RESEARCH PAPER

Efficacy of Short Course (<4 Days) of Antibiotics for Treatment of Acute Otitis Media in Children: *A Systematic Review of Randomized Controlled Trials*

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Objective: To determine the efficacy of a short course of antibiotics (<4 days) in comparison to a longer course (≥4 days) for the treatment of acute otitis media in children.

Data sources: Electronic databases, hand search of reviews, bibliographies of books, abstracts and proceedings of international conferences.

Review Methods: Randomized controlled trials of the empiric treatment of acute otitis media comparing antibiotic regimens of <4 days versus ≥4 days in children between four weeks to eighteen years of age were included. The trials were grouped by pharmacokinetic behavior of short-course antibiotics into short-acting antibiotics, parenteral ceftriaxone, and long-acting azithromycin.

Results: We reviewed 35 trials, which provided 38 analytic components. Overall, there was no evidence of an increased risk of treatment failure until one month with a short-course of antibiotics (RR=1.06, 95% CI 0.95 to 1.17, P=0.298). Use of short-acting oral antibiotic in short-course was associated with a significantly increased risk of treatment failure (RR=2.27, 95% CI: 1.04 to 4.99). There was a slightly increased risk of treatment failure with parenteral ceftriaxone (RR=1.13, 95% CI 0.99 to 1.30). The risk of adverse effects was significantly lower with short-course regimens (RR=0.58, 95% CI: 0.48 to 0.70).

Conclusion: There is no evidence of an increased risk of treatment failure with short course of antibiotics for acute otitis media. Among the short-course regimens, azithromycin use was associated with a lower risk of treatment failure while short-acting oral antibiotics and parenteral ceftriaxone may be associated with a higher risk of treatment failure.

Key Words: *Acute otitis media, Antibiotics, Children, Management, Short-course therapy, Systematic review.*

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Otitis media is one of the most common childhood infections, the leading cause of visits to doctors by children, and the most frequent reason children consume antibiotics or undergo surgery in developed countries(1,2). Although there is some debate regarding the utility and specific guidelines for prescribing antimicrobials in acute otitis media(2-6), these drugs are frequently employed in practice.

The optimal duration of prescribed antibiotic treatment for acute otitis media is still unclear, and varies worldwide. Expert opinion has recommended a reduction in antimicrobial use from 10 to 5 days for the treatment of uncomplicated otitis media in children over the age of six years(7). Many narrative and systematic reviews have assessed the quality of scientific evidence to support a short course of antibiotic treatment(3,8-10). The existing World Health Organization (WHO) recommendation for antibiotic treatment of acute otitis media is to give oral cotrimoxazole or amoxicillin for five days(11). However, on the basis of recent data, the WHO now recommends antimicrobials for only three days

(instead of five days) in non-severe pneumonia(12,13). It would therefore be useful to explore the comparative efficacy of a short course of any antibiotic with a longer course of the same or another antibiotic for the empirical treatment of acute otitis media. The current systematic review was conducted to update the evidence on this subject including bacteriologic outcomes to factor for the possibility of "Pollyanna phenomenon"(14-16).

METHODS

Objectives: To determine the efficacy of a short-course of antibiotics (<4 days) in comparison to a longer course (≥4 days) for the treatment of acute otitis media in children. Subgroup analyses of children less than two years old, children with a perforated ear drum and children with recurrent otitis media were conducted to address concerns that these groups may have less favorable outcomes.

Types of trials: Randomized controlled trials of empiric treatment of acute otitis media, comparing two antibiotic regimens of different duration were included.

Participants: Children between the ages of four weeks and eighteen years, with a clinical diagnosis of acute otitis media and no history of immediate antibiotic use, immune deficiency, chronic disease or head and neck abnormalities.

Intervention: Empiric antibiotic therapy of a treatment arm for <4 days (short-course), and of a comparison arm for ≥4 days (long-course). The antibiotic could be the same or different in the two treatment arms. Trials providing additional non-antibiotic interventions (analgesics, decongestants, or both) were eligible if the only difference between the treatment arms was antibiotic duration.

Outcome measures: The primary outcome was treatment failure, which included 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 as treatment failure.

