Linezolid for treatment of ventilator-associated pneumonia: a cost-effective alternative to vancomycin
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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
The use of linezolid for the treatment of ventilator-associated pneumonia (VAP) caused by both methicillin-sensitive and methicillin-resistant Staphylococcus aureus (MSSA and MRSA, respectively). The comparator used in the study was vancomycin.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The target population was a hypothetical cohort of 1,000 patients in intensive care units (ICUs) and diagnosed with VAP, who were being treated with an antibiotic regimen including agents directed against S. aureus. The age of the target population seems to have been 62 years, but the gender was not defined.

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

Dates to which data relate
The effectiveness data related to studies published between 1997 and 2003. The resource data related to studies published in 2002-03. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and a number of assumptions or estimates.

Modelling
A decision tree model was used to estimate and compare the benefits (additional survivors, life-years saved and quality-adjusted life-years) and costs of two different pharmacologic strategies for patients in ICUs with a clinical diagnosis of VAP. Linezolid was compared with vancomycin for the treatment of suspected S. aureus VAP. There were two possible pathways for each treatment strategy and the two possible ends of each strategy were survival or death.

Outcomes assessed in the review
The outcomes assessed were:
the incidence of S. aureus VAP in the cohort,

the attributed mortality of VAP, and

the odds ratio for survival with linezolid relative to vancomycin.

**Study designs and other criteria for inclusion in the review**
Not stated.

**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**
Three studies were included in the review.

**Methods of combining primary studies**
The effectiveness estimates were not combined. The data were based on a pooled analysis of more than 20 studies (reference 18) and a pooled analysis of two randomised controlled trials (reference 13), supplemented by a cohort study (reference 19).

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

**Results of the review**
The incidence of VAP due to S. aureus was 20.4% (range: 15.3 - 25.5).

The mortality of VAP due to S. aureus was 27.1% (range: 20.3 - 33.9).

The odds ratio for survival with linezolid relative to vancomycin was 1.6. The authors estimated the relative risk reduction (RRR) to be 37.5% (95% confidence interval, CI: 3.5 - 58.3). The RRR was then reduced by approximately 10% to be set at 33.3%.

**Methods used to derive estimates of effectiveness**
The authors made assumptions, based on three other published studies, to augment the data from the literature.

**Estimates of effectiveness and key assumptions**
VAP survivors lived 9 years and the health utility of each year of survival was 0.83 quality-adjusted life-years (QALYs). The authors also assumed that a 62-year-old person without VAP would live for 18 years, and that VAP reduced the long-term survival to half in a way similar to severe sepsis. The authors reduced by 10% the health utilities
derived from survivors of acute respiratory failure necessitating mechanical ventilation, which were obtained using the
time trade-off tool.

Measure of benefits used in the economic analysis
The health benefit measures used were VAP survivors, life-years saved and QALYs (see Estimates of Effectiveness and
Key Assumptions for QALY estimates).

Direct costs
The study perspective was that of a third-party payer. The direct costs reported comprised the costs of a hospital
episode of VAP, the marginal drug costs of using linezolid instead of vancomycin, and post-hospitalisation lifetime
health care costs. The marginal costs of linezolid were derived from a regional non-federal hospital pharmacy. The
hospitalisation costs were obtained from a prospective, observational study of patients admitted to hospital who
developed VAP. The post-hospitalisation annual costs were derived from a cost-effectiveness study of a drug to treat
severe sepsis, and were adjusted to account for nursery home costs. The quantities and the costs were not reported
separately. The costs were discounted at 3% per year and were incurred during 9 years. The price year was 2001 and the
costs were reflated using the medical component of the Consumer Price Index.

Statistical analysis of costs
The data were treated deterministically, but ranges were provided for the sensitivity analysis.

Indirect Costs
No indirect costs were included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
A one-way sensitivity analysis was performed on all variables included in the model. The original values were varied by
plus or minus 25%, except for the RRR (95% CI used) and discount rate (0 to 6%). A two-way sensitivity analysis was
also performed for some pairs of variables. A Monte Carlo simulation was used to estimate the 95% CI for the
incremental cost-effectiveness of linezolid. However, the distributions attributed to the probabilities of the various
inputs used in the simulation were not reported.

