Cost-effectiveness of IV-to-oral switch therapy: azithromycin vs cefuroxime with or without erythromycin for the treatment of 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
Two alternative strategies for treating patients with community-acquired pneumonia (CAP) were examined. One strategy was intravenous (IV) to oral azithromycin (AZI), an azalide antimicrobial with a spectrum of activity for respiratory pathogens similar to the combination of a second-generation cephalosporin plus a macrolide, but without enteric Gram-negative coverage. The other strategy was cefuroxime (CEF), a second-generation cephalosporin commonly employed for the treatment of CAP, followed by erythromycin (ERY; a macrolide) for patients suspected of having atypical pathogens (Mycoplasma, Legionella or Chlamydia). ERY was given at the discretion of the physician. AZI was administered at a dose of 500 mg IV once daily (qd) for 2 to 5 days, followed by 500 mg orally qd for a total of 7 to 10 days of therapy. CEF was administered at a dose of 750 mg IV every 8 hours for 2 to 7 days, followed by CEF axetil 500 mg orally twice daily for a total of 7 to 10 days of therapy. ERY was administered at a dose of 500 to 1,000 mg IV every 6 hours, or 500 mg orally four times daily, for up to 21 days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with a new infiltrate on chest radiograph and a clinical diagnosis of CAP that required treatment with IV antibiotics. Patients were excluded if they had major allergic reactions to macrolides or beta-lactams, or were using terfenadine, loratidine or astemizole. Those with significant renal, hepatic, cardiovascular or haematologic disease were excluded, as were those with human immunodeficiency virus infection, acquired immune deficiency syndrome, metastatic tumour, septic shock or cystic fibrosis. Other criteria for exclusion were mechanical ventilation, infection due to non-Haemophilus influenza Gram-negative organisms, and female patients who were pregnant or nursing.

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

Dates to which data relate
The effectiveness and resource use data were gathered from November 1993 to May 1995. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the main details of which were published elsewhere (Plouffe et al., see Other Publications of Related Interest).
Link between effectiveness and cost data
The costing was performed retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The appropriate sample size was calculated on the basis of the anticipated evaluability rate and expected clinical response rate. Of the 403 people enrolled, an overall sample of 268 clinically evaluable patients was identified. However, the final sample comprised 266 patients as one patient in each group was not economically evaluable. There were 136 patients (58 men) in the AZI group and 130 (61 men) in the CEF group. The mean age was 60.5 (+/- 17.6) years in the AZI group and 60.1 (+/- 17.7) years in the CEF group. Sixty-four patients in the CEF group also received ERY. It was not stated whether some patients refused to participate or were excluded from the initial study sample for any reason.

Study design
This was an open-label, randomised controlled trial, which was carried out in 36 centres. The patients were randomised 1:1 to the two study groups, but the method of randomisation was not described. No blind assessment of the outcome was performed. A first assessment was carried out 10 to 14 days post-therapy. The length of follow-up was 4 to 6 weeks after therapy. The loss to follow-up was not reported, but it appears that all patients were clinically evaluable at the end of the observation period.

Analysis of effectiveness
The authors did not state whether the analysis was carried out on an intention to treat basis. The primary health outcome used in the effectiveness study was the success rate (cure or improvement). Adverse events were also observed. The two groups were comparable at baseline in terms of the demographic and clinical characteristics.

Effectiveness results
At 10 to 14 days post-therapy, the success rate was 78% in the AZI group and 75% in the CEF group, (p=0.54).

At 4 to 6 weeks post-therapy, the success rate was 75% in the AZI group and 71% in the CEF group, (p=0.46).

Adverse events were observed in 11.8% of the patients in the AZI group and in 21.5% of those in the CEF group (7.6% among patients receiving only CEF and 35.9% among those who also received ERY).

Clinical conclusions
The effectiveness analysis showed that the two treatments were equally effective in terms of the success rate.

Modelling
A modelling approach was used to estimate the expected costs and benefits of the two alternative treatment strategies. The basis of the model was a decision tree. The branches of patients who were or were not receiving ERY were considered separately. Therefore, the final number of alternative options was three. The structure of the tree was reported in the paper. The model was deterministic and a sensitivity analysis was conducted to evaluate the impact of changing model parameters.

Measure of benefits used in the economic analysis
The summary benefit measure was the success rate. This was derived from the effectiveness study and then entered into the decision model. No discounting was applied. Adverse effects were not considered.

Direct costs
The cost/resource boundary of the study was that of the hospital. The health services considered in the economic analysis were hospital stay, procedures performed, medications administered, adverse events, clinical response and other factors. The documented procedures were listed. The costs were analysed from three different levels. Level 1 related to drug-acquisition costs. Level 2 corresponded to antibiotic-related costs, including preparation and administration, therapeutic drug monitoring, and the additional costs of treating adverse events and therapeutic failures. Level 3 related to prior resources and hospitalisation costs. Resource use was estimated using patient-level actual data that were obtained from the sample of patients involved in the effectiveness study. Other costs were derived from direct prices and from a weighted-average for inpatient stay. The source of some categories of costs was not reported. Resources that were not directly related to the treatment of CAP were not considered.

