A cost-effectiveness analysis of antibiotic therapy in macrolide-resistant community-acquired pneumonia

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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 an extended-release (ER) formulation of amoxicillin/clavulanate (AMX/CLA) for the treatment of macrolide-resistant community-acquired pneumonia (CAP). This was compared with the advanced macrolide, clarithromycin ER.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 1,000 outpatients presenting with signs and symptoms of CAP with a first-line therapy of AMX/CLA ER or clarithromycin ER. The patients were assumed to be adult patients without cardiopulmonary disease or modifying factors.

Setting
The setting was an outpatient clinic, which we assume to be a secondary care setting. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence was derived from papers published between 1999 and 2005. The costs and resources used were derived from standard US sources and studies published between 1997 and 2004. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a synthesis of published studies and clinical opinion.

Modelling
A decision tree model was used to simulate the occurrence of CAP in adults. The time horizon of the model was unclear.

Outcomes assessed in the review
The incidence of and resistance to bacteria, and the cure rates were obtained from an ad hoc review. The incidence of adverse events was obtained from product labels.
Study designs and other criteria for inclusion in the review
The review was ad hoc and no inclusion criteria were reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Nine primary studies (6 of which were randomised controlled trials) were included in the review.

Methods of combining primary studies
The authors provided a narrative explanation of how the study results were combined. The approach generally used weighted averages of different rates. The range of results among the included studies was used in a sensitivity analysis of some of the parameters.

Investigation of differences between primary studies
Not reported.

Results of the review
The incidence of Streptococcus pneumoniae (S. pneumoniae) was 40.0% (Range: 20.0 to 60.0).

The incidence of other bacteria causing CAP was 45.0% (Range: 25.0 to 65.0).

The nonbacterial incidence was 15.0%.

The incidence of both susceptible and nonsusceptible pathogens to each antimicrobial therapy was 71.0% (macrolide susceptible, AMX/CLA susceptible), 1.3% (macrolide susceptible, AMX/CLA nonsusceptible), 22.0% (macrolide nonsusceptible, AMX/CLA susceptible), and 5.7% (macrolide nonsusceptible, AMX/CLA nonsusceptible).

The cure rate for susceptible strains was 90.0% (Range: 80.0 to 98.0) for both AMX/CLA ER and clarithromycin ER.

The cure rate for other bacteria was 90.0% (Range: 80.0 to 98.0) for both AMX/CLA ER and clarithromycin ER.

A cure rate of 95% was assumed for both AMX/CLA ER and clarithromycin ER in cases of nonbacterial pathogens.

The probability of diarrhoea was 0.156 with AMX/CLA ER and 0.060 with clarithromycin ER.

The probability of nausea or vomiting was 0.022 with AMX/CLA ER and 0.030 with clarithromycin ER.

Methods used to derive estimates of effectiveness
Expert opinion was used to derive model parameters and the ranges of values used.
Estimates of effectiveness and key assumptions
A clinical cure rate of 15.0% was estimated through expert opinion for both AMX/CLA ER and clarithromycin ER against their respective nonsusceptible pathogens.

Measure of benefits used in the economic analysis
The measures of benefits used were the percentage and the number of patients cured.

Direct costs
The direct costs of the insurer were reported. These included the costs of treatment (first-line therapy and initial physician visit), treatment failure (physician visit, second-line antibiotics, diagnosis, therapy and hospitalisations) and the treatment of adverse events. The cost of first-line therapy was estimated from the usual dosing obtained from the Physician's Desk Reference, and the average wholesale price from the Red Book. The unit costs of the relevant resources were estimated using the Resource-Based Relative Value Scale. The drug cost of a second-line antibiotic was estimated by taking the average cost of other prescribed antimicrobials for treating CAP. The data on hospitalisation were obtained from a study (Niederman et al. 1998, see .Other Publications of Related Interest- below for bibliographic details) using the National Healthcare Cost and Utilization Project's National Inpatient Sample, the National Ambulatory Medical Care Survey, and the National Hospital Ambulatory Medical Care Survey. All data were updated to 2004 dollars. Discounting was not carried out.

Statistical analysis of costs
The cost data were deterministic.

Indirect Costs
The indirect costs were not included because, although the authors stated that a societal perspective had been adopted, the actual perspective was that of an insurer.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were conducted on six parameters:

the incidence of S. pneumoniae;

the incidence of macrolide-nonsusceptible S. pneumoniae and AMX/CLA- nonsusceptible S. pneumoniae;

the AMX/CLA-susceptible S. pneumoniae and other bacteria cure rate;

the AMX/CLA-nonsusceptible S. pneumoniae cure rate;

the macrolide-susceptible S. pneumoniae and other bacteria cure rate; and

the macrolide-nonsusceptible S. pneumoniae cure rate.

For each parameter, the range of values was derived from the literature and clinical opinion.

