Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database


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
Patients with community-acquired pneumonia (CAP) were given one of nine types of antibiotic treatments, five of which were monotherapies and four of which were dual therapies. The monotherapies were ceftriaxone, macrolides, "other" cephalosporins, fluorinated quinolones and penicillins. The dual therapies were the antibiotics used as monotherapies (apart from macrolides) followed by macrolides.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients over the age of 18 years who had been hospitalised with CAP. Patients were excluded if they had initially required stay in an intensive care unit, required mechanical ventilation during their stay, or had incomplete data on the antibiotic therapy. They were also excluded if they had human immunodeficiency virus infection, had been hospitalised with CAP in the last 30 days, had less than 24 hours in hospital, or fell into a severely ill category.

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

Dates to which data relate
The effectiveness and resource evidence both related to 1997 to 1999. The price year was 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 retrospectively on the same patient sample as that which provided the effectiveness evidence.

Study sample
No power calculations to determine the sample size were reported. All of the patients who met the inclusion criteria were included in the study. Of the 188,627 patients who were initially considered for inclusion, 44,814 of these met the
inclusion criteria. There were 25,986 patients receiving monotherapy and 18,818 receiving dual therapy. In the monotherapy group, 8,884 received ceftriaxone, 8,729 other cephalosporins, 3,918 macrolides, 3,130 penicillin and 1,335 quinolones. In the dual-therapy group, for their first antibiotic, 9,605 received ceftriaxone, 7,175 other cephalosporins, 1,420 penicillins and 618 quinolones. All of the dual-therapy patients then received macrolides.

Study design
This was a cohort study that examined the patients' records from several hospitals (the exact number was not given) whose records were in a centralised (hospital claims-made) database (HBSI EXPLORE, Solucient, LLC). This was a non-randomised study. The patients were studied for 30 days.

Analysis of effectiveness
This was an observational study that accounted for all the patients in the analysis. The primary health outcomes were the length of hospital stay (LOS) and the 30-day mortality. The different therapy groups were described in terms of their age, gender, race and one of four risk factors (A to D, where A represented the lowest risk). Among the patients receiving monotherapy, those in the macrolides group were younger and more likely to be in the lower risk group. The patients in the different treatment groups were not shown to be comparable in terms of their age, gender, race and health status. However, the authors attempted to take differences in health status into account by categorising the patients according to risk when assessing the effectiveness of the different antibiotic therapies.

Effectiveness results
From the tabulated results for the monotherapy patients, the LOS was 4.99 (standard deviation, SD=4.19) for ceftriaxone, 5.82 (SD=4.80) for other cephalosporins, 5.04 (SD=4.12) for macrolides, 6.09 (SD=4.26) for penicillins and 6.71 (SD=5.78) for quinolones. The mortality rates were 6.31 (ceftriaxone), 5.11 (other cephalosporins), 2.19 (macrolides), 8.15 (penicillins) and 4.94 (quinolones), respectively.

It was reported that the patients in the macrolides group had the lowest mortality, (p<0.001), but they were younger and likely to be in a lower risk category. In the text it was also reported that patients in the ceftriaxone group had the shortest LOS. However, this was not consistent with the tabulated results.

From the tabulated results for the dual-therapy patients, the LOS was 4.98 (SD=3.51) for ceftriaxone, 5.60 (SD=3.80) for other cephalosporins, 6.08 (SD=3.82) for penicillins and 6.47 (SD=4.76) for quinolones. The mortality rates were 2.76 (ceftriaxone), 2.16 (other cephalosporins), 2.46 (penicillins) and 2.91 (quinolones), respectively.

The tabulated results comparing dual therapy with monotherapy for four antibiotics showed a lower mortality rate for dual therapy, which was statistically significant for all apart from the quinolones, (p<0001). A shorter LOS was found for ceftriaxone dual therapy, which was described as statistically significant, (this is hard to reconcile given that the numbers were so close). Non statistically significant reductions in LOS were shown for the other cephalosporins. The results for penicillins showed a non statistically significant increase in LOS.

When the outcomes were divided according to risk category, the tabulated results showed the following were statistically significant (p<0.0001) for dual therapy:

- ceftriaxones, groups B and C increased LOS while groups C and D showed lower mortality rates;
- other cephalosporins, group C showed a lower mortality rate;
- penicillins, group C showed a lower mortality rate.

When the patients were divided into those aged above and below 65 years, the tabulated results showed the following statistically significant differences between dual therapy and monotherapy:

- for the younger age group, an increase in LOS and a reduction in the mortality rate with ceftriaxone;
for the older age group, an increase in LOS and a reduction in mortality rate with ceftriaxone, and a reduction in mortality with other cephalosporins and penicillins.