Estimated benefits used in the economic analysis
Compared with vancomycin, the strategy of treating VAP with linezolid generated 18 additional survivors and an
additional 121.1 QALYs.

The possible side effects of either treatment were not included in the study.

Cost results
The lifetime incremental cost of linezolid was $3,501,839 compared with vancomycin. The costs were discounted at an
annual rate of 3%.

Synthesis of costs and benefits
The costs and benefits were combined by calculating an incremental cost-effectiveness ratio (ICER).
The ICER of linezolid against vancomycin was $67,202 per additional life saved, $22,072 per additional life-year saved, and $29,945 per additional QALY.

The sensitivity analysis showed that the results were most sensitive to the RRR of linezolid, with the cost per life saved ranging from $43,855 to $170,536, and the cost per QALY ranging from $26,425 to $45,526.

The results were also sensitive to the value of the health utility for each survival year, with the cost per QALY of using linezolid ranging from $24,854 to $39,927.

The incremental cost per QALY of linezolid ranged from $13,324 in the best-case scenario to $101,143 in the worst-case scenario. The authors also reported that if the treatment with linezolid led to at least two more survivors than vancomycin, its cost-effectiveness would still be below $100,000 per QALY.

From the results of the Monte Carlo simulation, the 95% CI of the cost-effectiveness of linezolid was $23,637 to $42,785.

**Authors’ conclusions**

Compared with vancomycin, linezolid was a cost-effective alternative for the treatment of ventilator-associated pneumonia.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the comparator used. It was the only readily available treatment option for VAP caused by MRSA. However, the incidence of MRSA was not included in the model. You should decide if this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state whether a systematic review of the literature was undertaken, but data were derived from a pooled analysis of more than 20 studies and a pooled analysis of two randomised clinical trials. The authors did not report any effectiveness data pertaining to possible adverse events from the two treatment strategies under evaluation. No measure of incidence of VAP due to MRSA was derived and included in the model. Given that other drug alternatives exist for MSSA (e.g. flucloxacillin and cephalosporins), this issue should have been addressed. Hence, not all feasible and practical treatment options relating to the decision problem were evaluated. The method by which the RRR value was obtained from the odds ratio for survival with linezolid was not explicitly reported. This is important given that the odds ratio only approximates the relative risk when the outcome is rare. The issue of antibiotic resistance was not addressed in the model, but the authors acknowledged this limitation.

In conclusion, the structure of the model and the data inputs represent a limitation to the external validity of the study. However, appropriate sensitivity analyses, over plausible ranges, were conducted and this enhances the validity of the results.

**Validity of estimate of measure of benefit**

The estimation of benefits was modelled. The measures of benefits (lives saved, life-years saved and QALYs) were valid, although it was unclear whether the authors included any undesirable side effects of the treatments in their QALY calculation and if the survivors of acute respiratory failure were very similar to VAP survivors. The use of QALYs enhances the comparability of the intervention in relation to other health care programmes that use QALYs.

**Validity of estimate of costs**

The study perspective was that of a third-party payer. As such, all the categories of cost relevant to this perspective were included in the analysis. The costs and the quantities were not reported separately, which presents limitations about the generalisability of the results. Relevant costs (i.e. costs of adverse effects, and costs due to the development of
antibiotic resistance) might have been omitted from the analysis. The costs were appropriately discounted at an annual rate of 3%, but the total costs of each individual strategy were not provided. The price year was reported, which will enable reflation exercises to be performed.

Other issues
The authors compared their findings with those from other studies. However, they did not specifically address the issue of the generalisability of the study results to other settings. Sensitivity analyses were conducted, but the authors failed to state which distributions were assumed for the data inputs in the Monte Carlo simulation. The authors do not appear to have presented their results selectively. In addition, they acknowledged several limitations in their study. First, resistance to drugs was not addressed. Second, the authors made assumptions. Third, a great deal of uncertainty was present in most inputs. Fourth, the optimal duration of antibiotic therapy for VAP is unknown. Finally, the data only apply in hospitals with more than 20% incidence of MRSA VAP.

Implications of the study
The authors concluded that linezolid was a valid intervention to replace vancomycin for the empirical treatment of VAP, and it was as cost-effective as other interventions used in ICUs. They recommended the use of linezolid be minimised so as to limit the potential for the development of resistance.

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