Antibiotic optimization: an evaluation of patient safety and economic outcomes
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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
Patient-specific, antibiotic-related suggestions given to the attending physician by a team consisting of an infectious disease fellow and a clinical pharmacist for adult patients receiving parenteral antibiotics.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Adult inpatients receiving 1 or more of the following 10 designated parenteral antibiotics for three or more consecutive days: vancomycin, tobramycin, cefazidime, a combination product of ampicillin and sulbactam, ciprofloxacin, cefuroxime, a combination product of imipenem and cilastatin, fluconazole, cefotetan and ceftriaxone sodium.

Setting
Hospital. The economic study was carried out in Portland, USA.

Dates to which data relate
The study data corresponded to patients receiving parenteral antibiotics from January to March 1994. The price year was not explicitly reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was prospectively undertaken on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. 252 patients were identified. 141 patients were randomly included in the intervention group, and 111 in the control group. Patients were assigned to 1 of 4 medical service groups based on where they were treated at the beginning of the study. An infectious disease fellow and a clinical pharmacist reviewed the patients’ medical records. A total of 259 reviews was available for inclusion in the analysis. A total of 225 was finally included in the analysis. Of these, 127 reviews corresponded to the intervention group (with an average age of 64.6 years) and 98 to the control group (with an average age of 65.4 years). Thus, 13.1% of the total original sample was excluded.
Study design
This was a randomised controlled trial, carried out in a single centre. The duration of follow-up was three days after the end of antibiotic therapy. The patients were randomised to each group by means of a computer-generated random number table.

Analysis of effectiveness
The analysis was based on the intention to treat principle, since all those cases in which an unsolicited direct contact with either the physician or the patient was established were excluded from the study. The primary health outcome was microbiological and clinical response, antibiotic-associated adverse events, and mortality rate. The clinical response was determined if two or more of the following criteria were met on the same day:

1. a decline in peak temperature by 1.7 degrees C or return to normal;
2. a decline in the white blood cell count by at least 15% or a return to normal values; and
3. eradication of signs of infection or pathogen from the site of the infection.

A microbiological response was determined whenever there was evidence of sterilization at the site of the infection on repeat culture. The response was rendered “indeterminate” in the absence of repeated cultures or when the original cultures were negative. The groups were reported as comparable in terms of age, comorbidity score and sites and types of infection. However, no patient in the intervention group came from the urology or cardiothoracic services, compared to 6.1% of the patients in the comparator group, (p=0.01).

Effectiveness results
A total of 74 suggestions was made for 62 intervention group patients(49%). Of those, approximately 63 (85%) were implemented. The microbial response was 9.4% in the intervention against 5.1% in the comparator. Microbial non-responders were 3.2% of the intervention group, and 5.1% of the control (the rest of the patients in each group consisted of indeterminate cases). Clinical response was achieved in 79.5% of the intervention group, against 80.6% of patients in the control group. The clinical non-responders comprised 18.9% of the intervention group and 17.3% of the control group. These differences were reported as statistically insignificant. Only in terms of an outcome measured indirectly did the groups show significantly different results. The percentage of patients needing readministration of antibiotics within a follow-up of up to 7 days after termination of therapy was 4.7% for the intervention and 13.3% for the comparator, (p=0.02). Antibiotic-associated adverse events were reported to be similar for both groups. The mortality rate was 13.4% in the intervention group versus 11.2% in the control group.

Clinical conclusions
Patient outcomes in terms of clinical and microbiological response to therapy, antibiotic-associated toxic effects, length of stay, readmission, and in-hospital mortality were not affected by these interventions.

Measure of benefits used in the economic analysis
No summary benefit measure was identified in the economic study, and only separate health outcomes were reported.

Direct costs
Quantities were not required to be discounted due to the short time frame of the study. The quantities were reported separately from the prices. The costs measured were those associated with antibiotic use (duration of therapy was reported but not priced). The boundary adopted was the hospital. The resource and cost estimation was based on actual data. The source of costs was actual charges to patients in the study institution. The data corresponded to patients receiving parenteral antibiotics between January and March 1994. The price date was not explicitly reported. The cost analysis did not cover the costs of running the programme or ancillary costs such as routine daily hospital charges,
laboratory tests, labour, supplies, and complications associated with parenteral drug administration.

**Statistical analysis of costs**
Nonparametric analysis was used to compare the groups in terms of costs. A multivariate analysis was used in order to control for potential differences in characteristics between groups that might explain some of the effects associated with each intervention. In particular, the dependent variables analysed were antibiotic charges, hospital length of stay, and post-randomisation length of stay. The variables available for selection into the model were sex, age, randomization to the intervention group, comorbidity score, medical service, and in-hospital death.

**Indirect Costs**
Not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was conducted.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
Mean antibiotic charges per patient in the intervention group were $1,287.12, and $1,673.97 in the comparator group, (p=0.05). In terms of IV antibiotic charges per patient only, the charge per patient in the intervention group was $1,232.49, and was $1,624.06 in the comparator group, (p<0.04). The oral antibiotic charge difference was $4.78, with intervention having a mean cost per patient of $54.69 and the comparator having a cost of $49.91.

**Synthesis of costs and benefits**
Costs and benefits were not combined since the intervention was found to be the weakly dominant strategy (with equal efficacy and lower charges).

**Authors’ conclusions**
This is the first randomised study to evaluate whether antibiotic choices can be influenced in a cost-effective fashion without sacrificing patient safety. The study demonstrated that 50% of patients initially treated with expensive parenteral antibiotics can have their regimens refined after 3 days of therapy and that these modifications result in good clinical outcomes with a substantial reduction in antibiotic expense.

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

**Validity of estimate of measure of benefit**
The study results are likely to be internally valid due to the randomised design used in the study. Since the study lacked a summary benefit measure, it may be regarded as a cost-consequences study.
Validity of estimate of costs
The quantities of resource use were reported separately from the prices and adequate details of methods of cost estimation were given with the exception of the price date used in the analysis. The costs of complications were omitted from the analysis as well as overhead costs and those associated with the duration of hospital stay. The study lacked a comprehensive cost analysis, as acknowledged by the authors: "more detailed and formally developed economic analyses are essential ... .".

Other issues
The issue of generalisability of the results to other settings or countries was not addressed, although some comparisons were made with other (nonrandomised) studies in terms of the effect of intervention aimed at influencing physicians’ behaviour with respect to antibiotic prescribing. Those comparisons supported the study findings. The results were not presented selectively.

Implications of the study
This study highlights the need for well designed economic evaluations that incorporate all relevant economic elements both in terms of cost and benefits. With respect to costs, all the relevant costs from the point of view of the hospital should be considered (complications, length of hospital stay, overhead costs, etc.), whereas, if quality of care is the issue, a utility assessment of clinical outcomes could be performed, and, therefore, a less restricted assessment of benefits could be obtained.

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