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A systematic review of randomized controlled efficacy trials

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DEPARTMENT OF CHILD AND ADOLESCENT HEALTH AND DEVELOPMENT

WORLD HEALTH ORGANIZATION

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Executive Summary

Background

The current World Health Organization (WHO) recommendation for antibiotic treatment of acute otitis media is to give oral co-trimoxazole (trimethoprim 4 mg/kg/sulfamethoxozole 20 mg/kg twice a day) or amoxicillin (15 mg/kg three times a day) for five days. On the basis of recent data, WHO now recommends antimicrobials for only three instead of five days in non-severe pneumonia. Participant countries are thus naturally interested to see whether a similar reduction in duration of antibiotic therapy is appropriate for acute otitis media. In this age of rising health-care costs, increasing concern about emergence of resistant bacteria from the overuse of antibiotics and poor compliance with medication following symptomatic relief, it is desirable to know the shortest duration of antibiotic treatment that would result in favourable outcomes for acute otitis media in children. The available relevant systematic reviews on this subject were performed through literature searches conducted eight to ten years ago, were primarily based on clinical outcomes and did not specifically address the efficacy of a three-day antibiotic course. The current systematic review was therefore conducted to update appropriately the evidence base including bacteriologic outcomes.

Methods

The objective of the review was to determine the effectiveness of a short course of antibiotics (less than four days) in comparison with a longer course (four days or greater) for the treatment of acute otitis media in children. Randomized controlled trials of the empiric treatment of acute otitis media, comparing two antibiotic regimens of different duration, were considered for inclusion in the review. The participants included children between the ages of four weeks to 18 years with a clinical diagnosis of acute otitis media and no history of immediate prior antibiotic use, immune deficiency, chronic disease or head and neck abnormalities. The types of intervention eligible for the review were empiric antibiotic therapy for less than four days (defined as the short course), compared with equal to or greater than four days (defined as the long course). The antibiotic choices could be the same or different in the two treatment arms. Trials providing non-antibiotic interventions (for example analgesics, decongestants, or both) were considered if the only difference between the treatment arms was antibiotic duration as defined above.

The primary outcome was treatment failure (lack of clinical resolution or relapse or recurrence of acute otitis media or bacteriologic failure - wherever culture results by tympanocentesis were available) at an evaluation point until one month (31 days) after initiation of therapy. Clinical resolution meant that the presenting signs and symptoms of acute otitis media had improved or resolved. Requirement of second antibiotic was considered treatment failure. Secondary outcomes were: (a) clinical or bacteriologic failure shortly after treatment, at 10 to 14 days; (b) the cumulative number of treatment failures, relapses and recurrences reported from time of diagnosis until a final evaluation point between one and three months; and (c) any adverse effects of therapy. Middle ear effusion was not classified as a treatment failure because of its documented persistence during the course of the disease, regardless of treatment.

Using a carefully designed search strategy, the trials were identified from simultaneous searches of the various medical databases (till 26 August 2007), reference lists of identified articles, hand searches of reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings, and with help from donor agencies, 'experts' and authors of recent reviews.

Data abstraction was done using preformed questionnaires. The trials were grouped by the pharmacokinetic behaviour of the antibiotic used in the short course arm as follows: (i) short-acting oral antibiotics, for example penicillin, amoxicillin, cefaclor, cefuroxime; (ii) oral azithromycin or other macrolides; or (iii) parenteral ceftriaxone. Quality assessment of the trials was performed using the three standard criteria – allocation concealment, completeness of follow-up and blinding.

Data entry and analysis were done with SPSS and STATA softwares. The presence of bias was evaluated by funnel plot, and confirmed by Begg's and Egger's methods. Pooled estimates [relative risk (RR) with 95% confidence intervals (CI)] were calculated by both fixed and random effects models but the latter was used for depiction. Formal tests of heterogeneity were performed, namely, the statistic Cochran Q and I-squared (variation in pooled estimate attributable to heterogeneity). Pre-specified sensitivity and subgroup analyses were planned to be conducted for the

following: (i) quality of trial (allocation concealment, completeness of follow-up, and blinding); (ii) age (<2 years or >2 years); (iii) perforated tympanic membrane (yes or no); (iv) recurrent otitis media (yes or no); (v) trial site (developed or developing country); (vi) pharmacokinetic behaviour of the antibiotic used in the short course treatment arm (as defined above); (vii) duration of treatment in the long course treatment arm (recorded as a continuous variable with attempt to stratify as <10 days, or ≥10 days); (viii) outcome assessment time (within 10 to 14 days, until 31 days, or until 32 to 90 days); (ix) co-interventions (yes or no); (x) compliance monitoring (yes or no); (xi) intention to treat analysis (yes or no); and (xii) microbiological isolates (*S. pneumoniae* and *H. influenzae* versus others). Separate sensitivity and subgroup analyses were also attempted to assess the robustness of outcome criteria by redefining clinical resolution to include cured, but not improved symptoms. As no analytic components were identified, which were exclusively conducted in the pre-specified strata for age group, perforated tympanic membrane, recurrent otitis media or microbiological isolates, these subgroup analyses were done separately for those studies providing disaggregated information for outcomes on these variables. The subgroup analyses for outcome assessment time were implicit in the primary and secondary outcomes evaluation. The contribution of these variables to heterogeneity was also explored by metaregression.

Results

Forty-six potentially eligible randomized controlled trials were identified. Among these, eight studies were excluded, as these were ineligible. Of the 38 trials satisfying the inclusion criteria, three were excluded by outcome. Thirty-five trials were finally evaluated, which provided 38 analytic components.

These studies were primarily conducted in developed countries (11 in Europe, 10 each in North America and Asia, and four were multicentric from different continents). The duration of antibiotic use in the long course arm was 10 days in 33 analytic components, 7-14 days in two analytic components, seven days in two analytic components, and five days in one analytic component. Of the 35 trials, three used short-acting oral antibiotics, 21 used azithromycin, and 11 used parenteral ceftriaxone in the short course arm. Among the short-acting oral antibiotics group, similar antibiotics had been used in the short and long course arms. In the 23 analytic components, which had used oral azithromycin in the short course arm, only four had employed macrolides in the long course arm while the remaining had administered short-acting oral antibiotics, either amoxicillin or amoxicillin-clavunate (n=14), or cephalosporins (n=5). In studies addressing parenteral ceftriaxone use in the short course group (n=12), only short-acting oral antibiotics had been employed in the long course arm, primarily amoxicillin or amoxicillin-clavunate (n=9).

Primary outcome (treatment failure until one month)

The funnel plot was symmetrical suggesting the absence of publication bias, which was confirmed using the Egger's (weighted regression) method (P for bias=0.994) and the Begg's (rank correlation) method (continuity corrected P= 0.763). There was no evidence of an increased risk of treatment failure with a shorter course of antibiotics (≤ 3 days). The overall relative risk for treatment failure with a short course of antibiotics in comparison to a longer course was 1.06 (95% CI 0.95 to 1.17, P=0.298; test for heterogeneity: Cochran Q=37.02, I^2=0.1%, P=0.468). Use of a short-acting oral antibiotic in the short course arm was associated with a significantly increased risk of treatment failure (2.27, 95% CI 1.04 to 4.99). The slightly increased risk of treatment failure with parenteral ceftriaxone (1.13, 95% CI 0.99 to 1.30) was not statistically significant; however, the lower limit of confidence interval was close to 1. On combined scrutiny of sensitivity, subgroup and metaregression analyses, azithromycin use in the short course arm