Cost-analysis of four diagnostic strategies for Pneumocystis carinii pneumonia in HIV-infected subjects

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ABSTRACT: The aim of this study was to analyse the cost-effectiveness ratio of four diagnostic strategies for Pneumocystis carinii pneumonia (PCP) in patients infected with human immunodeficiency virus (HIV).

Two hundred and ten HIV-infected patients with suspected PCP underwent induced-sputum (IS) followed, if negative, by bronchoalveolar lavage (BAL). The following strategies were analysed: BAL strategy whenever PCP is suspected; IS strategy (induced sputum followed by BAL if negative); exercise test (ET) strategy, (ET followed by BAL if the results are abnormal); and the ES (exercise sputum) strategy (i.e. BAL only after abnormal ET and negative IS). The cost of each strategy was calculated by taking into account only direct costs; the conditions in which two given strategies would be cost-equivalent were also evaluated.

The prevalence of PCP in this population was 31%; IS had 100% specificity and 71% sensitivity, whilst ET had 100% sensitivity and 77% specificity. The costs of BAL, IS, ET and ES strategies were 210,000, 191,940, 140,700 and 112,700 FF, respectively. The ES strategy is, thus, most suitable for our unit. The most economic strategy depends not only on the cost and characteristics of the procedures, but also on the prevalence of PCP in the test population.

In conclusion, we developed a model for use by diagnostic centres in choosing the most suitable strategy, on the basis of the local prevalence of PCP.

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Patients and methods

Patients

Two hundred and ten human immunodeficiency virus (HIV)-infected patients referred between January 1 and December 31, 1992, to the bronchial endoscopy unit of the Hôpital Saint Antoine with suspected PCP underwent IS followed, if negative, by BAL. Eighty five of these patients agreed to participate and were able to undergo an indirect diagnostic test, prior to IS and BAL. No complications were encountered during these procedures.

Diagnostic tests

Indirect diagnostic test. Arterial oxygen saturation was recorded during a treadmill exercise test (ET), with increasing 2 min constant-speed steps (2, 4, 6 and 8 km·h⁻¹). The test was interrupted if the arterial oxygen saturation fell below 85%. The result was considered abnormal when the saturation at the end of the exercise period was decreased by more than 3% when compared with the value at the beginning. This threshold value was derived from a receiver operating characteristics (ROC) curve, yielding the strongest specificity for 100% sensitivity [15].

IS and BAL. Sputum production was induced by inhalation of hypertonic (3%) saline solution [17]. Bronchoalveolar lavage was performed according to European recommendations [18]. IS specimens were stained using Giemsa, Musto (a silver stain) and a monoclonal antibody specific for P. carinii; BAL samples were stained using only Giemsa and Musto [19]. The slides were examined in blinded fashion by pathologists unaware of the clinical status of the patient. If P. carinii was detected in IS and/or BAL samples, the patients were judged to have PCP. The patients without P. carinii in BAL samples were followed for one month after the procedure. After one month, in the absence of any clinical or radiological features of PCP, the patients were considered as PCP-free.

Cost analysis

The effectiveness criterion was whether the strategy was diagnostic for PCP, or ruled out the disease, in all the patients [17, 20]. The cost of each strategy was established by calculating the number and type of tests required to meet the effectiveness criterion. Only direct costs (patient charges by the hospital) were taken into account. These costs were the cost of the tests and the cost of microscopic analysis. The costs of analyses carried out before the tests (e.g. chest radiograph, blood gases and laboratory tests) were not taken into account, and were considered identical for each diagnostic strategy. The costs of hospitalization before and after PCP procedures were not taken into account as they were dependent on PCP characteristics (severity).

Table 1. – Number of patients, percentage (P) of PCP, and percentage sensitivity (Se) of induced sputum (IS) in patients who did and did not undergo an exercise test (ET)  

<table>
<thead>
<tr>
<th>Population</th>
<th>Cases</th>
<th>Cases of PCP (P)</th>
<th>IS diagnosis (Se)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>210</td>
<td>66 (31)</td>
<td>47 (71)</td>
</tr>
<tr>
<td>Without ET</td>
<td>125</td>
<td>47 (38)</td>
<td>35 (74)</td>
</tr>
<tr>
<td>With ET</td>
<td>85</td>
<td>19 (22)</td>
<td>12 (63)</td>
</tr>
</tbody>
</table>

PCP: Pneumocystis carinii pneumonia.

