Non-invasive management of fever and breathlessness in HIV positive patients


Non-invasive management of fever and breathlessness in HIV positive patients.

ABSTRACT: In a prospective study of 72 human immunodeficiency virus (HIV) positive patients presenting with fever and breathlessness, a non-invasive management protocol, incorporating a scanning technique using radioactively labelled diethyleneetriamine penta acetate (DTPA) and sputum induction, was found to be highly sensitive and specific in the early detection of Pneumocystis carinii pneumonia (PCP). At presentation, the DTPA scan was abnormal in 34 of 36 cases of PCP, irrespective of smoking history, whilst the chest radiograph was diffusely abnormal in 21 cases. Sputum induction identified 7 of 14 patients with PCP in the first six months of its use and 7 of 10 patients over the last six months. The DTPA lung scan and induced sputum examination are non-invasive techniques which can be used to investigate out-patients. In combination they detected all cases of PCP at presentation, reduced the need for bronchoscopy, resulted in a low case fatality (5.4%) and reduced the need for admission.


Keywords: Acquired immunodeficiency syndrome; diethyleneetriamine penta acetate (DTPA) lung scan; Pneumocystis carinii pneumonia; sputum induction.

Respiratory illness, often recurrent, occurs in over 60% of patients with acquired immune deficiency syndrome (AIDS) [1]. Pneumocystis carinii pneumonia (PCP) accounts for 85% of pneumonia in human immunodeficiency virus (HIV) positive patients and is also the most frequent presentation of AIDS [2]. Early treatment of PCP improves the prognosis [3] but it is recommended that the diagnosis is confirmed histologically or cytologically prior to therapy [4–6]. Bronchoscopy and bronchoalveolar lavage (BAL) with or without transbronchial biopsy (TBBx) are sensitive and specific but there is a risk for both patient and bronchoscopist [6]. In addition, the demand for bronchoscopy may become excessive because of increasing numbers of patients [7].

Recently it has been demonstrated that empirical treatment of PCP based on typical clinical and radiological features would result in the correct management in the majority of cases [8]. However, in about 15% of patients with PCP the radiograph is normal or atypical at presentation and in these cases the diagnosis may be missed or delayed [8]. Furthermore, in the out-patient department minor respiratory symptoms are frequent and may be difficult to distinguish from the nonspecific early symptoms of PCP. A non-invasive out-patient screening test would be of practical importance if it were sensitive and specific in diagnosing early PCP especially in those presenting with a normal or atypical chest radiograph.

Sputum induction with cytological examination is a promising technique. However, the diagnostic yield varies [9, 10] and is dependent upon the severity of the disease, adequate sputum production and cytopathological recognition. The impact of the use of non-invasive techniques of diagnosis, in reducing the need for bronchoscopy, has not been evaluated [11].

In a retrospective study [12] we have previously demonstrated the high sensitivity of diethyleneetriamine penta acetate (DTPA), labelled with 99mTc, scanning for PCP in HIV positive patients, a finding recently confirmed by other investigators [13]. We present the results of a prospective study to assess the clinical usefulness of DTPA scanning and induced sputum examination in the initial out-patient assessment of respiratory illness in HIV positive patients, in particular in the early detection of PCP and to assess the influence of such a management scheme on the need for bronchoscopy.

Patients and methods

Over an 18 mth period, 72 consecutive patients with confirmed HIV infection, presenting with fever, cough
and breathlessness were investigated. At presentation the following investigations were performed in all patients: arterial blood gases, chest radiograph, a DTPA scan (reported independently of the chest radiograph) and serological examination for Legionella pneumoniae, Mycoplasma pneumoniae, Toxoplasma and cytomegalovirus (CMV) infection.

The transfer of nebulized 99mTc DTPA aerosol from lung to blood was measured as described previously [12, 14]. A half time of transfer (T1/2) of less than 3 min (normal 15–87 min) with a biphase, rather than monoexponential curve, is typical of PCP. The test is well-tolerated and the result was available within 90 min.

Induced sputum was examined in 36 patients during the final 12 mths of the study. Sputum was induced as described by Brossy et al. [15] with strict adherence to protocol and was examined for Pneumocystis carinii by both modified Grocott [16] and mouse immunofluorescent monoclonal antibody [17]. The induction of sputum and laboratory processing yielded a result the same day. A positive test was defined as more than five pneumocysts per high powered field. Sputum was also examined by fluorescence microscopy and culture for mycobacteria and for other bacteria by Gram staining and culture.

