Azithromycin vs. clarithromycin and co-amoxiclav: clinical and economic comparison in the treatment of acute otitis media in children

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of azithromycin, clarithromycin and co-amoxiclav in the treatment of children with acute otitis media (AOM).

Azithromycin was administered orally as SUMAMED suspension (100 mg/5mL) or SUMAMED forte (30 mL, 200 mg/5mL), once daily for 3 days, one hour before or two hours after a meal. The average daily dose was 10 mg/kg.

Clarithromycin was administered orally as Klacid suspension (60 or 100 mL bottles, 125 mg/5 mL), every 12 hours for 10 days. The average daily dose was 15 mg/kg.

Co-amoxiclav was administered orally as Augmentin suspension (156 mg or 312 mg/5mL), every 8 hours for 10 days. The average daily dose was 50 mg/kg.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children with AOM. Patients were included if they were 6 months to 12-years-old and their parents gave consent for their participation. They were also included if middle ear effusions (as shown by pneumatic otoscopy) were present, or if they had ear pain, ear drainage, fever (38 degrees axillary or 38.5 degrees rectally), irritability, vomiting or diarrhoea.

Setting
The setting was a hospital. The economic study was performed in Chorzow, Poland.

Dates to which data relate
The dates to which the effectiveness and cost data related were not reported. The price year was also not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample population as that used in the effectiveness analysis.
Study sample
The authors did not report that sample size calculations were performed in the planning phase of the study to assure a certain power. Children who visited three laryngological clinics were considered for the study. In total, 170 patients were included in the study. These were randomised to either the azithromycin group (58 patients), the clarithromycin group (53 patients) or the co-amoxiclav group (59 patients). The authors did not provide evidence that the study sample was representative of the study population. Patients were excluded for several reasons. For example, if they had a history of allergy macrolides and/or beta-lactamase antibiotics and/or clavulanic acid, or if they had marked renal or hepatic impairment (creatinine clearance less than 40 mL/minute or elevation of liver aminotransferases twice above the reference limit). They were also excluded if they had chronic otitis media, and if they had antimicrobial treatment within 7 days (more than one daily dose) or 4 weeks (any long-acting penicillin injection) of study enrolment.

Study design
The study was a randomised-controlled trial, which was carried out in three laryngological clinics using blind investigators. Sequential numbers were used to allocate the patients to one of the three groups. The duration of follow-up was for 6 weeks following the first clinical examination with symptoms of AOM. The method of randomisation was by sequential numbering, given in strict order of presentation.

Analysis of effectiveness
The basis for the effectiveness analysis seems to have been treatment completers only, since the authors reported that the clinical efficacy was evaluated in patients who finished the treatment without major protocol violations. The primary health outcomes used in the analysis were:

the percentage of patients in each of the groups who were described as cured in the second visit (after 7 days);

the number of cases of intolerance in each of the groups;

the compliance with the drugs; and

the number of days until patients reached full recovery in each one of the groups.

The parents were asked about regular administration of the medicine, in order to assess treatment compliance. The authors justified this choice because no valid proof of compliance could be obtained for outpatients. The bacteriological efficacy and bacterial sensitivity of the three alternative regimes were also analysed. The authors stated that the patient groups did not display important differences in terms of their age, weight, gender and bacteriological differences, although they did not provide any data to support this statement.

Effectiveness results
The percentages of patients described as cured in the second pre-therapy visit were 66.5% in the azithromycin group, 22% in the clarithromycin group, and 22% in the co-amoxiclav group.

There were two cases of food intolerance in the azithromycin group, two cases in the clarithromycin group, and three in the co-amoxiclav group.

For treatment compliance, the authors reported that there were very significant differences in favour of azithromycin, (p=0.001), and significant differences in favour of clarithromycin, (p=0.0063), although they did not report the comparison group for these statistical analyses.

Children in the azithromycin group were fully recovered after 6 days, compared with 9.7 days for the clarithromycin group and 9.3 days for the co-amoxiclav group. The bacteriological efficacy and sensitivity of the three groups of antibiotics did not vary significantly.

The authors reported that no side effects were observed.
Clinical conclusions
Compared with clarithromycin and co-amoxiclav, azithromycin seemed to be a more clinically efficient therapy in terms of fewer days needed for full recovery.

Measure of benefits used in the economic analysis
The authors assumed that the three treatments were equally effective and therefore performed a cost-minimisation study. Thus, no summary measure of health benefit was considered in the economic analysis.

Direct costs
The resource quantities and the costs were not reported separately. It was unclear which direct costs were included in the study, or which categories of costs were considered. The direct costs reported to have been included were the drug costs and 'other' costs (the authors did not clarify the costs included within this category). The authors reported the cost of treating one child, which seemed to include only those costs related to the drug during the treatment period. They also reported the real cost of treatment, which may have been the total cost of treatment per child, including also the number of visits (this is an assumption, since there were insufficient details of the costing).