Secondary outcomes were: (*a*) clinical or bacteriologic failure shortly after treatment, at 10 to 14 days, because this time is most reflective of the bacteriologic effect of the drug, and it is important to distinguish between relapse and a new infection (recurrence) when considering treatment failure, as a new infection can occur even when treatment was with the most effective drug(15); (*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. Data were however, sought on the number of children with persistent middle ear effusion at all evaluation points.

Search methods: The trials were identified by simultaneous searches of various medical databases till August 26, 2007 (search details available on request). There were no language restrictions. The title and abstract of identified trials were scanned to exclude obviously irrelevant trials. Full texts of remaining trials were retrieved and relevant articles identified. This was supplemented by hand searches of reviews, bibliographies of books and other unpublished relevant literature. Finally, donor agencies, 'experts' and authors of recent reviews were contacted for their knowledge of any additional trials.

Quality assessment: We assessed the quality of trials using recommended criteria for allocation concealment, loss to follow up and blinding(17).

Data abstraction: The data was abstracted in duplicate. The trials were grouped by pharmacokinetic behavior of the antibiotic used in the short-course: (*i*) short-acting oral antibiotics like penicillin, amoxicillin, cefaclor; (*ii*) oral azithromycin or other macrolides; or (*iii*) parenteral ceftriaxone. In 'multi-arm' trials, in order to examine heterogeneity characteristics, we split the 'shared' group into two or more groups with smaller sample

size, and included two or more (reasonably independent) comparisons(18) or analytic components.

Statistical Analysis: Data entry and analysis were done with SPSS (version 13.0) and STATA (version 9.2) softwares. The presence of bias was evaluated by funnel plot asymmetry(19), and confirmed by Begg's and Egger's methods(20,21). 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)(22). Pre-specified sensitivity and subgroup analyses (listed in results) were performed with the user written "metan" command ("by option") in STATA (version 9.2) software(20,23,24). A separate sensitivity and subgroup analyses was 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 groups, perforated tympanic membrane, recurrent otitis media or microbiological isolates, these subgroup analyses were done separately for those trials providing disaggregated information for outcomes on these variables. The contribution of these variables to heterogeneity was also explored by meta-regression(25).

RESULTS

We identified 46 potentially eligible randomized controlled trials(26-71). Amongst these, 8 trials were excluded(26-33), as these were ineligible (***Fig.* 1**). Of the 38 trials satisfying the inclusion criteria, 3 were withdrawn by outcome(34-36). We therefore finally evaluated 35 trials, which provided 38 analytic components.

These trials were primarily conducted in developed countries. Children above 12 years age were included in one trial while no trial was conducted exclusively in subjects below 2 years of age. The duration of antibiotic use in the long-course was 10 days in 33 analytic components, 7-14 days in 2 analytic components, 7 days in 2 analytic components, and 5 days in one analytic component. In most of the analytic components (22/36; 61%), apart from symptoms and signs of acute ear inflammation, presence of middle ear effusion was stated to be an essential diagnostic criterion (details available on request).

