopy’/exp OR otomicroscop*.

In order to identify “double tap studies” for the calculation of sensitivity/specificity measures, again Medline and Embase were searched for: trial AND acute otitis media OR aom AND ‘myringotomy’/exp OR ‘tympanocentesis’/exp OR ‘double-tap’ AND [humans]/lim.

Newly identified trials were screened by title and abstract to see if they fulfilled inclusion criteria. The full texts of the presumably eligible studies were then examined in order to establish whether the desired information was available.

2.4. Data extraction and management

Data on diagnostic criteria and number of treatment failures in each treatment arm were extracted from each study identified for the meta-analysis.

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