Questionable history of immediate-type hypersensitivity to penicillin in Staphylococcal endocarditis: treatment based on skin-test results versus empirical alternative treatment - a decision analysis
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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
Treatment with antibiotic therapy based on skin test results was compared with empirical treatment (no skin testing) in patients who had infective endocarditis (Staphylococcus aureus), susceptible to cloxacillin, and who had a questionable history of immediate-type hypersensitivity to penicillin.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with infective endocarditis due to Staphylococcus aureus that was susceptible to cloxacillin and who had a questionable history of immediate-type hypersensitivity to penicillin. No further study inclusion or exclusion criteria were reported.

Setting
The setting was secondary care. The economic study was carried out in Vancouver, Canada.

Dates to which data relate
The outcome, probability, and utility data were taken from literature published between 1984 and 1994. The price year was not reported.

Source of effectiveness data
The effectiveness data were based on a review/synthesis of previously completed studies.

Modelling
The authors used a decision-analytical model to calculate the maximum expected utility and maximum cost for skin testing or not skin testing patients who have endocarditis.

Outcomes assessed in the review
The outcomes used as input parameters to the model were the following probability values:

the probability of a positive skin test in the patient population;
the probability of a toxic reaction to vancomycin;
the probability of a microbiological cure with a vancomycin-based regimen;
the probability of a toxic reaction to penicillin in a patient who has a negative skin test;
the probability of a severe hypersensitivity reaction in a patient with a history of a penicillin allergy;
the probability of a negative skin test in a patient who has a questionable history of penicillin allergy;
the probability of death, given a severe hypersensitivity reaction to penicillin; and
the probability of a microbiological cure, with a cloxacillin-based regimen.

Study designs and other criteria for inclusion in the review
The design of studies included in the review was not explicitly stated.

Sources searched to identify primary studies
The authors did not report the sources searched to identify primary studies.

Criteria used to ensure the validity of primary studies
The criteria used to judge the validity of primary data sources were not reported.

Methods used to judge relevance and validity, and for extracting data
The criteria used to judge the relevance, validity, and extraction of data, were not reported.

Number of primary studies included
Approximately 9 primary data sources were included in the review.

Methods of combining primary studies
The authors did not report the method of combination of data from primary data sources.

Investigation of differences between primary studies
The difference between primary data sources, in terms of participants, intervention or outcome measures were not investigated or explained by the authors.

Results of the review
The results of the probability values used as input parameters to the model were as follows:
the probability of a positive skin test in the patient population ranged from 0.1 to 0.3;
the probability of a toxic reaction to vancomycin was 0.15 (range: 0.09 - 0.24);
the probability of a microbiological cure with a vancomycin based regimen was 0.7 (range: 0.62 - 0.79);
the probability of a toxic reaction to penicillin in a patient who has a negative skin test was 0.02 (range: 0 - 0.04);
the probability of a severe hypersensitivity reaction in a patient with a history of a penicillin allergy was 0.002;
the probability of a negative skin test in a patient who has a questionable history of penicillin allergy was 0.8;
the probability of death due to a severe hypersensitivity reaction was 0.1;
the probability of a severe hypersensitivity reaction in this setting was 0.0016 and the probability of death, given a severe hypersensitivity reaction to penicillin was 0.00016;
the probability of a microbiological cure with a cloxacillin-based regimen was 0.95.