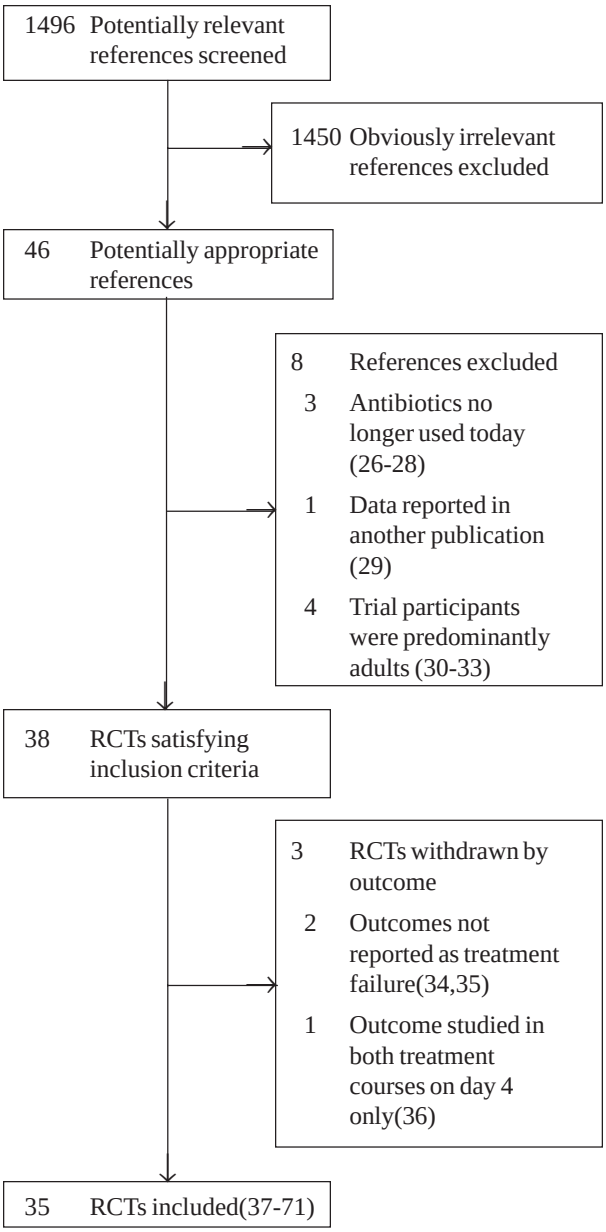

FIG. 1 *Flow chart for selection of randomized control trials included in the meta-analysis.*

In the short-course regimen, short-acting oral antibiotics were used in 3 trials, azithromycin in 21

and parenteral ceftriaxone in 11. Amongst 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 short-course arm, only 4 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). Amongst the parenteral ceftriaxone use in the short-course group (*n*=12), only short-acting oral antibiotics had been employed in the long-course, primarily amoxicillin or amoxicillin-clavunate (*n*=9). In 3 analytic components, information on both clinical and bacteriologic failures was available for all subjects.

Outcomes until 1 month

The funnel plot was symmetrical suggesting the absence of publication bias, which was confirmed using the Egger's (*P* =0.994) and Begg's (*P*= 0.763) methods.

Overall, there was no evidence of an increased risk of treatment failure with short-course (<4 days) (***Table* I, *Fig.*2**). On influence analysis, no single analytic component had a substantial impact on the quantification of summary relative risk. When treatment failure was redefined to include improved subjects, the risk of this outcome was significantly lower with short-course.

On sensitivity and subgroup analyses, significant (*P*<0.05) heterogeneity was evident for only two variables, namely, pharmacokinetic behavior of antibiotic used in short-course and compliance monitoring (details available on request). Use of short-acting oral antibiotic was associated with a significantly increased risk of treatment failure. The increased risk of treatment failure with parenteral ceftriaxone was not statistically significant; however, the lower confidence interval was close to 1 (***Table* I**). On univariable and multivariate meta-regression, use of azithromycin in short-course and compliance monitoring were identified as significant predictors of heterogeneity (***Table* II**).

Clinical treatment failure until 1 month in culture positive otitis media: There was no evidence of an increased risk of clinical treatment failure in trials(48,61,64,70,71) providing relevant information (***Table* I**). In one study(64), about two-thirds of the subjects had recurrent otitis media and the remaining persistent otitis media. However, disaggregated culture information was not provided for recurrent and persistent otitis media. As a sensitivity analysis, exclusion of this study did not alter the findings.

Bacteriologic failure until 1 month: Bacteriologic cultures from the middle ear had been performed in all subjects at recruitment and after initiation of antibiotic therapy in three analytic components only(61,63). In addition, in 4 analytic components(47,54,57), cultures were available at two time points in only a small proportion of recruited subjects. Overall, there was no evidence of an increased risk of bacteriologic failure (***Table* I**). The findings were similar when both the above subgroups were analyzed separately and there was no evidence of heterogeneity in the sub-groups.

Treatment failure in high risk groups: Stratified information in high risk groups [children below 2 years of age(45,47,65,66,70), perforated ear drum(44,45,47,59), recurrent otitis media(44,47,55, 64), and specific bacterial pathogens(39,48,61,63, 64,70,71) was depicted in some trials. There was no evidence of an increased risk of treatment failure with short-course antibiotics in these high risk groups (***Table* I**).

