Cost-effectiveness analysis of ambulatory treatment for adult patients with community-acquired pneumonia: according to Japanese Respiratory Society guidelines
Morimoto T, Koyama H, Shimbo T, Fukui T

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 oral antibiotics for community-acquired pneumonia for ambulatory treatment. The antibiotics compared were amoxicillin-clavulanate (AMX-CVA, 1,500 mg/day), azithromycin (AZM, 500 mg/day), clarithromycin (CAM, 400 mg/day), cefdinir (CFD, 300 mg/day), levofloxacin (LVF, 400 mg/day) and minocycline (MIN, 200 mg/day).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised hypothetical adult outpatients (30-year-old female non smoker, 50-year-old male smoker and 63-year-old patients with chronic lung disease) who were diagnosed as suffering from community-acquired pneumonia at mild to medium severity. In particular, the patients studied were those whose causative organisms were not determined.

Setting
The setting was secondary care. The economic study was conducted at the Kyoto University Graduate School of Medicine, Japan.

Dates to which data relate
The effectiveness data were derived from studies published in or after 1966. Although not stated clearly, the costs appear to have been based on those current at the time of the study.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, augmented with estimates and authors’ assumptions.

Modelling
A decision tree was constructed using Data 3.5 software to assess the cost-effectiveness of the six antibiotic strategies. The time horizon of the model was 2 weeks.

Outcomes assessed in the review
The outcomes assessed were:
the etiology of the community-acquired pneumonia;
the treatment success rates and mortality of ambulatory treatment with the six antibiotics; and
the inpatient treatment success rate with AMX-CVA plus erythromycin.

**Study designs and other criteria for inclusion in the review**
The authors included literature on the etiology (frequency of the causative organisms) of the community-acquired pneumonia, randomised controlled trials (RCTs) on the effectiveness of the antibiotics, and literature on the effective antibiotics for various causative organisms.

**Sources searched to identify primary studies**
MEDLINE was searched.

**Criteria used to ensure the validity of primary studies**
Of the RCTs reviewed, those targeted at patients outside the study protocol (e.g. inpatients who had been treated as outpatients) were excluded.

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

**Number of primary studies included**
There were 7 papers on the etiology of pneumonia and 18 RCTs on the effectiveness of antibiotics.

**Methods of combining primary studies**
The authors stated that they used the mode and range for frequency of causative organisms as found in the literature. The methods given in the "Sanford Guide" were used to calculate the success rate.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The most common causative organism for community-acquired pneumonia was S. pneumoniae. This was 40% for a 30-year-old female non smoker, 53% for a 50-year-old male smoker and 65% for patients with chronic lung disease. Other common organisms were Legionella (5, 10 and 5%, respectively), Chlamydia (10, 10 and 3%, respectively) and Mycoplasma (30, 5 and 2%, respectively).

The treatment success rates for AMX-CVA were 0.50 for a 30-year-old female non smoker, 0.60 for a 50-year-old male smoker, and 0.60 for patients with chronic lung disease.

The treatment success rates for CFD were 0.50 for a 30-year-old female non smoker, and 0.60 for the other two groups.

The treatment success rates were the same for all the other antibiotics (AZM, CAM, LVF and MIN), namely, 0.85 for all three groups.

Mortality of ambulatory treatment was 0.0001 for all the antibiotics for all three groups.

Inpatient treatment success rate was 0.95 for a 30-year-old non smoker and 0.80 for the other two groups.
Methods used to derive estimates of effectiveness
The authors made estimates to supplement the above data that were derived from the literature.

Estimates of effectiveness and key assumptions
Estimates were made in conjunction with the findings of the literature review. In addition, the duration of therapy was estimated:

- initial ambulatory treatment was 3 (range: 2 - 5) days for all sub-groups;
- follow-up or inpatient treatment was 7 (range: 4 - 10) days for all sub-groups.

Measure of benefits used in the economic analysis
The measure of benefit used in the economic analysis was the quality-adjusted life-days (QALDs). Quality of life weights were derived from interviews conducted with healthy volunteers and patients with chronic lung disease (elicited from rating scales).

Direct costs
The direct costs included were for oral antibiotics, intravenous antibiotics (e.g. solutions and devices), ambulatory treatment for initial visits (e.g. examination, chest X-rays and preparation for medication), hospitalisation, daily costs, and costs related to death. Hospitalisation costs covered treatment and examinations such as chest X-rays, blood tests and electrocardiogram. Daily costs were those related to the actual stay in a hospital and meals. The costs and the quantities were only reported separately for antibiotics. Discounting was not relevant due to the short period of analysis (2 weeks). The cost data were derived from the actual payment data for ambulatory and inpatient treatment at a general hospital and Japanese insurance point chart for the model cases. The price year was not stated.

Statistical analysis of costs
Not undertaken.

Indirect Costs
The indirect costs were not included.

Currency
Japanese yen (Y).

Sensitivity analysis
Sensitivity analyses were carried out to examine the variability of the cost and effectiveness results. The parameters varied were treatment success rate, mortality of ambulatory treatment, inpatient treatment success rate, duration of therapy and the number of times antibiotics were taken per day.

Estimated benefits used in the economic analysis
The QALDs for MIN, AZM, CAM and LVF were the same, 7,066.5 for 30-year-old female non smokers, 5,633.2 for 50-year-old male smokers, and 4,351.5 for patients with chronic lung disease.

