Comparison of linezolid with oxacillin or vancomycin in the empiric treatment of cellulitis in US hospitals


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
Three antibiotics for the empiric treatment of cellulitis in hospitalised patients were compared. The antibiotics were linezolid, oxacillin and vancomycin. The alternative treatments evaluated were intravenous (IV) oxacillin (2 g every 6 hours, with an option to switch to oral dicloxacillin 500 mg every 6 hours), IV vancomycin (1 g every 12 hours), and linezolid (600 mg every 12 hours, initiated IV with an option to switch to oral).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The target population for the model were hospitalised patients with cellulitis.

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

Dates to which data relate
The effectiveness evidence was taken from 2000 to 2001. The costs of health service use were taken from 1997 to 2001. A single price year was not reported (the 'price year' ranged from 1997 to 1999).

Source of effectiveness data
The effectiveness data were derived from the synthesis of two completed randomised clinical trials (Stevens et al. and Leach et al., see Other Publications of Related Interest), and also from authors' assumptions.

Modelling
A decision analytical model was built to estimate the effectiveness and to calculate the total direct medical cost of treating cellulitis among hospitalised patients. The model consisted of a decision tree with three main branches, one for each treatment option, based on the clinical pathway for cellulitis treatments. The initial antibiotic was continued or switched to a clinically appropriate alternative based on the results of a bacterial culture and sensitivity test (C&S). The scenarios for the second-line antibiotic treatment were as follows:

for an initial IV linezolid treatment, switching to IV oxacillin if the pathogen was found to be methicillin susceptible, or maintaining linezolid if the pathogen was found to be methicillin resistant or when the pathogen remained unknown;
for an initial IV oxacillin treatment, switching to vancomycin if there was methicillin resistance, or maintaining oxacillin in the case of methicillin susceptibility or unknown susceptibility;

for an initial IV vancomycin treatment, switching to IV oxacillin in the case of methicillin susceptibility, or maintaining vancomycin if there was methicillin resistance or unknown susceptibility.

Although third-line treatment failure was possible, this extension was not included in the model. Thus, the time horizon covered the period of treatment initiation until no more than three treatment switches.

Outcomes assessed in the review
Three clinical outcomes were modelled. These were success (i.e. improvement in or recovery from an infection), failure due to lack of efficacy, and failure due to adverse events. Death as a possible outcome was not included in the model, as patients rarely die of cellulitis.

Study designs and other criteria for inclusion in the review
The effectiveness evidence was mainly derived from two randomised clinical trials (see Other Publications of Related Interest). The main source of effectiveness included data on 124 patients treated with linezolid, 133 patients treated with oxacillin, and 66 patients treated with vancomycin.

Sources searched to identify primary studies
Not stated.

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
The authors reported that two randomised clinical trials provided the effectiveness evidence (see Other Publications of Related Interest).

Methods of combining primary studies
Since the trials were not designed to detect a difference in efficacy between antibiotics, but rather to demonstrate equivalent efficacy, the authors used the average clinical success rates from the two trials.

Investigation of differences between primary studies
The authors did not investigate the differences between the primary studies.

Results of the review
The success rate for infection with methicillin-susceptible pathogens was 91.1% for linezolid, 91.1% for oxacillin, and 79.85% for vancomycin. For infection with methicillin-resistant pathogens, the success rates were 79.85% (linezolid), 0% (oxacillin) and 79.85% (vancomycin), respectively.

For infection with methicillin-susceptible pathogens, the failure rate due to lack of efficacy was 4.6% for linezolid, 4.6% for oxacillin, and 15.85% for vancomycin. For infection with methicillin-resistant pathogens, the failure rates
were 15.85% (linezolid), 95.7% (oxacillin) and 15.85% (vancomycin), respectively.

For infection with methicillin-susceptible and -resistant pathogens, failure due to adverse events was 4.3% for all three antibiotics.

Methods used to derive estimates of effectiveness
The authors also made some assumptions in the analysis.

Estimates of effectiveness and key assumptions
The authors made some key assumptions in the base-case scenario. First, patients initiated antibiotic treatment in the hospital. Second, the clinical success rate for vancomycin in managing methicillin-susceptible gram-positive infections was equal to that for vancomycin in managing methicillin-resistant staphylococci infections. Third, for patients whose pathogens remained unknown, the risk of patients being infected with methicillin-resistant pathogens was assumed to be equal to the proportion of patients infected with methicillin-resistant pathogens among patients with known pathogens. Finally, the base-case rate of patients whose pathogens remained unknown was assumed to be 80%.

Measure of benefits used in the economic analysis
No summary measure of benefit was used in the economic evaluation. The cost and effects were left disaggregated, and the study was therefore classified as a cost-consequences analysis.

Direct costs
The cost estimates for direct medical care were derived from an estimation of the units of health care use and their respective costs. The costs and the quantities were reported separately. The costs were derived from current costing data for US hospitals, including the price to the hospital of medications, procedures, consultations and the hospital bed. The costs for home IV antibiotic administration were also included for those patients who were discharged while on IV antibiotic treatment, as it was assumed that these costs would be a burden to the hospital as well, although this is not common practice.

The unit costs were derived from average wholesale prices for medication use (1999), CPT codes (1999), and Medicare relative value units (1998) for procedures. The average costs for hospital bed days were obtained from 1997 MEDPAR data. Direct prices from the manufacturer were used for the main antibiotics used in the study, although this could represent an underestimation of current prices for the hospital.

