Is antibiotic prophylaxis for bacterial endocarditis cost-effective?
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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 present study compared eight management strategies, including a no prophylaxis option, for bacterial endocarditis (BE) in medical and predental antibiotic prophylaxis for patients with underlying heart disease. The strategies were:
- no antibiotics;
- oral amoxicillin 2 g, administered 1 hour before the procedure;
- oral clarithromycin 500 mg, administered 1 hour before the procedure;
- oral clindamycin 600 mg, administered 1 hour before the procedure;
- oral cephalexin 2 g, administered 1 hour before the procedure;
- intravenous or intramuscular ampicillin 2 g, administered 30 minutes before the procedure;
- intravenous or intramuscular cefazolin 1 g, administered 30 minutes before the procedure; and
- intravenous clindamycin 600 mg, administered 30 minutes before the procedure.

In addition, the results were evaluated for both the whole group of underlying heart disease as well as a high-risk sub-group.

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 10 million US adults (age 40 years) who required antibiotic prophylaxis before undergoing a dental procedure. All patients had native heart valves and met the latest AHA criteria for endocarditis prophylaxis, based on the presence of underlying cardiac conditions associated with moderate or high risk of endocarditis. The patients were to undergo an invasive dental procedure, as defined by the AHA criteria.

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

Dates to which data relate
The epidemiological, effectiveness and utility data were taken from several studies published between 1965 and 2002.
The costs and resource use data were taken from several sources dating from 1995 to 2000. The price year was 2003.

**Source of effectiveness data**
The effectiveness data were derived from published studies, with some estimates based on authors’ assumptions.

**Modelling**
A decision model, which was described in detail, was used. The decision model compared each of the recommended antibiotic regimens, as detailed in the latest AHA guidelines, to a no-antibiotic prophylaxis strategy. It consisted of a decision tree that represented the short-term consequences for patients undergoing a dental procedure that had required antibiotic prophylaxis. In addition, a 4-state Markov process (state transition) was used to model long-term survival.

All persons were assumed to be in a state of good current health. Patients could experience any or a combination of the following short-term health outcomes based on the decision to receive antibiotic prophylaxis versus no prophylaxis: development of nonfatal side effects from an antibiotic; development of fatal side effects from an antibiotic; and development of BE and death from complications of acute BE. Patients who survived acute infection might require immediate valve replacement or survive without complications. Patients who survived the acute episode of BE and patients who did not develop endocarditis were entered into the Markov sub-tree, with the following long-term health states:

- patients who did not develop endocarditis and those who recovered without any complications were considered to be in good health;
- patients with valve replacement;
- patients with congestive heart failure and valve replacement; and
- dead.

During each Markov cycle (cycle length 1 year), patients could remain in their current state or move to another state. The transition probabilities between health states were derived from the review of the literature. The timeframe for the intervention (prophylaxis strategy) was limited to a one-time need for a prophylactic antibiotic prior to a dental procedure. An analytic horizon of 55 years was chosen to include all the future costs and health effects that would have occurred over the life expectancy of the study cohort.

**Outcomes assessed in the review**
The parameters used in the model included:

- antibiotic effectiveness;
- the risk for developing endocarditis for persons with valve disease and in dental procedures;
- compliance;
- the outcomes of acute endocarditis infection; and
- the probabilities for adverse treatment effects.

Utilities for different chronic health states and tolls for temporary states were also incorporated.

**Study designs and other criteria for inclusion in the review**
A review of the literature was performed. The authors reported that they used randomised controlled trials, cohort studies, case-control studies, observational studies and published literature. The criteria for the search were to identify
relevant human studies using the key terms "bacterial endocarditis", "antibiotic prophylaxis" and "chemoprophylaxis".

Sources searched to identify primary studies
An electronic search of MEDLINE, HealthSTAR, Cochrane and PreMEDLINE databases was performed. The dates of the search were not reported. This search was supplemented by a manual search of the bibliographies of the retrieved articles.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The authors reported that at least 25 primary studies were included in the review.

