Five different strategies for the management of adult pharyngitis were investigated in the study. The five strategies were:

- Observation only, that is, neither test nor treat (observation strategy);
- Empirical antibiotic treatment of all patients without testing (empirical therapy);
- Throat culture for all patients, with antibiotic treatment for positive results (culture);
- Optical immunoassay (OIA) followed by culture to confirm negative OIA test result only, with antibiotic treatment for positive results on either test (OIA-culture); and
- OIA alone for all patients, with antibiotic treatment for positive results (OIA alone).

**Type of intervention**
Diagnosis and treatment.

**Economic study type**
Cost-utility analysis.

**Study population**
The study population comprised a hypothetical cohort of adults in the general US population. The study excluded patients with a history of acute rheumatic fever or glomerulonephritis.

**Dates to which data relate**
The effectiveness data were derived from studies published between 1953 and 2002. The dates to which the resource use data related were unclear. The price year was 2000.

**Source of effectiveness data**
The effectiveness data were derived from a review and synthesis of published studies.

**Modelling**
A decision model was used to evaluate the short-term (i.e. one year after diagnosis) cost-effectiveness of common strategies for managing adult patients with pharyngitis. In creating their decision model, the authors made several...
simplifying conditions. The authors assumed that no patient would develop acute rheumatic fever with another complication, and that patient adherence and follow-up were 100%. The authors also assumed that all tests were conducted in an on-site reference laboratory and that the results of OIA would be available before the patient left the office. The authors provided further details of their literature review and model in an appendix available from www.annals.org.

**Outcomes assessed in the review**
The outcomes assessed were:

- the prevalence of GAS pharyngitis;
- the sensitivity and specificity of OIA;
- the probability of penicillin-induced rash or anaphylaxis;
- the probability of death from anaphylaxis;
- the probability of acute rheumatic fever;
- the probability of complicated acute rheumatic fever;
- the probability of death from acute rheumatic fever;
- the effectiveness of penicillin versus acute rheumatic fever;
- the probability of peritonsillar abscess;
- the effectiveness of penicillin versus abscess; and
- the utility values associated with several health states. More specifically, untreated pharyngitis, treated GAS pharyngitis, penicillin-induced rash or anaphylaxis, peritonsillar abscess, uncomplicated rheumatic fever, rheumatic fever resulting in valvular disease, and death from penicillin reaction or rheumatic fever.

The utilities were converted to lost quality-adjusted life-days.

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

**Sources searched to identify primary studies**
The authors identified studies of rapid antigen testing using MEDLINE subject heading terms pharyngitis and streptococcal infections, and diagnosis. No further details on the sources searched to identify studies for other model parameters were reported.

**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**
Approximately 37 studies were included in the review. Amongst them was a meta-analysis of outcomes of streptococcal pharyngitis performed for the Cochrane Collaboration.

**Methods of combining primary studies**
As several good-quality studies using 'gold' standard designs were found for studies of rapid antigen testing, the authors averaged the sensitivity findings of OIA (with weighting for the number of patients in each study) to estimate an overall sensitivity and specificity.

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

**Results of the review**
The prevalence of GAS pharyngitis was 0.097 (range: 0.02 - 0.68).

The sensitivity of OIA was 0.884 (range: 0.70 - 0.99) and the specificity was 0.944 (range: 0.80 - 0.99).

The probability of penicillin-induced rash was 0.02 (range: 0.005 - 0.04) and that of anaphylaxis was 0.0001 (range: 0.00005 - 0.0002).

The probability of death from anaphylaxis was 0.1 (range: 0.05 - 0.2).

The probability of acute rheumatic fever was 0.0005 (range: 0.0 - 0.03).

The probability of complicated acute rheumatic fever was 0.1 (range: 0.05 - 0.2).

The probability of death from acute rheumatic fever was 0.01 (range: 0.005 - 0.02).

The effectiveness of penicillin versus acute rheumatic fever was 0.70 (range: 0.55 - 0.80).

The probability of peritonsillar abscess was 0.023 (range: 0.0 - 0.056).

The effectiveness of penicillin versus abscess was 0.84 (range: 0.65 - 0.93).

The utilities (lost quality-adjusted life-days) associated with the following health states were:

- 0.25 (range: 0 - 0.5) for untreated pharyngitis;
- 0.15 (range: 0.1 - 0.25) for treated GAS pharyngitis after OIA;
- 0.20 (range: 0.15 - 0.25) for treated GAS pharyngitis after culture;
- 0.625 (range: 0.15 - 1.50) for penicillin-induced rash;
- 9 (range: 3 - 18) for penicillin-induced anaphylaxis;
- 5 (range: 1.65 - 10) for peritonsillar abscess;
- 76.5 (range: 9 - 744) for uncomplicated rheumatic fever;
- 744 (range: 56 - 744) for rheumatic fever resulting in valvular disease; and
- 14,874 for death from penicillin reaction or rheumatic fever.
Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-days lost. The authors estimated that pharyngitis was associated with a utility of 0.95, which was the utility associated with other minor symptoms such as diarrhoea and dyspepsia. On the basis of a survey that assessed how patients valued pharyngitis relative to mild penicillin reaction, severe penicillin reaction, and acute rheumatic fever, the authors assigned utilities to these outcomes. This survey did not assess the utility estimate for peritonsillar abscess, so the authors based the utility estimate on a prior study that used expert opinion.