Estimates of length of stay for patients treated successfully with first-line antibiotics were derived from the two clinical trials. Estimates for other forms of health care use were derived from experts’ opinions using a modified Delphi method. The questionnaire used was validated prior to interviews with the experts.

Discounting was not carried out. The costs were not adjusted for inflation and do not seem to have been reported in a common price year. The costs of infections caused by non gram-positive pathogens were not assessed in the model.

Statistical analysis of costs
No statistical tests were carried out.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).
Sensitivity analysis
Sensitivity analyses were carried out to test the impact of the following on the overall cost for each of the three treatment branches in the model:

- variations in the risk of infection with methicillin-resistant pathogens;
- the percentage of patients (or likelihood of a patient) whose pathogens remain unknown;
- the first-line treatment success rate of oxacillin for infections caused by methicillin-resistant pathogens; and
- the first-line success rates of all three comparator drugs, using point treatment success rates from the two trials.

An additional sensitivity analysis explored the impact of excluding IV antibiotic treatment at home.

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

Cost results
Increasing the risk of being infected with methicillin-resistant pathogens resulted in an increase in the average cost per patient. When considering 0% and 100% risks of being infected with methicillin-resistant pathogens as extreme cases, the results were as follows.

In the case of a 0% risk of infection with methicillin-resistant pathogens, the total average cost per patient whose treatment was initiated with linezolid was $4,370, compared with $4,163 per patient treated with oxacillin and $4,180 per patient treated with vancomycin.

When the risk of being infected with methicillin-resistant pathogens was 100%, the total average cost per patient on linezolid was $11,267, compared with $11,627 per patient treated with oxacillin and $11,645 per patient treated with vancomycin.

The risk at which the cost of treatment initiated with linezolid equalled the cost of treatment initiated with oxacillin was 18.7% (when the rate of unknown pathogens was 80%). That rate increased to 21.05% when the rate of unknown pathogens was 30%, thus showing a small impact on the results.

Treatment initiated with vancomycin was more expensive than treatment with linezolid across the full spectrum of the risk of being infected with methicillin-resistant pathogens.

The total costs were broken down by type of resource use. This showed that the major cost drivers for all three treatments were the cost of hospital stay and the cost of antibiotics. Antibiotic costs alone were highest in the linezolid arm, although antibiotic costs in the oxacillin arm increased rapidly as the risk of resistance increased.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-consequences analysis was conducted.

Authors’ conclusions
Under the principle of appropriate use, linezolid appears to be at least as effective as vancomycin or oxacillin for the empiric treatment of hospitalised cellulitis patients. It is likely to be less costly than vancomycin in all cases and less costly than oxacillin when the risk of infection with methicillin-resistant pathogens exceeds 18.7%, a usual figure in the USA. The clinical advantage of linezolid lies in its comparable efficacy with these two drugs. Its potential in cost-savings is probably related to its oral formulation, which might reduce length of stay compared with vancomycin, or its superior efficacy to oxacillin for methicillin-resistant pathogens and to vancomycin for methicillin-sensitive pathogens,
which might reduce the costs associated with treatment failures.

CRD COMMENTARY - Selection of comparators

The choice of the comparator was explicitly justified. The justification given for the choice of the drugs was based on published literature and standard clinical practice. You should judge whether these drugs are relevant in your setting, or whether other comparators from other drug classes could also have been relevant.

Validity of estimate of measure of effectiveness

The authors used data from published sources. The main sources of the effectiveness evidence were two randomised clinical trials of linezolid (see Other Publications of Related Interest). Despite this, it is unclear whether a systematic review of the literature was undertaken. The effectiveness estimates, which were derived from the primary studies and from the authors’ assumptions, were combined. The authors reported the methods used to derive estimates of effectiveness (success and failure rates) and justified their choice of assumptions with reference to the medical literature. These estimates were investigated in sensitivity analyses.

Validity of estimate of measure of benefit

The authors did not derive a measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

Validity of estimate of costs

The authors reported that the costs were estimated from a US hospital perspective. Therefore, the indirect costs were appropriately not included. Although some costs might have been omitted from the analysis, these are unlikely to have affected the authors’ conclusions as they were common to both therapies. The drug acquisition price obtained from the manufacturer might have underestimated the real costs for the hospital. In addition, the IV treatment at home might have increased the hospital costs. Discounting was unnecessary as all the costs were incurred during a short time. A single price year was not reported, which will limit any inflation exercises.

To estimate the total direct costs, the authors considered the health service use costs and the drug acquisition cost, although they were taken from different sources and years and no adjustment was reported. The resource use quantities and prices were taken from published sources and an expert panel. Uncertainty in these parameters was appropriately evaluated in sensitivity analyses.

Other issues

The authors compared their findings with those from other studies, showing in general that their findings were in agreement with prior studies. The issue of the generalisability was addressed explicitly, as the authors stated that the three treatment options were chosen because of the availability of clinical data needed for the model, and that they might not be standard clinical practice in some institutions. The authors appear to have presented their results selectively, although their conclusions reflected the scope of the analysis.

The authors explicitly stated some limitations to their study. First, the study did not test statistically differences between the comparators. Second, the assumptions made to obtain some input data might have influenced the model results. Third, the use of input data from a panel of experts might have introduced subjectivity and large variation in the estimates. Finally, the authors used clinical data which typically provide clinical efficacy instead of effectiveness.

Implications of the study

The authors suggested that this study could (in fact 'should') be validated by future prospective studies.

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