Methods of combining primary studies
Since studies of antibiotic effectiveness reported conflicting estimates of protective efficacy and these results were not statistically significant, the authors conducted pooled analyses of the data from these studies. Pooled odds ratios with 95% confidence intervals were calculated, after testing for heterogeneity, using the Mantel-Haenszel procedure. In other parameters, individual study results were used.

Investigation of differences between primary studies
To evaluate antibiotic effectiveness, tests for heterogeneity were performed in order to pool the study results. For other parameters, the authors used differences between the individual studies for the ranges selected for the sensitivity analysis.

Results of the review
The base case rates for selected outcomes were as follows:

- the prevalence of valve disease in 40-year-old persons was 20%;
- the proportion of BE patients with predisposing cardiac lesion was 53%;
- the proportion of BE cases attributable to dental procedure was 16.8%;
- the number of dental visits was 2.0 per person/year;
- the baseline compliance with prescribing prophylaxis was 0.5;
- the relative risk of developing endocarditis after a dental procedure if antibiotic prophylaxis was used was 0.46;
- the probability of mortality from acute endocarditis infection was 0.16; and
- the relative risk of death per year after endocarditis was 3.3.

The probability of developing congestive heart failure was 0.50 after endocarditis and 0.05 without endocarditis.

The probability of valve replacement surgery was 0.28 for 1 year after BE, 0.042 for 1 to 15 years after BE, and 0.01
The probability of death from valve replacement surgery was 0.125.

The probability of nonfatal hypersensitivity was:
- to amoxicillin or ampicillin, 0.02;
- to clarithromycin, 0.003;
- to clindamycin, 0.004; and
- to cephalexin or cefazolin, 0.017.

The probability of fatal anaphylaxis was:
- from amoxicillin and ampicillin, 20/1,000,000;
- from cephalexin and cefazolin, 1/1,000,000; and
- from clarithromycin and clindamycin, 0.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
The authors made several simplifying assumptions. Due to a lack of data on the effectiveness of individual antibiotic regimens, it was assumed that antibiotic effectiveness and compliance were similar for all antibiotic regimens in the model. Although the study cohort comprised persons with underlying cardiac conditions associated with a moderate or high risk of endocarditis, for the base-case analysis, this state was assumed to be equivalent to a baseline state of good health and there was no disutility assigned to this state. For the purpose of discounting, it was assumed that all future costs and benefits occurred at a steady rate over the expected life expectancy of the population.

Measure of benefits used in the economic analysis
The health outcomes measured in the decision model were the cases of endocarditis prevented, lives saved and quality-adjusted life-years (QALY) saved. All future benefits were discounted at a rate of 3%.

Adjustments for decrements in QALYs were performed by assigning a utility to each of the long-term health states. The utility values for these states were derived from the literature. Adjustments for short-term health states were performed by assigning a QALY decrement for days spent in the following short-term health states: a nonfatal antibiotic side effect; an acute endocarditis infection; and hospitalisation for valve surgery.

Direct costs
The direct medical care costs included antibiotics, hospital costs, outpatient medical care for patients with valve replacement and for patients with congestive heart failure (including physician visits, laboratory test and medications), and the treatment of a nonfatal antibiotic side effect (i.e. an allergic reaction). The latter included the cost of nurse time, physician time, and a 2-day course of oral diphenhydramine (12.5 mg, 4 times a day). The cost for each antibiotic regimen comprised the average wholesale price of the drug, as published in Drug Topics Red Book 2000, plus an average dispensing cost based on published data. The hospital costs were estimated using the Medicare cost from the Nationwide Inpatient Sample for specific Medicare diagnosis-related groups in 1997. Additional costs were based on published estimates.
The price year was 2003. All cost data were adjusted to 2003 based on the medical care component of the Consumer Price Index. All future costs were discounted at a rate of 3%. The quantities and the costs were not analysed separately. The estimations of the quantities and costs were derived using modelling.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs of patient or caregiver time lost were estimated. The value assigned to a lost workday was the amount for a fulltime wage earner, and the value assigned to a lost "no work" day was the amount as reported by the Bureau of Labor Statistics. Patients requiring intravenous antibiotic administration were estimated to have lost the productivity equivalent of a 0.5 workday.

