Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis

Courter JD, Baker WL, Nowak KS, Smogówicz LA, Desjardins LL, Coleman CI, Girotto JE

CRD summary
The review found that paediatric patients with acute otitis media and treated with macrolide antibiotics compared to first-line antibiotics may be more likely to have clinical failures. The authors' conclusions reflect the evidence presented, but limitations in the quality of many of the included studies mean the conclusions should be considered tentative.

Authors' objectives
To assess whether clinical failure is more likely with macrolide antibiotics when compared to first line oral agents in children with acute otitis media.

Searching
MEDLINE, EMBASE and IPA were searched from inception to end of September 2008; search terms were reported. Reference lists of retrieved studies and review articles were searched.

Study selection
Eligible studies were blinded randomised controlled trials (RCTs) that compared the clinical failure rate of guideline-recommended first-line antibiotics (such as amoxicillin or amoxicillin/clavulanate) with macrolide antibiotics in children (<18 years) with acute otitis media. Clinical failure was defined as the proportion of patients who experienced no improvement of signs or symptoms or required additional antibiotic therapy within 10 to 16 days after initiation of treatment. Where studies did not report clinical failure rates, the proportion of patients who did not experience clinical success was assumed as clinical failure.

In the included studies, patients ranged in age from six months to 15 years. Some studies were restricted to young children less than 4 years. First-line antibiotics included amoxicillin alone or amoxicillin regimens combined with clavulanate. Dose ranged from 40mg/kg/day to 90mg/kg/day twice or three times daily for seven to 10 days. Macrolide antibiotics included azithromycin and clarithromycin. Dose ranged from 5mg/kg/day to 30mg/kg/day once or twice daily for one to 10 days; some studies used loading doses. Outcomes were measured 10 to 16 days after treatment.

Two reviewers independently selected studies for the review. Disagreements were resolved by a third reviewer.

Assessment of study quality
The included studies were assessed for quality using a modification of the Jadad scale; criteria included description and appropriateness of the randomisation and allocation concealment method and description of withdrawals and dropouts. The Grading of Recommendations, Assessment, Development (GRADE) profiler was used to create a GRADE evidence table that reported the judgments made about the quality of evidence.

Two reviewers independently assessed the quality of the included studies. Disagreements were resolved by a third reviewer.

Data extraction
Relative risks (RRs) and their 95% confidence intervals (CIs) were extracted for individual studies on the clinical success or failure of treatment, incidence of adverse drug reactions (diarrhoea, nausea, vomiting, abdominal pain, generalised rash and total of any type) and reason for withdrawal on standardised forms. For study data with an absence of clinical events in a treatment arm, a nominal value of 0.5 was added to the 2x2 cells.

Two of three reviewers independently extracted data. Disagreements were resolved by a third reviewer.
Methods of synthesis
Studies were pooled in meta-analyses and summary estimates calculated using a Der Simonian and Laird random-effects model. Statistical heterogeneity was assessed using $X^2$ ($p=0.10$ was considered significant) and $I^2$. Inspection of the funnel plot, Egger's regression test and trim-and-fill analysis were used to assess and adjust for publication bias.

Subgroup analyses were undertaken to evaluate differential effects in younger (less than four years) versus older (four years and above) children, high- versus low-dose first-line antibiotics (amoxicillin 40mg/kg/day three times a day or 90mg/kg/day twice daily and amoxicillin 40 to 45mg/kg/day twice daily), studies with Jadad score of at least 3 or less than 3 and studies that assessed azithromycin versus clarithromycin.

Results of the review
Ten RCTs ($n=2,766$ patients, sample size 47 to 553) were included in the review. All RCTs were prospective. Four trials received a Jadad score of 3 or more and six received a score of 2. GRADE assessments indicated that the quality of the evidence base was moderate.

Risk of failure: Macrolide antibiotics were associated with a higher risk of failure than amoxicillin-containing antibiotics (RR 1.31, 95% CI 1.07 to 1.60; 10 studies) with no evidence of heterogeneity. When analysed separately in subgroup analyses, there was no evidence of a statistical difference in subgroups of younger or older children, high-dose amoxicillin-containing regimens, studies with Jadad score of 3 or more or studies that evaluated clarithromycin. Subgroup results for low-dose amoxicillin-containing regimens, studies with Jadad scores less than 3 and studies of azithromycin supported the overall results that indicated a benefit for amoxicillin-containing antibiotics. Calculation of the number needed to harm indicated that 32 patients would need to be treated with azithromycin rather than first-line antibiotics to cause one additional failure.

Adverse events: Macrolide antibiotics were associated with a significantly lower risk of any adverse reaction (RR 0.74, 95% CI 0.60 to 0.90; unknown number of studies) or developing diarrhoea (RR 0.41, 95% CI 0.32 to 0.52; unknown number of studies). There was no evidence of a difference between treatments in rates of vomiting, abdominal pain, nausea and generalised rash.

Authors' conclusions
Children treated with macrolide antibiotics for acute otitis media may be more likely to have clinical failures. Macrolides should be reserved for patients who are allergic to amoxicillin-containing antibiotics.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared appropriate. Relevant sources were searched for eligible studies. Appropriate search terms were used. All included studies were published in English; it was not reported whether the searches were restricted to studies in English and so language bias could not be ruled out. Formal methods were used to assess and adjust for publication bias. Appropriate methods were used for study selection, quality assessment and data extraction.

More than half of the studies were considered to be low quality (Jadad score <3). Several studies were only single blind and had no intention-to-treat analyses. The GRADE evidence table assessed the quality of the evidence base as moderate; this grade of assessment was considered to indicate that further research could have an impact on the confidence in the estimate of effect and may change the estimate. Participants ranged in age from very young babies to adolescents. Doses and timing of first-line and macrolide antibiotics varied. Subgroup analyses were undertaken to take into account the clinical heterogeneity of participants, interventions and quality and assess differential effects, but these analyses tended to be underpowered. Assessment of heterogeneity was comprehensive. Study synthesis was appropriate.

The authors' conclusions reflect the evidence presented, but limitations in the quality of many of the included studies mean the conclusions should be considered tentative.
Implications of the review for practice and research

**Practice**: The authors stated that macrolide antibiotics should not be used in patients with acute otitis media unless they had an allergic reaction to first-line antibiotics.

**Research**: The authors stated that further research may alter the findings of the review.

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