The QALDs for AMX-CVA and CFD were the same, although lower than for the other antibiotics. The QALDs were 6,941.5 for 30-year-old female non smokers, 5,342.7 for 50-year-old male smokers, and 4,127.1 for patients with chronic lung disease.
In the sensitivity analysis, which considered the number of times antibiotics were taken per day and the duration of therapy, AZM turned out to have the most QALDs. The QALDs were 7,069.98 for 30-year-old female non smokers, 5,637.42 for 50-year-old male smokers, and 4,354.00 for patients with chronic lung disease.

MIN then CAM had the next most QALDs. The QALDS with MIN were 7,069.67 for 30-year-old female non smokers, 5,637.03 for 50-year-old male smokers, and 4,354.00 for patients with chronic lung disease. The QALDs with CAM were 7,069.00 for 30-year-old female non smokers, 5,636.07 for 50-year-old male smokers, and 4,353.67 for patients with chronic lung disease.

**Cost results**

The total medical costs per patient were lowest with MIN. These were Y55,070 for a 30-year-old female non smoker, Y59,208 for a 50-year-old male smoker, and Y59,208 for a patient with chronic lung disease.

The second lowest were the costs with AZM, Y56,049 for a 30-year-old female non smoker, Y60,188 for a 50-year-old male smoker, and Y60,188 for a patient with chronic lung disease. The next lowest costs were with CAM (Y56,171, Y60,309 and Y60,309, respectively) and LVF (Y61,988, Y66,127 and Y66,127, respectively).

The costs for AMX-CVA (Y133,797, Y122,432 and Y122,432) and CFD (Y134,649, Y123,375 and Y123,375) were similar and highest among the six antibiotics.

The sensitivity analyses revealed that the initial treatment success rate was the most influential factor affecting the cost variability.

**Synthesis of costs and benefits**

MIN, AZM, CAM and LVF had the same effectiveness results, 7,066.5 QALDs for 30-year-old female non smokers, 5,633.2 QALDs for 50-year-old male smokers, and 4,351.5 QALDs for patients with chronic lung disease. However, MIN was found to be the least expensive antibiotic (Y55,070 - Y59,208) followed by AZM (Y56,049 - Y60,188) and CAM (Y56,171 - Y60,309). Thus, MIN was the most cost-effective antibiotic as it dominated (either weakly or strongly) all other strategies.

When the number of times antibiotics were taken per day and the duration of therapy were taken into account, AZM was found to have an incremental cost-effectiveness ranging from Y917,179 to Y1,152,694/QALY over MIN. This result was not applicable for patients with chronic lung disease.

**Authors’ conclusions**

Minocycline (MIN), followed by azithromycin (AZM) and clarithromycin (CAM), was found to be the most cost-effective antibiotic in empirically treating adult patients with community-acquired pneumonia on an ambulatory basis. For adults without co-morbidity, AZM provides a higher quality of life at a generally acceptable marginal cost.

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparators was clear. They are indicated for use by the Japanese Respiratory Society, which has formulated practice guidelines for the treatment of adult patients with community-acquired pneumonia. The guidelines recommend the use of various oral antibiotics at the discretion of the individual physician. You should decide if these alternatives are relevant to your own setting.

**Validity of estimate of measure of effectiveness**

The authors appear to have undertaken a systematic approach to locating relevant literature and they have provided a clear description of which studies were used for each parameter. A systematic approach was also undertaken in terms of combining the results of a number of studies to derive point estimates and ranges. A number of estimates and assumptions were used, either in conjunction with the literature review or separately to populate the model. The quality
of evidence was assessed according to modified guidelines, initially developed by the US Preventive Services Task Force. The authors undertook sensitivity analyses to assess variability in the data. This enhances the validity of the results.

Validity of estimate of measure of benefit
The authors used the QALDs as quality of life weights. These were derived from interviews conducted with healthy volunteers and patients with chronic lung disease (elicited from rating scales). These data were synthesised within the modelling and appear to have been handled appropriately. As the weights were derived from real patients their validity is likely to be high.

Validity of estimate of costs
The cost calculations reflected the perspective adopted in the economic analysis (the Japanese health care system). All the relevant cost items appear to have been included. However, the costs and the quantities were only reported separately for antibiotics and a price year was not given. These aspects of the cost analysis limit the generalisability of the results to other settings. The validity of the cost data was enhanced through the sensitivity analyses, which also addressed variability in the cost estimates.

Other issues
The authors compared their findings with other studies in relation to the antibiotics used (or not used). In terms of the generalisability of their results, the sensitivity analyses undertaken will strengthen this aspect of their findings. Further, the source of the effectiveness data was considered, as the authors used the findings of RCTs and other studies from populations outside Japan. Studies of this nature are available in Japan, but the authors considered these may be adversely affected by bias and, therefore, on balance, supported the use of evidence gathered outside of a Japanese setting. The success rate and frequency of causative organisms differs according to country and setting. This issue was dealt with in the sensitivity analyses that considered the antibiotics separately. Thus, the authors addressed the issue of generalisability in a comprehensive manner, which would help the reader to assess the applicability of the findings to their own setting.

Implications of the study
The findings principally supported the use of MIN from clinical and economic perspectives. For adults without co-morbidity, however, AZM provides a higher quality of life at a generally acceptable marginal cost. No recommendations for further research were made.

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