The utility of a microbiological cure in skin test positive patients who receive vancomycin without adverse reactions was 0.95 (outcome 1).
The utility of a microbiological failure in skin test positive patients who receive vancomycin and have no adverse reaction was 0.85 (outcome 2).
The utility of microbiological cure in skin test positive patients who receive vancomycin and have an adverse reaction was 0.90 (outcome 3).
The utility of microbiological failure in skin test positive patients who receive vancomycin and have an adverse reaction was 0.75 (outcome 4).
The utility of microbiological cure in skin test negative patients who receive cloxacillin and do not have any allergic reaction was 0.985 (outcome 5).
The utility of microbiological failure in skin test negative patients who receive cloxacillin and do not have any allergic reaction was 0.885 (outcome 6).
The utility of microbiological cure in skin test negative patients who receive cloxacillin and suffer a penicillin reaction and survive was 0.92 (outcome 7).
The utility of microbiological failure in skin test negative patients who receive cloxacillin and suffer a penicillin reaction and survive was 0.82 (outcome 8).
The utility of skin test negative patients who receive cloxacillin and suffer a penicillin reaction and die was 0 (outcome 9).
The utility of microbiological cure in patients who are not skin tested and who receive vancomycin without adverse reactions was 0.97 (outcome 10).
The utility of microbiological failure in patients who are not skin tested and receive vancomycin without adverse reactions was 0.875 (outcome 11).
The utility of microbiological cure in patients who are not skin tested and receive vancomycin and suffer adverse reactions was 0.92 (outcome 12).
The utility of microbiological failure in patients who are not skin tested and receive vancomycin and suffer adverse reactions was 0.87 (outcome 13).

**Measure of benefits used in the economic analysis**
The measure of benefit used in the economic analysis was the utility values determined by patients’ preferences for 13 different outcomes. The authors reported that one patient was asked to value their preferences for the 13 health states described in the decision-tree. The patient was not able to complete this task and a nurse, who cares for patients with infective endocarditis, was asked to value the health states using the standard gamble approach.

**Direct costs**
Costs and quantities were not reported separately. The following direct costs were included in the analysis:

cloxacillin = Can$1.25 per 2g dose;
vancomycin = Can$21.00 per 1g dose;
rifampin = Can$0.65 per 300mg dose;
measurements of serum vancomycin concentration = Can$31.51;
penicillin skin tests = Can$123.15 each;
and hospitalisation costs = Can$500 per day.

The authors reported that all costs were obtained from the laboratory and pharmacy departments of St Paul's Hospital in Vancouver, Canada. The price year was not reported. Discounting was not undertaken because costs and benefits were accrued over a short time period.

**Statistical analysis of costs**
No statistical analysis of costs was conducted.

**Indirect Costs**
No indirect costs were included in the analysis.

**Currency**
Canadian dollars (Can$). No currency conversions were reported.

**Sensitivity analysis**
The authors reported that one-way sensitivity analyses were carried out in three different ways. Firstly with expected utility as the outcome, while each probability and utility were allowed to vary individually. Secondly with total cost as the outcome, while each cost and probability were allowed to vary individually. Thirdly, with average cost-utility as the outcome while each cost, probability and utility were allowed to vary individually. The authors reported the individual ranges for the probability values used in the sensitivity analysis.

**Estimated benefits used in the economic analysis**
The maximum expected utility for skin-testing was 0.965.
The maximum expected utility for no skin-testing was 0.936.

**Cost results**
The minimum expected cost for skin testing was Can$14,927.26.
The minimum expected cost for no skin testing was Can$16,375.25.

**Synthesis of costs and benefits**
The study did not report incremental cost-utility ratios.
The study reported the average cost-utility of the two different treatment strategies.
The average cost-utility for skin testing was Can$15,468.69.

The average cost-utility for no skin testing was Can$17,492.46.

The sensitivity analysis showed that, with expected utility as the outcome, skin testing was preferable to no skin testing in most circumstances. For example the authors reported that the threshold above which one would choose no skin testing for the probability of a positive skin test was 0.62, a value that the authors reported was much higher than in any of the literature. The authors reported that sensitivity analysis for the probability of a toxin reaction to vancomycin showed no threshold and that skin testing was always preferable.

The threshold values for the utility values were as follows:

microbiological cure in skin test negative patients who receive cloxacillin and do not have an allergic reaction =< 0.95;

microbiological failure in skin test negative patients who receive cloxacillin and do not have any allergic reaction =< 0.16;

microbiological cure in skin test positive patients who receive vancomycin and have no adverse reactions =< 0.71;

microbiological failure in skin test positive patients who receive vancomycin and have no adverse reactions =< 0.28;

microbiological failure in patients who are not skin tested and who receive vancomycin without adverse reactions => 0.99.

The authors reported that for all other utilities, skin testing was always preferred.