At the time of the study the cost of BAL with parasitological analysis was 1,000 French francs (FF), and the IS/BAL and ET/BAL cost ratios were respectively 0.1 and 0.2. To determine the consequences of variations in the different parameters (prevalence of PCP, cost, sensitivity and specificity of the various tests), we calculated iso-cost-curves between these strategies. Using BAL strategy as reference, we calculated cost reductions obtained by the use of the other strategies.

Results

PCP diagnosis

In the overall population, the diagnosis of PCP was confirmed in 66 patients, by IS in 47 cases and BAL in 19. During the 1 month follow-up, none of the patients with negative BAL results showed features of PCP. The prevalence of PCP in the total study population was, thus, 31%. IS had a sensitivity of 71% and a specificity of 100%.

There were 47 cases of PCP (prevalence 38%) among the 125 patients who did not undergo an indirect test (table 1); 35 of these cases were diagnosed by means of IS (sensitivity 74%). By comparison, there were 19 cases of PCP (prevalence 22%) among the 85 patients who underwent ET, and 12 of these cases were diagnosed by means of IS (63%). The prevalence of PCP was higher (p<0.05) in patients who did not undergo an ET; there were no significant differences in terms of the sensitivity of IS between the patients who underwent the ET and those who did not (table 1).

Among the patients who underwent the ET, the 19 with PCP had abnormal results (100% sensitivity), but this was also the case for 15 patients without PCP (77% specificity).

Type and number of diagnostic tests in each strategy

To make a firm diagnosis in every case, given the 100% sensitivity of the indirect test and the 100% specificity of IS, the diagnostic tests required for a population of n patients with a PCP prevalence of P (with Se the sensitivity of IS and Sp the specificity of ET), would be as shown in figure 1.
1) BAL strategy: $n \times \text{BAL}$

2) IS strategy: $n \times \text{IS}$ and $n \times \text{BAL} 	imes (1 - \text{Se}) \times \text{BAL}$ (IS in patients with false-negative IS); and $n \times \text{BAL} \times (1 - P) \times \text{BAL}$ (IS in patients with true-negative IS);

3) ET strategy: $n \times \text{ET}$ and $n \times \text{BAL} \times [1 - (1 - P) \times \text{Sp}] \times \text{ET}$ (ET in all patients except those with normal ET results);

4) ES strategy: $n \times \text{ET}$ and $n \times \text{IS} \times [1 - (1 - P) \times \text{Sp}] \times \text{IS}$ (ES in all patients except those with normal ET results); and $n \times \text{BAL} \times [1 - (1 - P) \times \text{Sp}] - n \times P \times \text{Se} \times \text{BAL}$ (ES in all patients who underwent IS, except those with positive IS).

In this study, the costs of BAL, IS, ET and ES strategies were, 210,000, 191,940, 140,700 and 112,700 FF, respectively. The ES strategy is, thus, most suitable for our unit.

Conditions in which two given strategies are cost-equivalent

Conditions in which BAL and IS strategies are cost-equivalent. As the IS technique is 100% specific, the costs of these two strategies are equivalent when the IS/BAL cost ratio ($IC/BC$) is equal to the product of the sensitivity of IS and the prevalence of PCP ($IC/BC = \text{Se} \times P$) (see Appendix). Using the BAL strategy as reference, the cost savings due to the use of the IS strategy grow with the prevalence of PCP and the sensitivity of IS (fig. 2). In our study, with an IS/BAL cost ratio of 0.1 and an IS sensitivity of 60%, the prevalence threshold above which it is cost-effective to introduce IS was 16.6%.

Conditions in which BAL and ET strategies are cost-equivalent. As the exercise test is 100% sensitive, the costs of these two strategies are equivalent when the ET/BAL cost ratio ($EC/BC$) is equal to the specificity of ET multiplied by one minus the PCP prevalence ($EC/BC = (1 - P) \times \text{Sp}$) (Appendix). Using the BAL strategy as reference, the cost savings due to the use of the ET strategy grow as the prevalence of PCP falls and the specificity of ET rises (fig. 2). In the study population, with an ET specificity of 77% and an ET/BAL cost ratio of 0.2, it is cost-effective to introduce ET if the prevalence of PCP is below 74%.