The authors reported that the prices of the drugs were an average, based on five pharmacies from the area in which the study was performed. They did not report any other source of the direct costs. The price year was not given. Discounting did not appear to have been performed, but it was irrelevant since the duration of follow-up was 6 weeks.

Statistical analysis of costs
The authors stated that they performed factor variance analysis and the Tukey test to compare differences in the costs among the therapies under study.

Indirect Costs
The only data reported on the indirect costs were the number of days of sick leave for the guardian of the sick child. However, the authors did not report if these costs were included in the total costs.

Currency
Euros (Eur) and Zloty (Zl). The conversion rate was Eur1 = Zl 3.75.

Sensitivity analysis
No sensitivity analysis was reported.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
It appears that what the authors meant by 'real cost of treatment' was the total cost per patient of the therapy. This was Eur 455.4 (Zl 1,685.04) for the azithromycin therapy, Eur 25.06 (Zl 2,343.99) for clarithromycin, and Eur 924.19 (Zl 3,465.72) for co-amoxiclav.

Synthesis of costs and benefits
Not combined due to the cost-minimisation approach adopted.
Authors' conclusions
There was a high level of comparable efficiency of the antibiotics used. The use of azithromycin was supported on the grounds of clinical and economic efficiency, and that it was simple to comply with (one daily dose required, compared with several doses per day for the other drugs.

CRD COMMENTARY - Selection of comparators
Several alternative strategies were compared at analysis, but none was specifically reported to be the comparator. It appears that the authors chose the drugs under study because they were currently used in their setting. You should consider whether these are antibiotics available for the treatment of AOM in your own setting.

Validity of estimate of measure of effectiveness
Although the study was a randomised-controlled trial, and randomisation maximises the probability that the groups were comparable at analysis, there were several limitations in the design used. The authors reported that the investigators were blind to the randomisation method, but it was not reported whether the doctors and patients were also blinded to the treatment allocation, and this may have influenced the outcomes reported. The authors reported that there were no important differences in the patient groups in terms of age, gender, weight and bacteriological differences at baseline, although they did not state what they understood by important differences (since results from statistical analyses were not reported). Further, there may have been some important characteristics of the patients that were not considered at analysis and which may have acted as confounders, such as a recent illness of any type. The fact that group a much higher percentage of patients in the azithromycin were cured at the second visit might have been due to these children being less ill than the others, and therefore, the groups would not have been comparable at analysis. In such a case, the effectiveness results of the study would have been uncertain.

The effectiveness analysis considered only patients who completed the treatment without major protocol violations, which may have biased the results. Moreover, the authors did not report how many patients were finally accounted for when analysing the clinical efficiency of the therapies. This makes it difficult to interpret the results. The authors did not report how they measured the patients' compliance with the treatments and they only reported final conclusions, without any supporting data from the primary outcome. The study sample was not shown to be representative of the study population, although the fact that patients from three different laryngological clinics were considered at analysis may have increased the likelihood that it was representative.

Validity of estimate of measure of benefit
The authors did not derive any summary measure of health benefit since a cost-minimisation analysis was performed. As the authors reported, a cost-minimisation analysis has limited application since it is rare that the same results are obtained using different programmes. Further, differences among the therapies were shown in terms of the period required for full recovery. The assumption of equal effectiveness between the three alternatives is, therefore, questionable.

Validity of estimate of costs
Since the perspective was not reported, and the costs considered at analysis were not fully described, it cannot be stated whether all the categories of cost relevant to the analysis were included. The costing had limitations arising from inadequate reporting. The costs and the quantities were not reported separately. Although the authors stated that they performed statistical analyses to test for differences in the costs of the alternative therapies, the results of these statistical analyses were not reported. The informal care (in terms of the number of days that carers had to care for children with AOM) was reported, but it was unclear whether the total costs actually included this cost. The dates to which the costs related were not reported, and neither was the price year. All these facts introduce uncertainty into the reliability of the conclusions and hinder reflation exercises to other settings.

Other issues
The authors did not make appropriate comparisons of their findings with those from other studies. In addition, the issue
of generalisability of the results to other settings was not addressed. The authors appear to have presented their results selectively, since some important results were not reported. For example, the comparability of the groups at baseline, or the results for compliance with each one of the therapies.

**Implications of the study**

The results of this study should be taken cautiously because of the several limitations and the lack of reporting, both in the effectiveness and the cost analyses.

**Source of funding**

None stated.

**Bibliographic details**


**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by CRD

**MeSH**

Acute Disease; Amoxicillin-Potassium Clavulanate Combination /therapeutic use /economics; Anti-Bacterial Agents /economics /therapeutic use; Azithromycin /therapeutic use /economics; Child; Clarithromycin /therapeutic use /economics; Cost-Benefit Analysis; Drug Therapy, Combination /therapeutic use /economics; Humans; Otitis Media /drug therapy

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