Estimated benefits used in the economic analysis
The expected cure rate per patient was 88.7% with AMX/CLA ER and 82.4% with clarithromycin ER.
For 1,000 patients, the incremental number of patients cured was 62 with AMX/CLA ER compared with clarithromycin ER.

**Cost results**
The average cost to treat one patient was $437.70 with AMX/CLA ER versus $548.14 with clarithromycin ER.

The average cost per cure was $493.74 with AMX/CLA ER versus $664.90 with clarithromycin ER.

The incremental cost of AMX/CLA ER over clarithromycin ER was -$110.44 per patient (the authors reported it as an additional savings of $110.44 per patient to a payer).

The incremental cost of treating 1,000 patients with AMX/CLA ER over clarithromycin ER was -$110,440 (the authors reported it as an additional savings of $110,440 to a payer).

**Synthesis of costs and benefits**
The costs and benefits were combined by calculating the incremental cost-effectiveness ratio (ICER). The authors reported that the ICER of AMX/CLA ER over clarithromycin was $1,778.38. Since AMX/CLA ER was the dominant strategy (i.e. more effective and less costly), the ICER may be interpreted as an incremental cost-saving per cure for 1,000 patients.

The sensitivity analysis of key parameters showed AMX/CLA ER to be cost-saving in comparison with treatment with clarithromycin ER for most parameters within their allowable ranges. The ICER and budget-impact results were most sensitive to changes in the susceptible S. pneumoniae and other bacteria clinical cure rates.

Treatment with AMX/CLA ER over clarithromycin ER remained cost-saving as long as the AMX/CLA ER clinical cure rate for susceptible S. pneumoniae and other bacteria was higher than 84.6%, and was cost-effective when the clinical cure rate was as low as 82.4% with an incremental cost per cure of $41,624.

AMX/CLA ER was more effective and less costly as long as the clinical cure rate for clarithromycin ER was below 95.9%. If the cure rate increased to 98%, AMX/CLA ER was no longer cost-saving, but it was cost-effective with an incremental cost per cure of $13,194.

When the cure rate of AMX/CLA ER for nonsusceptible S. pneumoniae decreased from a baseline of 15% to 5%, the cost saved per 1,000 treated patients decreased from $110,440 to $103,418, whereas the number of additional patients cured per 1,000 treated patients decreased from 62 to 59. AMX/CLA ER remained cost-saving to a payer even if the clinical cure rate of clarithromycin ER for nonsusceptible S. pneumoniae increased to the upper bound of its range of 25%.

If the incidence of S. pneumoniae was as low as 20%, the cost saved per 1,000 treated patients was $31,700 when treating with AMX/CLA ER. When the incidence of nonsusceptible clarithromycin S. pneumoniae was as low as 18%, or the incidence of nonsusceptible AMX/CLA S. pneumoniae was as high as 11%, the costs saved per 1,000 treated patients were $50,500 and $97,900, respectively, when treating with AMX/CLA ER. The additional number cured per 1,000 patients was 38 and 57, respectively.

**Authors’ conclusions**
Based on the data and assumptions described in the study, treating community-acquired pneumonia (CAP) with amoxicillin/clavulanate (AMX/CLA) extended release (ER) provided significant economic benefits by reducing the costs and increasing the rate of effectiveness compared with clarithromycin ER.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the comparator used. It represented a first-line therapy for adult outpatients with CAP that was recommended by treatment guidelines in the USA. You should decide if this represents a widely used health
technology in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from the literature and from clinical opinion. The authors did not report that a systematic review had been undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors clearly reported the methods used to derive the estimates of effectiveness, and the weighted average results from randomised controlled trials were adopted. The estimates of effectiveness were derived credibly from the studies identified. The authors did not report how the experts whose opinions were elicited were selected.

Validity of estimate of measure of benefit
The measure of benefit used was the number of patients cured. The authors did not report the duration of the benefit measured.

Validity of estimate of costs
The authors reported that the study had been conducted from a societal perspective, but the indirect costs were not included. For the actual perspective adopted, namely an insurer’s perspective, all the relevant costs appear to have been included in the analysis. The costs and the quantities were reported separately. Resource quantities were derived from published sources. No justification was given for the assumptions made about resource use. No sensitivity analysis of the quantities was conducted and this may limit the interpretation of the study findings. The costs were treated deterministically. Charges were used to proxy prices and this was appropriate given the perspective. It was unclear for how long the costs were incurred. The price year was reported.

Other issues
The authors did not compare their findings with those from other studies, so it is impossible to assess how far their results agree with other published results. The issue of the generalisability of the results to other settings was addressed. The authors also stated that, since the analysis did not consider differences in various patient sub-populations such as children or the elderly, the results were only generalisable to the patient population being modelled. The authors reported, as a further shortcoming of their study, that the results may differ because of different negotiated costs of different payers.

Implications of the study
The authors did not report any implications of their study.

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