Pharmacoeconomic analysis of selected antibiotics in lower respiratory tract infection
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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
Antibiotics (clarithromycin, cefixime, amoxicillin/clavulanate, erythromycin, cefuroxime, ampicillin and cefaclor) to treat community-acquired lower respiratory tract infection (LRTI).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with acute exacerbation of chronic bronchitis, pneumonia, acute exacerbation of chronic bronchitis and pneumonia, or sinusitis.

Setting
Primary care. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness data were based on patients enrolled between 1987 and 1992. The price year was 1995.

Source of effectiveness data
The evidence for final outcomes was based on a review of previously completed studies.

Modelling
A computer-based economic model was used to incorporate the relevant outcomes associated with the treatment of community-acquired LRTI for each of the seven antibiotics and 18 categories of organisms. ADEs that resulted in costs to the healthcare system were modelled.

Outcomes assessed in the review
The outcomes assessed in the review were the incidence rates and management of 'possibly', 'probably' and 'definitely' drug-related ADEs.

Study designs and other criteria for inclusion in the review
All patients who were included in the randomized controlled studies recorded on the clinical trials database and who received at least one dose of the selected antibiotic were considered in the analysis.
**Sources searched to identify primary studies**
A clinical trials database was the primary source of efficacy and safety data. These clinical trials comprised all the pivotal comparative studies submitted as part of the New Drug Application for approval of clarithromycin. A MEDLINE search was conducted in order to obtain efficacy data for the amoxicillin/clavulanate comparison.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
12 primary studies from the clinical trials database were included in the review. These prospective, randomized, controlled clinical trials comprised 2,377 patients; 1,102 treated for acute exacerbation of chronic bronchitis, 591 for pneumonia, 201 for either of the two conditions and 483 sinusitis patients. Seven clinical trials of amoxicillin/clavulanate for the treatment of acute exacerbations of chronic bronchitis or pneumonia were retrieved by a MEDLINE search.

**Methods of combining primary studies**
The data from the clinical trials database were pooled from the studies to represent the population of patients treated in the outpatient setting for LRTI. A mean clinical response rate, weighted by sample size, was calculated across the seven studies of amoxicillin/clavulanate.

**Investigation of differences between primary studies**
Severity of illness was categorised as mild, moderate or severe at study entry by blinded clinicians according to the following definitions: mild - does not interfere with normal activities; moderate - interferes with normal activity or sleep; and severe - prevents normal activities.

**Results of the review**
For common infecting organisms the percentage of patients successfully treated varied with the antibiotic. Fifty-one types of ADEs resulting in healthcare resource utilization were identified. The seven antibiotics varied considerably with respect to the type and incidence rates of these ADEs. The highest percentage of patients requiring hospitalisation and a switch in therapy, resulting from abdominal pain and tracheitis, had been given cefuroxime (2.6%). Patients in the ampicillin and amoxicillin/clavulanate groups experienced the highest numbers of ADEs that were treated in the outpatient setting and that did not require a switch in antibiotic therapy (21.1% and 17.7% respectively), whereas patients given cefixime experienced the lowest number (4.7%). Patients in the ampicillin and erythromycin groups had the highest number of ADEs requiring a switch in antibiotic treatment in the outpatient setting (6.8% and 18.2% respectively).

**Measure of benefits used in the economic analysis**
Complication-free cure (CFC) was used as the outcome measure in the economic analysis. A CFC was defined as a full course of therapy with a successful response, and no ADEs.

**Direct costs**
The cost calculation was based on the cost of a course of therapy for each antibiotic (based on drug acquisition costs) and dosage form utilization and the mean number of doses received by the successfully treated patient for each agent.
The average wholesale prices were used to calculate the medication costs associated with the management of ADEs. Data on the costs for clinic visits and hospital days were retrieved from a Midwest Independent Practice Association model managed care organisation with 300,000 members. Cost components of ADEs requiring hospitalisation included the cost of hospitalisation, cost of medications required in order to manage the ADE, and the cost of a course of an orally administered second-generation cephalosporin. Costs and quantities were reported separately.

Indirect Costs
Not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analysis was used to test the stability of the results to changes in costs and outcomes. In particular, the authors focused on the effects of altering resistance rates, incidence rates of atypical organisms, and acquisition costs of the antibiotics.

Estimated benefits used in the economic analysis
The proportion of patients with CFCs was:

- erythromycin, 37.5%;
- clarithromycin, 51%;
- ampicillin, 29.1%;
- amoxicillin/clavulanate, 58.9%;
- cefixime, 60.4%;
- cefaclor, 36.3%;
- cefuroxime, 51.9%.

The lowest proportion of patients experiencing CFCs had received ampicillin, a result that reflects both the lower efficacy of this agent and the higher incidence of ADEs. The highest proportion of CFCs was associated with cefixime, as this agent demonstrated both increased efficacy and a relatively better side effects profile.

Cost results
The range in mean total cost per episode varied between $137 (erythromycin) and $267 (cefuroxime). The clinical costs (including treatment failures) exceeded the drug costs for all the antibiotics studied.

Synthesis of costs and benefits
The range of mean cost per complication-free cure varied between $307 for clarithromycin and $612 for cefaclor. When ranked from most to least cost-effective, the order was as follows: clarithromycin, cefixime, amoxicillin/clavulanate, erythromycin, cefuroxime, ampicillin and cefaclor. The cost per additional CFC compared to erythromycin ranged from $144.74 for clarithromycin to $899.17 for cefuroxime.

Authors' conclusions
Clarithromycin was the most cost-effective agent. Whilst recognising the limitations of using retrospective analyses and modelling the authors suggested that the techniques adopted were appropriate for this analysis, given the frequency of LRTI, the interest in outpatient management of patients with LRTI, the relative expense of new antibiotics, and the perceived equivalence of these agents.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of the comparators is clear.

**Validity of estimate of measure of benefit**
As the authors noted, with any retrospective analysis and modelling exercise the validity of the results may be limited by the abbreviated evaluation period of the therapies studied, the lack of certainty of outcomes projection over time, the expected increased compliance, the increased rate in reporting ADEs and populations differing from those in the 'real world'.

**Validity of estimate of costs**
Resource quantities were not reported separately from prices. As the authors noted, the model did not allow for hospitalisation for treatment of LRTI

**Other issues**
The authors' conclusions were justified given the uncertainties in the data, and the issue of generalisability to other countries or settings was addressed.

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