Persistent middle ear effusion: Data on persistent middle ear effusion till 1 month was available from six trials(48,51,55,66,67,71). Except one study(55), which had used parenteral ceftriaxone, other trials had prescribed azithromycin in the short-course arm. Overall, there was no evidence of an increased risk for persistent middle ear effusion (***Table* I**). There was no evidence of heterogeneity (*P*=0.165) between the two subgroups. However, the risk for persistent middle ear effusion was significantly lower when azithromycin was used as the short-course antibiotic (RR=0.81, 95% CI 0.67 to 0.98, *P*= 0.031; I^2=0.0%).

Relapse and recurrence: Overall, there was no evidence of an increased risk for relapse or

TABLE I SUMMARY OF POOLED ANALYSES FOR ALL OUTCOMES

Outcome	No	Random effects model RR (95% CI)	*P* value	Tests for heterogeneity I^2 (%) (*P* value)	*P* value for heterogeneity in subgroups
Outcomes until 1month					
Overall treatment failure	38	1.06 (0.95, 1.17)	0.298	0.10 (0.468)	Not applicable
Short-course antibiotic used					
Short acting oral	3	2.27 (1.04, 4.99)	0.040	0.00 (0.561)	
Azithromycin	23	0.93 (0.79, 1.09)	0.350	0.00 (0.713)	
Parenteral ceftriaxone	12	1.13 (0.99, 1.30)	0.071	0.00 (0.464)	0.027
Treatment failure redefining subjects showing improvement as failure	28	0.83 (0.70, 0.98)	0.024	46.50 (0.004)	Not applicable
Clinical treatment failure in culture positive otitis media	5	1.05 (0.75, 1.46)	0.796	20.0 (0.287)	Not applicable
Bacteriological failure	7	0.97 (0.66, 1.44)	0.880	0.0 (0.912)	Not applicable
Persistent middle ear effusion	6	0.86 (0.72, 1.02)	>0.05	0.0 (0.457)	Not applicable
Relapse	12	0.99 (0.73, 1.34)	>0.05	0.0 (0.992)	Not applicable
Recurrence	7	1.33 (0.66, 2.7)	>0.05	0.0 (0.771)	Not applicable
Treatment failure in high risk groups until 1 month					
Age (years)					
< 2	5	0.87 (0.61, 1.25)	0.454	35.30 (0.186)	
> 2	5	0.96 (0.63, 1.48)	0.864	25.70 (0.250)	0.758
Perforated eardrum*					
Yes	4	0.80 (0.39, 1.63)	0.535	0.00 (0.428)	
No	1	1.31 (0.60, 2.87)	0.499	*Not applicable*	0.365
Recurrent otitis media					
Yes	4	0.70 (0.48, 1.03)	0.070	0.00 (0.992)	
No	3	1.07 (0.65, 1.76)	0.784	0.00 (0.382)	0.186
Isolated microorganisms					
S. pneumoniae/H. influenzae	8	1.03 (0.81, 1.33)	0.797	0.00 (0.528)	
Others	7	0.97 (0.49, 1.88)	0.916	0.00 (0.546)	1.000
Outcomes at 10 to 14 days					
Treatment failure	30	1.12 (0.97, 1.3)	0.130	0.00 (0.939)	Not applicable
Persistent middle ear effusion	6	1.02 (0.92, 1.14)	0.668	0.00 (0.910)	Not applicable
Outcomes between one and three months					
Treatment failure	3	0.84 (0.66, 1.08)	0.171	0.00 (0.379)	Not applicable
Persistent middle ear effusion	3	0.79 (0.42,1.49)	0.469	0.00 (0.958)	Not applicable
Relapse	2	1.18 (0.72, 1.95)	0.514	0.00 (0.660)	Not applicable
Recurrence	3	0.56 (0.36, 0.85)	0.007	0.00 (0.670)	Not applicable
Adverse effects					
Overall	20	0.58 (0.48, 0.70)	<0.001	0.00 (0.821)	Not applicable
Diarrhea	20	0.61 (0.38, 0.97)	0.036	81.20 (<0.001)	Not applicable
Vomiting	12	0.67 (0.46, 0.98)	0.038	0.00 (0.812)	Not applicable
Rash	17	0.82 (0.58, 1.15)	0.244	0.00 (0.500)	Not applicable
Abdominal pain	9	1.32 (0.67, 2.60)	0.426	5.1 (0.392)	Not applicable