**Clinical conclusions**
Dual-therapy antibiotic regimes were more effective than monotherapy antibiotics. This was true of both age categories.

**Measure of benefits used in the economic analysis**
No summary measure of benefit was calculated, as this was a cost-consequences analysis.

**Direct costs**
The costs were not broken down into the resource quantities and the unit costs. No discounting was carried out, which was appropriate since the costs were incurred in less than one year. The costs were based on actual data, taken from the hospital claims database. The costs included were the total hospital charges and antibiotic charges. The price year was not reported.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were included.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was carried out.

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

**Cost results**
Among the monotherapy patients, the mean total hospital charges were $7,270 (SD=5,109) for ceftriaxone, $9,306 (SD=7,940) for other cephalosporins, $8,232 (SD=8,629) for macrolides, $10,430 (SD=8,201) for penicillins and $10,943 (SD=1,071) for quinolones.

Among the dual-therapy patients, the mean total hospital charges were $7,941 (SD=6,044) for ceftriaxone, $9,694 (SD=7,565) for other cephalosporins, $10,689 (SD=8,331) for penicillins and $11,292 (SD=7,515) for quinolones.

Knock-on costs, including in-hospital charges, would be included.

**Synthesis of costs and benefits**
The costs and benefits were not combined as the study was, effectively, a cost-consequences analysis.
Authors' conclusions
Dual therapy, when macrolides were the second antibiotic, was more effective than monotherapy. When the different monotherapy costs were compared, the lowest cost option was ceftriaxone. In terms of the cost differences between monotherapy and dual therapy, there was an inconsistency in the tabulated results and the authors' conclusions, which the authors did not address. The table showed no statistically significant increase in the costs for quinolones and penicillins, but did show a statistically significant increase in the costs for ceftriaxone and other cephalosporins. The authors did not think that any cost difference that does occur would be sufficient to deter the use of dual therapy. When taking into account the costs and effectiveness results, the authors recommended dual therapy comprising ceftriaxone and a macrolide as the best antibiotic treatment for community-acquired pneumonia (CAP).

CRD COMMENTARY - Selection of comparators
The justification for the choice of the comparators was that they were widely used in the authors' setting. You should decide whether they are widely used in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from a single observational study, which used a hospital claims database of more than 185 health care organisations. There were certain weaknesses in the study design, as this was a retrospective study that used information that had not been produced for the purposes of the study. The authors acknowledged many of these weaknesses. The exclusion criteria meant that very sick patients (category E) were not included. Also, patients with incomplete data were not included and this might have biased the results. The main weakness was that the patients were not randomly allocated to the different antibiotic treatments, and there were insufficient data on the patient records to know precisely why each patient had received a particular antibiotic treatment or the exact dosage of the antibiotics. Therefore, the patient groups were not shown to be comparable at analysis, which means there is uncertainty surrounding the precise reason for the different patient outcomes. Any difference in outcomes between the antibiotic groups could be a result of initial differences (confounding) between the patients (i.e. the reason why a different antibiotic was prescribed).

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit since this was a cost-consequences analysis. The health benefits are those associated with the effectiveness results.

Validity of estimate of costs
From the cost perspective adopted there were certain omissions. Only hospital costs were included. The costs incurred once the patient was back home were not included. No indirect costs were included. The authors used hospital charges as a proxy for costs and, as such, the cost results do not represent opportunity costs. The costs were not broken down into prices and quantities, and the price year was not given. This limits the generalisability of the results to other settings. There was no information on the dose or duration of the antibiotic therapy.

Other issues
The authors made appropriate comparisons of their results with those from other studies. They did not, however, address the issue of whether or not their results were generalisable to other settings. The authors reported several limitations of their study. For example, the lack of information on antibiotic dosage meant that there could be wide variation in the dosage, also the therapy could sometimes be administered orally and sometimes parenterally. Newer fluoroquinolone agents, such as levofloxacin moxifloxacin and gatifloxacin, were poorly represented. Also, there were no data on antibiotic use prior to admission to hospital. The authors stated that decreased LOS and lower hospital costs could occur because of increased mortality, but they do not appear to have made any allowances for this in their analysis. Despite these limitations, the authors were confident that their results showed dual therapy to be superior to monotherapy. Within dual therapy, the authors were confident that ceftriaxone dual therapy showed the best combination of effectiveness and lower costs. Such confidence may be misplaced because of the reservations already made in this abstract.
The authors do not appear to have been aware of the limitations of their cost data. In particular, that it has not been broken down into prices and quantities, that there was no adjustment to a common price year, and that it omitted both non-hospital costs and indirect costs.

**Implications of the study**
The authors recommended dual antibiotic therapy for patients with CAP, and expressed a preference for ceftriaxone on cost grounds.

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