Pleural fluid interferon-gamma and adenosine deaminase levels in tuberculosis pleural effusion: a cost-effectiveness 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
Two diagnostic tests to differentiate tuberculosis (TB) from non-TB pleural effusions were examined. These were based on levels of adenosine deaminase (ADA) and levels of interferon (IFN)-gamma. Pleural fluid was analysed for ADA by spectrophotometry and for IFN-gamma using an enzyme-linked immunosorbent assay (ELISA).

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with evidence of pleural effusion on chest radiographs. Individuals on corticosteroids and/or immunosuppressive agents were excluded. Also excluded were patients with evidence of any major organ system dysfunction, such as renal or hepatic disease, and all pregnant females.

Setting
The setting was a hospital. The economic study was carried out in India.

Dates to which data relate
The clinical and economic data were gathered from January to July 2003. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was not carried out on the sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not performed. A sample of 68 consecutive patients with evidence of pleural effusion on chest radiographs was initially identified. After applying the exclusion criteria, 52 patients were included in the study. The characteristics of the initial study sample were not reported. However, demographic and clinical information was provided for those patients with TB and non-TB pleural effusion. The patients with TB pleural effusion (n=35; 25 men) had a mean age of 28.5 (+/- 9.2) years, while those with non-TB pleural effusion (n=17; 12 men) had a mean age of 49.6 (+/- 13.1) years. The patients in the non-TB group were significantly older than those with TB pleural effusion.
Study design
This was a diagnostic study that was carried out in a single institution in New Delhi, India. A single group of patients underwent both diagnostic evaluations. Each patient was subjected to thoracocentesis and pleural fluid was analysed. Whenever lesser invasive means failed to yield the diagnosis, the patients were subjected to pleural biopsy. Ultrasonography and computed tomography of the chest, wherever indicated, were performed to establish the etiology of pleural effusion. The criteria used to make a diagnosis of TB pleural effusion were reported. Those patients with TB were followed up to evaluate the response to anti-tuberculosis treatment (ATT). All patients showed clinical as well as radiological response to ATT. No patient was lost to follow-up.

Analysis of effectiveness
All of the patients included in the initial study sample were accounted for in the analysis of effectiveness. The outcome measures used were:
pleural fluid levels among patients in the TB and the non-TB groups;
the sensitivity and specificity; and
the numbers of true-negative, true-positive, false-negative and false-positive cases.

In addition, sensitivity and specificity were plotted for various cut-off levels for pleural fluid IFN-gamma and ADA in order to construct the receiver-operator characteristics (ROC) curve. The area under the ROC curve (AUC) was assessed to compare the diagnostic utility of IFN-gamma levels with ADA for the diagnosis of TB pleural effusion.

Effectiveness results
The median levels of pleural fluid assessed using IFN-gamma were significantly higher among TB patients (2,100 pg/mL; range: 70 - 14,000) than among non-TB patients (3 pg/mL; range: 0 - 160).

Similarly, the mean levels of pleural fluid assessed using ADA were significantly higher among TB patients (93.1 +/- 62.3 IU/L) than among non-TB patients (15.4 +/- 8.7 IU/L).

ROC curves were plotted. These showed that both IFN-gamma and ADA had high AUC values, although IFN-gamma was marginally superior to ADA, 0.997 (95% confidence interval, CI: 0.988 - 1.006) versus 0.963 (95% CI: 0.915 - 1.011). The best cut-off was 167.5 pg/mL for IFN-gamma and 33 IU/L for ADA.

The best cut-off for IFN-gamma resulted in a sensitivity of 97.1% for diagnosis of TB pleural effusion, and a negative predictive value of 94.4%. The specificity and positive predictive value were both 100%.

The best cut-off for ADA resulted in a sensitivity of 91.4% and a negative predictive value of 85%. However, both the specificity and positive predictive value were both 100%.