*# - Number of analytic components; *Outcome until 2 months.*

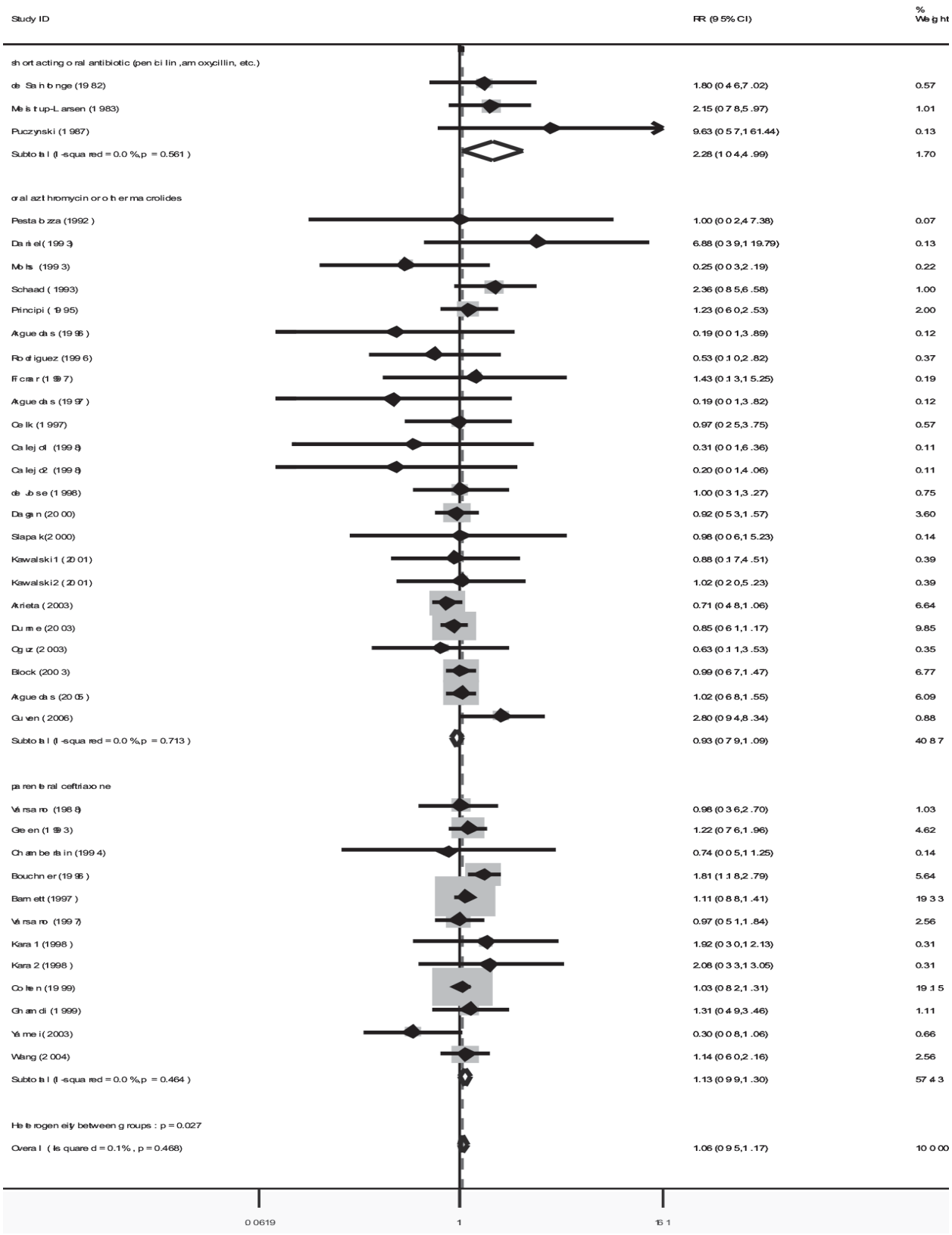

FIG. 2 *Forest plot for treatment failure until 1 month from random effects model for short-course vs long-course in relation to pharmacokinetics of antibiotic used in short-course (analytic components = 38).*

recurrence until 1 month (***Table* I**). There was no evidence of heterogeneity in the sub-groups according to the pharmacokinetic behavior of the antibiotic used in the short-course.