Conditions in which IS and ES strategies are cost-equivalent. As the sensitivity of ET and the specificity of IS are both 100%, the costs of the two strategies are equivalent when the cost ratios of the different procedures are related to the prevalence of PCP and the specificity of ET (Appendix). Thus, for given cost ratios, one can construct a cost-equivalence curve for IS and ES strategies according to the specificity of the exercise test.
The economic validity of introducing a 100% sensitive indirect diagnostic test depends not only on its specificity and cost, but also on the prevalence of PCP in the test population. When the prevalence is low, as in our study (31%), the ET strategy, which involves an indirect test with a specificity of 77%, provides a saving of 45%.

In contrast, in centres where the prevalence of PCP is high, the introduction of these indirect tests is not warranted [22]. Thus, in the San Francisco and Denver centres [20], which use the IS strategy, equivalence of IS and ES strategies is achieved for a specificity of the indirect diagnostic test of 70 and 60%, respectively. Below these specificities, ES strategy is more expensive than IS strategy.

More recently, Werner et al. [23] showed the importance of the organization of diagnostic procedures. These authors set up a prospective control system in which four respiratory medicine physicians screened all requests for IS to determine the pretest likelihood of PCP. In a 1 year period, they denied 22 of 102 requests, due to a low clinical suspicion for PCP; none of the 22 patients developed PCP, with a follow-up of several weeks. Among the remaining 80 patients, IS revealed PCP in 34 cases; 32 of the 46 patients with negative IS results agreed to undergo BAL, which revealed a further 15 cases of PCP. Four of the patients who refused BAL were diagnosed as having PCP on the basis of having PCP; the control system increased the prevalence from 52% (53 out of 102) to 66% (53 out of 82). The authors concluded that, even taking into account the cost of the extra examinations by chest specialists, the control system was cost-effective.

In conclusions, the choice of the most cost-effective diagnostic strategy for PCP in HIV-infected subjects depends not only on the cost and intrinsic characteristics (sensitivity and specificity) of each procedure, but also on the prevalence of PCP in the test population. It is, therefore, essential to optimize the selection of patients with clinical signs of PCP and to analyse local conditions when evaluating the most cost-effective strategy for diagnosing PCP.

Appendix 1

For n patients, where P is the prevalence of PCP, BC the cost of bronchoalveolar lavage (BAL), IC the cost of induced sputum (IS), EC the cost of an exercise test (ET), Se the sensitivity of IS and Sp the specificity of
ET, the cost of the different PCP diagnostic strategies are as follows:
1) BAL = n x BC;
2) IS = n x IC (cost of IS for all patients) + BC x [n x P x (1-Se)] (cost of BAL for all false-negative IS) + (n x 1 - P) (cost of BAL in true-negative IS).
3) ET = EC x n (cost of indirect diagnostic test for all patients) + BC x n [1 - ((1-P) x Sp)] (cost of BAL for all patients with abnormal results in the indirect test).
4) ES = EC x n (cost of indirect diagnostic test for all patients) + IC x n [1 - ((1-P) x Sp)] (cost of IS for all patients with abnormal indirect test results) + BC x [n x 1 - ((1-P) x Sp)] - (n x B x Se) (cost of BAL for patients with abnormal indirect test results, with the exception of those with positive IS).

The costs of BAL and IS strategies are equivalent when:
\[ n \times BC = n \times IC + BC \times [n \times P \times (1-Se)] + n \times (1-P) \]
\[ IC/BC = SE \times P \]

The costs of BAL and ET strategies are equivalent when:
\[ n \times BC = n \times EC + BC \times n \times [1 - (1-P) \times Sp] \]
\[ EC/BC = (1-P) \times Sp \]

The costs of the IS and ES strategies are equivalent when:
\[ n \times IC + BC \times [n \times P \times (1-Se) + n \times (1-P)] = [EC \times n] + [IC \times n \times [1 - (1-P) \times Sp]] + BC \times [n \times [1 - (1-P) \times Sp]] - (n \times P \times Se) \]
\[ EC + BC = (IC + BC) \times Sp \times (1+P) \]

**References**