The price year was 2003. All cost data were adjusted to 2003 based on the medical care component of the Consumer Price Index. All future costs were discounted at a rate of 3%. The quantities and the costs were not analysed separately. The estimations of the quantities and costs were derived using modelling.

Currency
US dollars ($).

Sensitivity analysis
The authors reported the base-case probability estimates and the base-case cost values, both with respective ranges and literature references. To test the influence of all variables on the model results, one-way sensitivity analyses were conducted. The values of each model estimate for epidemiological parameters and health outcomes, health state utility values and costs were varied across the ranges listed.

Estimated benefits used in the economic analysis
Under the base-case assumptions, if 10 million patients underwent prophylaxis compared with the no-prophylaxis strategy, the outcomes would be:

119 cases of BE prevented but a net loss of 181 lives (-30,311 QALYs) with amoxicillin or ampicillin, secondary to anaphylaxis;

119 prevented cases of BE, 19 prevented deaths from BE, and 1,125 QALYs saved with clarithromycin;

119 prevented cases of BE, 9 prevented deaths from BE, and 827 QALYs saved with oral cephalaxin and intravenous cefazolin; and

119 prevented cases of BE, 19 prevented deaths from BE, and 1,118 QALYs saved with oral and intravenous clindamycin.

Secondary analyses were reported for patients with high-risk cardiac conditions only and with prior beta-lactam antibiotic use. In the high-risk group, if 10 million patients underwent prophylaxis with any of the seven prophylaxis strategies, there would be 237 endocarditis cases prevented for patients with prior BE and 475 cases prevented for patients with prosthetic heart valves.

Cost results
Model estimates for costs adjusted to year 2000 were reported individually for each variable with the base-case values, range values, and data sources and reference. The total intervention costs for the 55-year horizon time strategies were not reported in the text.
Synthesis of costs and benefits

For the base-case analysis, oral clarithromycin versus no prophylaxis had an incremental cost-effectiveness ratio (ICER) of $88,007 per QALY gained, while oral cephalexin versus no prophylaxis had an ICER of $99,373 per QALY gained. Oral clindamycin versus no prophylaxis had an ICER of $101,142 per QALY gained and was eliminated. For patients who could not take oral medications, prophylaxis with intravenous cefazolin cost $199,430 per QALY gained, while intravenous clindamycin cost $411,093 per QALY gained. These last two strategies were also eliminated.

For high-risk patients, in patients with prior endocarditis, the incremental cost-utility ratio was $40,334 for oral clarithromycin, $37,916 for oral cephalexin, $46,678 for oral clindamycin, $79,886 for cefazolin (intravenous), and $199,783(*) for clindamycin (intravenous). (* Although a figure of $199,783 was reported in the text, table 6 gave a figure of $199,029). The strategy was not effective for oral amoxicillin or for ampicillin (intravenous).

In patients with prosthetic valve, the incremental cost-utility ratio was $16,818 for oral clarithromycin, $14,060 for oral cephalexin, $19,936 for oral clindamycin, $33,480 for cefazolin (intravenous), $96,029 for clindamycin (intravenous), $160,871 for oral amoxicillin, and $498,488 for ampicillin (intravenous).

For the base-case analysis, clarithromycin prophylaxis was the most cost-effective strategy and cephalexin was second best. All other antibiotic regimens were eliminated based on simple dominance (i.e. they were more costly and less effective than clarithromycin). Amoxicillin and ampicillin were eliminated from consideration as they resulted in a net loss of lives.

The base-case findings were sensitive to changes in the risk of antibiotic fatal side effects, the incidence of bacterial endocarditis, potentially preventable cases, the cost of antibiotics, the incidence of dental visits requiring prophylaxis, age of the target population, and the discount rate. One-way sensitivity analyses of all other variables did not result in any of the antibiotic prophylaxis strategies achieving the predefined threshold of $50,000 or $100,000 per QALY gained.

Authors' conclusions

The results suggested that the routine use of amoxicillin and ampicillin for endocarditis prophylaxis is not safe. If the decision to provide prophylaxis for moderate-risk lesions is made, then clarithromycin should be recommended as the first-choice regimen, followed by oral cephalexin and oral clindamycin as second-line drugs. For patients with high-risk cardiac lesions (prosthetic valve or history of prior endocarditis), cephalexin should be the first choice and clarithromycin or clindamycin second choice. Intravenous regimens were less cost-effective, except in the case of cefazolin for patients with prosthetic valves.