Outcomes at 10 - 14 days and at 1 -3 months

At 10-14 days, there was no evidence of an increased risk of treatment failure or of persistent middle ear effusion (***Table* I**). Limited data (three trials) evaluating outcomes between 1-3 months also did not suggest an increased risk of treatment failure, relapse, recurrence or persistent middle ear effusion with short-course (***Table* I**).

Adverse effects

The risk of individuals reporting adverse effects was significantly lower with short-course (***Table* I**). There was no evidence of heterogeneity in the three subgroups for the number of individuals reporting adverse effects. There was a significantly lower risk of developing diarrhea and vomiting with short-course. Amongst the antibiotics used in the short-course, oral azithromycin was associated with a decreased risk of diarrhea (0.54, 95% CI 0.33 to 0.89) and rash (0.53, 95% CI 0.32 to 0.90) whereas parenteral ceftriaxone was associated with decreased risk of vomiting but an increased risk of injection site pain (single study data).

DISCUSSION

This systematic review did not document an increased risk of treatment failure until one month with a short-course of antibiotics (RR=1.06, 95% CI 0.95-1.17). On sensitivity, subgroup and meta-regression analyses, azithromycin use in short-course and compliance monitoring emerged as significant predictors of a lower risk of treatment failure. Limited data available did not suggest an increased risk of: (*i*) treatment failure in culture positive cases or in high risk groups, (*ii*) bacteriologic failure, (*iii*) relapse, (*iv*) recurrence, (*v*) persistent middle ear effusion until 1 month, or (*vi*) treatment failure or persistent middle ear effusion at earlier (10-14 days) or later (1-3 months) evaluation points. The risk of individuals reporting adverse effects was significantly lower in short-course (RR=0.58, 95% CI 0.48 - 0.70).

Strengths and limitations of analyses: This is an updated systematic review, which also incorporates relevant sensitivity, subgroup and meta-regression analyses. Non-English publications were also evaluated. There was no evidence of publication bias. The main conclusion regarding the primary outcome remained stable over a large spectrum of stratified analyses. Influence analysis did not reveal an overwhelming effect of any single trial. We also analyzed bacteriologic failure to factor for the possibility of "Pollyanna phenomenon"(14-16). Further, significant predictors of response were identified.

It would be prudent to consider the following limitations. First, a head to head comparison of different durations of the same antibiotic was done in only four trials(37-39,54). Of these, only two had compared amoxicillin. The results of the vast majority of individual trials could therefore reflect the differences in pharmacological properties of the antibiotics used in the short and long-course arms rather than the duration of drug use. Azithromycin is a long-acting drug, and in fact, the 3-day course means >7-day antibiotic influence and the 5-day course >10-day antibiotic influence. Second, interpretation is confounded by the wide variation in diagnostic and outcome criteria. Lack of stringent diagnostic criteria(72) could have resulted in treatment of children without acute otitis media. Differences in outcome may be imperceptible if assessed too early or too late. The "test of cure" end point, defined as clinical outcome 28-30 days after initiation of antimicrobial therapy, has been recommended for acute otitis media trials(15, 73). Clinical outcome was invariably measured until 14 days only, with no further follow up. Third, in only three analytic components both bacteriologic diagnosis and outcome measures were available for all subjects. This can undermine the true difference between the bacteriologic efficacies of two treatment courses because of high rate of spontaneous cure in cases of clinically diagnosed acute otitis media(15). Fourth, information on high-risk groups was limited. Fifth, majority of the trials (74% analytic components) were conducted in developed countries. However, trial site was not a significant predictor of risk of treatment failure, and thus

TABLE II META-REGRESSION ANALYSES FOR RELATIVE RISK OF PRIMARY OUTCOME (RESTRICTED MAXIMUM LIKELIHOOD METHOD)