The expected cost of the skin test group was lower than the no skin test group provided that any of the following factors were true: the cost of a dose of cloxacillin was less than Can$12.11; the cost of the penicillin test was less than Can$1571; the probability of a positive skin test was lower than 0.94, or the probability of microbiological cure in skin test negative patients who receive cloxacillin without allergic reactions was greater than 0.45.

The threshold values for the average cost-utility ratio to favour skin testing were:

the probability of a positive skin test = 0.8;

probability of a microbiological cure in skin test negative patients who receive cloxacillin without allergic reactions = 0.5;

a dose of cloxacillin = Can$16;

utility of microbiological cure in skin test negative patients who receive cloxacillin without allergic reactions = 0.85;

utility for patients who receive vancomycin without adverse reactions = 0.5.

The authors stated that, for all other utilities, skin testing had a lower average cost-effectiveness ratio than no skin testing over the entire range and there was no threshold for average cost-utility for the cost of the penicillin skin test. Skin testing was preferred over the full range of costs.

**Authors' conclusions**

The authors concluded that the decision analysis showed that penicillin skin testing was a favoured strategy in comparison to no skin testing in patients who have infective endocarditis due to Staphylococcus aureus that is susceptible to cloxacillin and who have a questionable history of immediate-type hypersensitivity to penicillin.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the choice of comparator used, namely that it represented common practice in the authors...
setting. You, as a user of this database, should decide if this is widely used health technology in your own setting. The authors reported that other options in this setting included using a first-generation cephalosporin as an alternative to vancomycin. This alternative was not, however, considered, because the authors stated that it appeared to be used less commonly than vancomycin and also because there was limited data about toxicity and cure rates for these treatments. Moreover, the authors reported that cephalosporins are not recommended for patients who have IgE-mediated hypersensitivity to penicillin. You, as a user of this database, should consider if these limitations are relevant to your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. The authors used data from the available studies selectively and did not consider the impact of the differences between primary data sources when estimating effectiveness. A further limitation reported by the authors was that the analyses were based on 4 weeks of antimicrobial therapy. The authors stated that, if therapy had continued for 6 weeks, the difference in favour of skin testing would have been amplified. Another limitation reported by the authors was that treatment failure was limited to microbiological failure. Haemodynamic failure was not considered. The clearest indication for valve replacement in the setting of endocarditis is refractory congestive heart failure. This event was not considered. The final limitation reported by the authors in relation to the study was that there is no commercially available preparation for minor skin determinants for penicillin skin testing. Thus, the authors stated that there may be some variability in the proportion of positive skin tests, depending on the local preparation of minor determinants.

Validity of estimate of measure of benefit
The estimation of benefits, utility, was determined from a standard gamble exercise with a nurse who gave proxy valuations for the health states under consideration. The authors reported that it was not possible to obtain patient-based valuations. However, it should be noted that proxy valuations will probably generate higher utility valuations than patients' valuations of the same health states. This means that the impact of the intervention may have been overestimated.

Validity of estimate of costs
All categories of cost relevant to the perspective adopted were included in the analysis. However, some relevant costs were omitted from the analysis. The authors reported that a more accurate hospitalisation cost would include all direct costs for services plus capital and allocated overhead costs. The authors reported that indirect costs, such as those incurred by lost time for the patients and their families were not considered. However, indirect costs do not appear to have been relevant to this study as is was carried out from the third party payer rather than a societal perspective. Costs and quantities were reported separately. No statistical analysis of prices or quantities was performed. However, a sensitivity analysis of both prices and quantities was performed and the ranges specified appeared appropriate. Appropriate currency conversions were not performed and discounting was not undertaken because of the short time frame of the study.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, but did not fully address the issue of generalisability to other settings outside Canada. Furthermore, the authors reported average rather than incremental cost-utility ratios which limits the generalisability of the study's findings.

Implications of the study
The authors concluded that, whether utility, cost, or average cost-utility was the outcome of interest, skin testing was preferred to no skin testing in most conditions. The authors stated that patients who have endocarditis due to Staphylococcus aureus, that is susceptible to cloxacillin, and have a questionable history of immediate-type hypersensitivity to penicillin should be skin tested prior to starting antibiotic therapy.
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