There were 17 true-negative cases with both techniques, 34 true positives with IFN-gamma and 32 with ADA, 1 false negative with IFN-gamma and 3 with ADA, and 0 false-positive cases with either tool. Thus, ADA missed diagnosis in 5.7% more patients (2) than what was missed by IFN-gamma estimation. Hence, 17.5 IFN-gamma estimations needed to be performed to diagnose one patient falsely labelled negative on the basis of the ADA estimation.

Clinical conclusions
The effectiveness analysis showed that the diagnostic accuracy of ADA was slightly lower than that of IFN-gamma.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was performed.
Direct costs
The perspective adopted in the study was unclear. The authors stated that, for simplicity, only the costs of the commercial kits for ADA and IFN-gamma were included in the analysis. The costs associated with expertise required and the type of equipment used (a simple spectrophotometer for ADA and an ELISA reader for IFN-gamma) were excluded because they would vary in different settings, thus limiting the transferability of the results of the cost analysis. The unit costs of the two kits were thus estimated and compared. The quantities of resources used were not assessed because the costs of a single test were compared. The source of the costs was not reported. Discounting was not relevant, owing to the short timeframe of the analysis, and was not carried out.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
Indian rupees (Rs). The costs were also reported in US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

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

Cost results
The cost of the commercial kit was Rs 0.25 (less than $0.01) for ADA and Rs 750 ($16) for IFN-gamma. Thus, to detect one case of ADA-negative TB by using IFN-gamma, nearly Rs 13,125 ($280.00; estimated by multiplying $16 x 17.5) would need to be spent. Since the average cost of 6 months of ATT was nearly Rs 2,000 ($42.5), the cost of detecting one patient with TB by IFN-gamma was equivalent to the cost of completing a course of ATT for more than six patients.

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

Authors’ conclusions
The substantial extra cost of interferon (IFN)-gamma did not justify its marginally higher accuracy in the detection of tuberculosis (TB) pleural effusion in comparison with adenosine deaminase (ADA), which appears to have been the optimal diagnostic strategy in developing countries.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators, which were appropriate for the objective of the study. Both diagnostic strategies were compared with more invasive approaches that represented the ‘gold’ standard for the definitive diagnosis of the etiology of pleural effusion. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness evidence came from a diagnostic study. This was appropriate for the study question since all participants were investigated using the two diagnostic approaches. A comparison group was therefore not required, thus limiting the impact of selection bias. The authors stated that the non-TB group represented a control group, but the diagnostic accuracy of the two interventions was investigated only among patients with TB pleural effusion. However, the sequence of tests was not described. Further, it was unclear whether some assessment bias could have affected the results of the analysis because details of the investigators evaluating the results of the interventions (i.e. number and expertise) were not reported. A detailed description of the criteria used to define the etiology of pleural effusion was reported. A relatively small sample of patients was enrolled into the study, and no statistical justification for the size of the sample was provided. The evidence came from a single centre and this might limit how representative the patient sample was. These issues might reduce the internal validity of the study.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The cost analysis considered only the cost of the commercial kits used to perform the diagnostic assessment. The authors stated that other categories of costs were excluded on the grounds of simplicity, as several factors (i.e. expertise and equipment) could have a strong impact on the costs of the two interventions and might vary substantially in different contexts. Therefore, the cost analysis was reduced to the unit cost of performing a single test. The cost estimate was specific to the study setting and alternative estimates were not investigated in the sensitivity analysis. The source of the data was unclear, although it could have been the authors' institution. The authors noted that the positive cases missed with ADA might result in further costs because untreated patients might infect other individuals. However, owing to the large cost-difference, ADA appears to remain the cheapest approach.

Other issues
The authors reported extensive results from other studies assessing the diagnostic accuracy of the two interventions. No comparison of the costs was undertaken. The issue of the generalisability of the study results was not specifically addressed, but the authors pointed out that their findings were valid for developing countries with both an epidemiologic context and treatment patterns comparable to those considered in the current study. The authors noted some limitations of their study, which have been highlighted already.

Implications of the study
The study results do not support the widespread use of IFN-gamma for the diagnosis of the etiology of pleural effusion in developing countries. It appears that ADA might be the optimal diagnostic strategy, although with a slightly lower accuracy but substantially lower cost.

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