Study characteristic	Univariable analysis		Controlling for additional variables	
	RR (95% CI); *I^2	*P*	RR (95% CI)	*P*
Study quality				
Allocation concealment (others *vs* adequate)	0.84 (0.52, 1.35); 0.01	0.456	1.43 (0.70, 2.91)	0.317
Attrition (>10% *vs* <10%)(*n*=36)	1.13 (0.90, 1.43); 0.05	0.291	1.03 (0.74, 1.42)	0.873
Blinding (others *vs* double blind)	1.16 (0.93, 1.45); 0.00	0.172	1.00 (0.64, 1.58)	0.982
Trial site (developed *vs* developing)	1.21 (0.89, 1.65); 0.00	0.216	1.15 (0.82, 1.63)	0.404
Short-course arm				
Other antibiotics *vs* oral short-acting	0.46 (0.20, 1.04); 0.00	0.062	DR	DR
Other antibiotics *vs* azithromycin	1.25 (1.01, 1.55); 0.00	**0.045**	3.31 (1.11, 9.89)	**0.034**
Other antibiotics *vs* parenteral ceftriaxone	0.85 (0.68, 1.05); 0.00	0.127	2.71 (0.93, 7.88)	0.066
Duration of long-course antibiotic (≥ 10 *vs* < 10 days)	0.73 (0.35, 1.50); 0.00	0.377	0.99 (0.40, 2.45)	0.982
Cointervention (no *vs* yes)	0.94 (0.69, 1.27); 0.00	0.668	1.11 (0.82, 1.51)	0.475
Compliance monitoring (others *vs* yes)	1.39 (1.05, 1.83); 0.00	**0.021**	1.52 (1.01, 2.28)	**0.046**
Intention to treat analysis (others *vs* yes)	1.16 (0.92, 1.47); 0.00	0.196	0.98 (0.66, 1.46)	0.924

*The number of analytic components in univariate model is 38 except where specifically stated otherwise; * Proportion of residual variation due to heterogeneity, I-squared; DR – Dropped in the analysis due to collinearity; Multivariate model – number of analytic components is 36 and the proportion of residual variation due to heterogeneity, I-squared is 0.0; In the multivariate analysis, as a sensitivity exercise, on dropping the variable attrition from the model due to missing observation in 2 units, the following variable was found significant; Compliance monitoring (others vs. yes): 1.50 (1.01, 2.23); P=0.046.*

extrapolation to developing country settings may be appropriate. Finally, we performed multiple analyses which increased the possibility of false positive results. The identified significant predictors of treatment failure should therefore be considered as exploratory in nature, rather than definitive.

There is a paucity of similar earlier analyses for direct comparison. A systematic review of randomized controlled trials, based on a search conducted in March 1998, compared the effectiveness of short and longcourses of antibiotic therapy; however, the definitions of short and long-course antibiotic therapy varied from this review (<7 days *versus* ≥7 days)(9,10). The authors concluded that five days of short-acting antibiotic is effective treatment for uncomplicated ear infections in children. In another later systematic review(3), risk differences instead of relative risks were used to compare outcomes for different antibiotic durations amongst various subgroups of antibiotics. In 3 trials comparing ceftriaxone with 7-10 days of amoxicillin, the combined failure rate difference was 3.4% (95% CI –1.6% to 8.5%). In a comparison of <5 days of azithromycin with 7-10 days of amoxicillin-clavunate, the pooled failure rate difference was 2.1% (95% CI 0.6% to 4.8%), which was reported as not significant.

The observed comparability between short and long-courses of antibiotics is biologically plausible, on the basis of(9,10): (*i*) spontaneous resolution of untreated otitis media, (*ii*) early eradication of pathogens after 3 to 5 days of treatment(74), (*iii*) poorer penetration of antibiotic into the ear with continued administration as inflammation decreases(75), and (*iv*) treatment of children without acute otitis media because of diagnostic uncertainty. Further, pharmacological properties offer plausible explanation. Azithromycin has a high tissue to serum ratio, elevated concentration in middle ear(76), and prolonged elimination half-life. Intramuscularly administered ceftriaxone achieves high peak serum levels after 2 hours(77) and also has a prolonged

WHAT IS ALREADY KNOWN?