The costs for procedures were estimated by applying the cost-to-charge ratio (70.46%) to the charges of a reference hospital. Adjustments were then made to reflect national costs. Discounting was not carried out, which was appropriate since the costs per patient were incurred during a short time. The unit costs and the quantities of resources used were not presented separately. The total costs per patients were obtained using the decision tree model. The price year was 1998.

**Statistical analysis of costs**

The costs were presented as geometric mean values due to the skewed distribution typically observed in clinical infectious disease studies. The statistical significance of differences in the estimated costs was tested using a Kruskal-Wallis one-way analysis of variance.

**Indirect Costs**

The indirect costs were not considered.

**Currency**

US dollars ($).

**Sensitivity analysis**

Sensitivity analyses were performed to assess the robustness of the estimated cost-effectiveness ratio (CER) to variations in the inpatient stay costs ($200 to $1,200 daily), antibiotic prices (+/- 50%) and clinical success rate (varied to the threshold value to force equal CER). One-way and threshold analyses were carried out. No justification for the choice of ranges used was provided.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.

**Cost results**

The (geometric) mean estimated costs per patient (level 3 perspective) were $4,104 (95% confidence interval, CI: 3,874 - 4,334) for AZI patients and $4,578 (95% CI: 4,319 - 4,873) for CEF patients. However, the difference, $474, did not reach statistical significance, (p=0.06). Similar results were observed when the sub-groups of patients receiving and not receiving ERY were considered separately.

**Synthesis of costs and benefits**

The authors calculated the average CERs to combine the costs and benefits of the alternative treatments. The CER was $5,265 per expected successful outcome for AZI patients and $6,145 per expected successful outcome for CEF patients, (p=0.05). An incremental analysis was not required since AZI represented a dominant alternative, as it was more effective and less costly than CEF. However, when the sub-groups of patients receiving or not receiving ERY were considered separately, the difference between the CERs was statistically significance when comparing AZI.
patients and CEF patients who also received ERY.

The sensitivity analysis showed that variations in the drug acquisition costs did not change the results of the analysis. However, variations in the costs of in-hospital stay favoured the AZI branch at the higher end of the range, while the cost-difference narrowed at the lower end. CEF, with or without ERY, would have to be more than 15% more effective than AZI to be cost-effective.

Authors' conclusions
Despite the higher initial acquisition cost, azithromycin (AZI) was as effective as cefuroxime (CEF) for the treatment of community-acquired pneumonia (CAP), but there was a trend towards shorter hospital stay and lower costs in AZI patients.

CRD COMMENTARY - Selection of comparators
The authors did not provide a formal justification for the choice of the comparators. However, it was apparent that both interventions represented alternative methods of current practice for the treatment of CAP in the USA. You should decide whether they are valid treatments in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on an open-label, randomised, controlled trial, which was appropriate for the study question. The internal validity of the analysis was enhanced by several factors. More specifically, the baseline comparability of the study groups, the appropriate sample size (although power calculations were reported in the primary publication), the multi-centre design, and the appropriate length of follow-up. Few details on the method of randomisation and the follow-up were reported. The study sample was likely to have been representative of the study population, although most of the details relating to sample selection were not reported.

Validity of estimate of measure of benefit
The summary benefit measure was derived from the effectiveness study. The choice of success rate as the benefit measure reduces the possibility of making comparisons with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. It appears that all the relevant categories of costs have been considered. In order to show that despite the higher initial drug acquisition costs AZI was cheaper than CEF, more limited perspectives were also considered in the economic evaluation. However, details on the unit costs and the quantities of resources used were not provided, which limits the possibility of replicating the study in other settings, although a breakdown of the cost items was given. The cost estimates were varied to reflect national prices. Charges were used to estimate the costs, but a cost-to-charge ratio was applied. The price year was reported, which simplifies reflation exercises. The authors considered the skewed distribution of the costs by calculating the geometric mean rather than the arithmetic mean.

Other issues
The authors compared their findings with those observed in another published study that reported comparable results. Some sensitivity analyses were conducted to address the problem of variability in the cost data. A threshold analysis was also performed in which the summary benefit measure was varied. However, the issue of the generalisability of the study results to other settings was not explicitly addressed. The study referred to patients with CAP and this was reflected in the conclusions of the analysis.

Implications of the study
The authors suggested that if the cost-savings observed in their study were applied to every appropriate patient
hospitalised with CAP in the USA, then an estimated annual saving of $400 to $700 million would be realised.

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**Other publications of related interest**


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