Direct costs
The resource use and costs were not reported separately. The direct costs included in the analysis were those of the health care service. These were for the tests, the costs associated with notifying patients of culture results and calling in a prescription to the pharmacist, penicillin therapy, and the costs associated with penicillin-induced rash and anaphylaxis, and rheumatic fever. The costs of tests were based on published manufacturers’ estimates. The authors surveyed 8 nurses and estimated the average time to inform patients of culture results and the average time to call in an antibiotic prescription for a patient. These average times were then valued using official nurse salaries. The costs of penicillin therapy were based on wholesale and pharmacy dispensing costs. The costs associated with penicillin-induced rash and anaphylaxis included physician time, a 2-day course of diphenhydramine, and a 10-day course of erythromycin. The costs associated with rheumatic fever included physician costs, laboratory and procedural costs, and the costs of a penicillin-induced rash.

Where possible, cost estimates in the analysis represented actual resource costs, rather than charges. Discounting was not relevant as all the costs were incurred during one year and, appropriately, was not performed. The study reported the average costs. All the costs were converted to 2000 prices using the medical care component of the Consumer Price Index.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included in the analysis. The authors reported that costs such as work lost because of short-term illness were assumed to be included in the decreased preference for illness. Further, three studies examining work days lost due to adult pharyngitis did not find a significant difference between lost work days in patients treated and those not treated with penicillin.

Currency
US dollars ($).

Sensitivity analysis
The authors conducted a series of one-way sensitivity analyses in which all probabilities, costs, and utilities were varied. The authors examined a range of estimates for each, with the range dictated by the published literature or 50 to 200% of the mean result, whichever was larger. A Monte Carlo simulation in which all variables were simultaneously varied was performed using 10,000 iterations. Each variable was entered as a probability distribution based on the reported 95% confidence intervals or as a reasonable range.

Estimated benefits used in the economic analysis
The quality adjusted life-days lost with each of the five strategies were:

with culture, 0.2668;
with observation, 0.2752;
with OIA alone, 0.2717;
with empirical therapy, 0.4083; and
with OIA-culture, 0.2716.

Cost results
The average cost for each of the five strategies was:
culture, $6.66;
observation, $9.84;
OIA alone, $11.73;
empirical therapy, $12.74; and
OIA-culture, $15.15.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the cost per quality-adjusted life-day lost prevented). Incremental cost-utility analyses were performed by rank ordering all five competing strategies by increasing effectiveness, then calculating incremental cost-effectiveness strategies for each strategy.

The culture strategy was dominant (i.e. both more effective and less costly) than the other four strategies.

The results were found to be sensitive to the prevalence of GAS pharyngitis, with OIA followed by culture proving most effective when GAS pharyngitis prevalence was greater than 20%. The effectiveness of the strategies was also very sensitive to the probability of anaphylaxis. When the probability of anaphylaxis was about half the baseline probability, OIA-culture was most effective, and when the probability was 1.6 times that of baseline, observation was most effective. Only at an OIA cost of less than half of baseline did the OIA alone strategy become less expensive than culture. The results were not sensitive to other variations in probabilities, or the costs of diagnosis or treatment of GAS pharyngitis.

Authors' conclusions
Observation, culture, and two rapid antigen test strategies for the diagnostic testing and treatment of suspected beta-haemolytic streptococcus (GAS) pharyngitis in adults had very similar effectiveness and costs, although culture was the least expensive and most effective strategy when the GAS pharyngitis prevalence was 10%.

CRD COMMENTARY - Selection of comparators
The authors compared five different strategies for the management of adult patients with pharyngitis, all of which appear to have been relevant. You should decide if these are widely used health interventions in 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 to identify relevant research and minimise biases. The authors provided some methodology of the review. For example, they clearly reported the methods used to identify GAS test characteristics and how estimates from different studies were synthesised. However, the authors failed to provide the methodology for the other estimates used to populate the model. Despite this, the authors undertook an exhaustive literature search, with more than 35 studies being included in the review.
Appropriate sensitivity analyses of the effectiveness measures were undertaken, using appropriate ranges.

**Validity of estimate of benefit**
The estimation of benefits was modelled using an analytic decision model, which was appropriate.

**Validity of estimate of costs**
Although the authors reported that the costs were estimated from a societal perspective, the indirect costs were not included. The authors reported that short-term productivity losses were assumed to be included in the decreased preference for illness, and that three studies found no significant differences in those patients treated and those not treated with penicillin. Therefore, the inclusion of lost productivity costs would probably not have affected the authors' results. All other categories of cost were included in the analysis, with all relevant costs being included. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The costs were derived from published sources and, where possible, the cost estimates represented actual resource costs rather than charges. A sensitivity analysis of the costs was undertaken, using appropriate ranges. Discounting was unnecessary as all the costs were incurred during and, hence, was not performed. The price year was reported, which will aid any possible inflation exercises.

**Other issues**
The authors compared their results with the American College of Physicians' guidelines, which recommended selective diagnosis and therapy based on clinical findings and the adoption of rapid diagnostic tests to replace the standard throat culture. The authors reported that their study supported the use of clinical findings in ways similar to those recommended by the guidelines, but suggested that several strategies, including culture, were reasonable. The issue of generalisability to other settings was addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors reported a number of further limitations to their study. First, many of the variables examined were not drawn from randomised trials. Second, the authors did not directly measure the utilities associated with the relevant health states. Third, the authors did not directly incorporate patients' preferences for antibiotic treatment (versus observation) into their analysis. The authors reported that many patients have strong opinions about whether they should take an antibiotic when they get a sore throat, hence influencing physicians' prescription practices. Fourth, the authors reported that strategies such as obtaining the culture and empirically treating were not studied. However, the authors reported that such a strategy does not reduce the risk for therapy in the first few days of treatment, and thus would be as effective as empirical treatment.

**Implications of the study**
The authors reported that empirical treatment, even though it was not the most effective or least expensive strategy at any prevalence of GAS pharyngitis, would be a reasonable strategy for individual patients at very high risk for GAS pharyngitis, as assessed by a clinical decision rule.

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