- Expert opinion recommends a reduction in antimicrobial use from 10 to 5 days for uncomplicated otitis media over the age of six years.

WHAT THIS STUDY ADDS?

- In comparison to a longer course (≥4 days) of any antibiotic treatment for otitis media, a short course (< 4 days) of long acting azithromycin was associated with a lower risk of treatment failure while a short-course of short-acting oral antibiotics and possibly parenteral ceftriaxone were associated with a higher risk of treatment failure.

half-life. However, penicillins and cephalosporins display minimal concentration dependent killing(78); the extent of bacterial killing for this group is largely dependent on the length of exposure. For time dependent agents, maintaining drug concentrations above the MIC for at least 40% of the dosing interval is the best predictor of efficacy, and the goal of dosing is to optimize the duration of exposure(78,79). This may explain the high risk of treatment failure with short-course amoxicillin or penicillin therapy.

It is difficult to explain the lower risk of treatment failure with compliance monitoring. This could represent a false positive result due to multiple testing. However, it is possible that compliance monitoring was selectively more important for the short-course arm, particularly for azithromycin.

Adverse effects are a common reason for poor patient compliance. This review documented a lower risk for individuals reporting adverse effects with short-course therapy. The risk of developing diarrhea and rash was lower with azithromycin use in short-course. Similar results have been reported earlier(80,81), resulting in better compliance with azithromycin. Parenteral ceftriaxone was associated with a reduced risk of vomiting but an increased risk of injection site pain.

On a *posthoc* analysis (univariable meta-regression for the entire data set), industry support emerged as a significant predictor of lower risk (0.73, 95% CI 0.57 to 0.94, P=0.015); however, with adjustment for other variables it did not remain a significant predictor (0.73, 95% CI 0.35 to 1.52, P=0.384). There is thus no concrete evidence on a *post hoc* analysis that industry supported trials have biased the pooled results; however, this possibility cannot be totally excluded.

Implications for practice and policy: A reduction in the WHO advocated oral antibiotic (cotrimoxazole or amoxicillin) therapy from five to three days cannot be proposed because of the possibility of an increased risk of treatment failure. Similarly, for parenteral ceftriaxone, higher treatment failure rates cannot be confidently excluded. Administration of a parenteral drug also raises logistic challenges. Cost effectiveness(43) and concern about enhanced bacterial resistance needs evaluation although compliance may be better(43,49,59,69). Therefore, it would be difficult to propose ceftriaxone as an alternative to the current WHO recommendation.

There was no evidence of an increased risk of treatment failure with short-course oral azithromycin while adverse effects were significantly lower, especially diarrhea and rash. Earlier trials have documented that consumers prefer shorter treatment courses(82), which result in better compliance. A methodologically weak study(63) suggests that azithromycin may be a cheaper choice than clarithromycin or amoxicillin-clavulanic acid but a detailed cost-effectiveness analysis is essential. The possible disadvantages of recommending azithromycin also need consideration. These include, the logistic implications for public health programs of recommending two separate antibiotics (cotrimoxazole or amoxicillin, and azithromycin) for different respiratory tract infections, namely, pneumonia and otitis media, and concerns about enhanced bacterial resistance.

Implications for research: Future areas for research, include: (*i*) data in high risk groups, (*ii*) trials with

outcome recording for longer periods (one month or more), (*iii*) comparison of different treatment durations for the same antibiotic, parti-cularly those currently recommended by the WHO, to confidently segregate the effects of therapy duration from antibiotic profile, (*iv*) data on bacteriologic failure and success rates, and (*v*) development of antibiotic resistance during follow-up.

Overall, there is no evidence of an increased risk of treatment failure until one month with a short course (<4 days) of antibiotics for treating acute otitis media in children. However, in the short-course group, long-acting azithromycin use was associated with a lower risk of treatment failure while short-acting oral antibiotics and possibly parenteral ceftriaxone may be associated with a higher risk of treatment failure. Further research is justified to explore the possibility of recommending short-course azithromycin for treatment of uncomplicated acute otitis media in individual practice or public health settings if prescribers or parents decide to use antibiotics.

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