CRD COMMENTARY - Selection of comparators

The authors justified their choice of the comparators on the basis of the lack of prospective data on antibiotic effectiveness from clinical studies, and the fact that very little is known about the relative efficacy of various antibiotic regimens available for prophylaxis. You should judge whether these strategies are relevant in your setting, or whether other comparators from other drugs could also be relevant.

Validity of estimate of measure of effectiveness

Although the authors did not state if the review of the literature was undertaken systematically, the methods were described clearly. It is certain that few authors' assumptions were made. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, expert opinion and their own assumptions. The sources of effectiveness evidence included pooled estimates from randomised clinical trials, which are an adequate source to estimate effectiveness. The authors justified their assumptions with reference to the medical literature. The estimates were investigated by sensitivity analyses using ranges from the literature, and the authors justified the ranges selected and reported.
Validity of estimate of measure of benefit
The authors used QALYs gained as a measure of benefits. These were derived from the utility value for each health state and the number of years spent in that health state. This measure of benefit enables comparisons across health technologies. The methods used in the literature to derive the utility weights were not reported. Sensitivity analyses over adjusted QALYs were conducted, and the ranges tested and sources were reported.

Validity of estimate of costs
The authors reported that the study had been conducted from a societal perspective but, although the indirect costs were included, they were not reported in sufficient detail. Patient costs were not considered. The unit costs were taken from published sources. The unit costs and the quantities of resources used were not reported separately, which would not enable the analysis to be easily reworked for other settings. No statistical analysis of the costs was undertaken. Sensitivity analyses of selected direct costs were conducted and were reported to have assessed the robustness of the estimates used. Discounting was appropriately carried out since the time horizon exceeded two years. Revaluation of the costs was carried out and the price year was reported, which will aid any future reflation exercise. The total intervention costs for the 55-year horizon time strategies were not reported in the text.

Other issues
The authors made appropriate comparisons of their findings with those from other studies that considered the predefined threshold of $50,000 or $100,000 per QALY gained. The authors did not explicitly address the generalisability of the results. They did, however, consider assessing the impact of the recommendations made for antibiotic prophylaxis for BE, although there are little convincing data that prophylaxis saves lives. Despite the fact that they have been repeatedly updated, traditional regimens for prophylaxis are complex and have been greatly simplified. Yet prophylaxis is far from universally adopted and remains a controversial issue, owing to lack of evidence from prospective randomised trials. The authors’ conclusions reflected the scope of the analysis.

The authors stated that the principal limitation of the model was that their decision model assumed no differences in protective efficacy between the recommended antibiotic regimens, though this assumption was supported by an experimental study that found that clarithromycin, amoxicillin and clindamycin were all equally effective in preventing S. viridans endocarditis. A second limitation acknowledged by the authors was the inability to account for the potential risk of propagating drug-resistant pathogens secondary to the use of antibiotics for dental prophylaxis. In addition, ICERs for non-dominated strategies were reported against a no-prophylactic strategy, which overestimates the cost-effectiveness against other more cost-effective non-dominated strategies.

Implications of the study
According to the authors, the current recommendations for antibiotic prophylaxis need to be re-evaluated in the light of the effectiveness and cost-effectiveness findings presented in the present study. In particular, the currently recommended regimen of amoxicillin, which could be associated with hazards.

Source of funding
None stated.

Bibliographic details

PubMedID
15951458

DOI
10.1177/0272989X05276852
Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; American Heart Association; Antibiotic Prophylaxis /adverse effects /economics /utilization; Cost-Benefit Analysis; Decision Support Techniques; Endocarditis, Bacterial /complications /etiology /mortality /prevention & control; Female; Heart Diseases /complications; Humans; Male; Markov Chains; Oral Surgical Procedures /adverse effects; Periodontics; Quality-Adjusted Life Years; Risk Assessment; Risk Factors; Software; Survival Analysis; Treatment Outcome

AccessionNumber
22005008228

Date bibliographic record published
31/07/2006

Date abstract record published
31/07/2006