Serological examination for evidence of previous or concurrent CMV infection was performed using a latex test for immunoglobulin G (IgG) and an enzyme immunoassay (EIA) for immunoglobulin M (IgM). Bronchoscopic washings were also examined for CMV infection using the Detection Early Antigen Fluorescence Foci (DEAFF) test.

Management was determined by assessing the clinical symptoms, blood gases, chest radiograph and DTPA scan. The management of the 72 patients is summarized in the flow chart (fig. 1). Patients with a typical clinical picture, diffusely abnormal chest radiograph and an abnormal DTPA lung scan (biphase and T1/2 less than 3 min) were treated for PCP without bronchoscopy. Patients with a normal or focally abnormal chest radiograph but a typically abnormal DTPA scan were also treated for PCP. A definitive diagnosis was sought only if the patient deteriorated or failed to respond to therapy with high dose co-trimoxazole. In these circumstances bronchoscopy (with BAL and TBBx) was performed, unless an induced sputum had confirmed the cause of the pneumonia.

If the DTPA scan was normal (monoexponential and T1/2 greater than 3 min) but the chest radiograph diffusely abnormal then bronchoscopy was performed. If the chest radiograph was focally abnormal, the patient was treated with a broad spectrum antibiotic and bronchoscopy was performed if there was radiological or clinical deterioration.

If both DTPA scan and chest radiograph were normal no specific treatment was given unless the sputum was purulent when a course of amoxycillin was started whilst awaiting the results of sputum microbiology.

---

**Fig. 1.** — Management flow chart. DTPA: diethylenetriamine penta acetate; CXR: chest X-ray; PCP: Pneumocystis carinii pneumonia.

**Results**

Seventy two consecutive patients (mean age 35 yrs, range 19–61 yrs) were investigated, of whom 24 were managed entirely as out-patients. All but three were male, five had haemophilia and three patients were intravenous (i.v.) drug users. At presentation the resting arterial oxygen tension (mean±SEM) in patients considered or proven to have PCP was 8.3±0.5 kPa with a range 4.7–14.7 kPa. In patients with a normal chest radiograph and an abnormal DTPA scan (n=6) the mean arterial oxygen tension was 13±0.9 kPa.

The results of this study are summarized in table 1. PCP was confirmed by cytology or histology in 22 cases. Induced sputum examination was diagnostic in ten cases, bronchoscopy (BAL and TBBx) in eight cases and in a further four patients the diagnosis was confirmed by both methods. The DTPA scan was indicative of PCP (biphase, T1/2<3 min) in 20 of these 22 proven cases (91%). At presentation, the chest radiograph was normal in three (14%), focally abnormal in five (23%) and diffusely abnormal in 14 (64%) of the confirmed cases of PCP.

In 14 cases PCP was diagnosed without cytological or histological confirmation. In 12 cases PCP was diagnosed on the basis of a typical clinical picture, a diffusely abnormal chest radiograph and an abnormal
Table 1. - The DTPA scan and presenting chest radiograph in initial assessment of fever and breathlessness in 72 HIV positive patients

<table>
<thead>
<tr>
<th>DTPA scan Result</th>
<th>CXR Result</th>
<th>Proven PCP</th>
<th>Unconfirmed PCP</th>
<th>Other infections</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CXR normal</td>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CXR focally abnormal</td>
<td>17</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CXR diffusely abnormal</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CXR normal</td>
<td>3*</td>
<td>3*</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CXR focally abnormal</td>
<td>4*</td>
<td>3*</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>CXR diffusely abnormal</td>
<td>13</td>
<td>8</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22</td>
<td>14</td>
<td>36</td>
<td>72</td>
</tr>
</tbody>
</table>

*: 5 of 7 patients with proven PCP and an atypical chest radiograph at presentation (normal (2), focally abnormal (3)) developed a diffusely abnormal radiograph during the illness; : 4 of 6 cases with unconfirmed PCP and an atypical chest radiograph at presentation (normal (1), focally abnormal (3)) developed a diffusely abnormal radiograph during the illness; : co-existent PCP and Kaposi sarcoma; DTPA: diethylenetriamine penta acetate; CXR: chest X-ray; PCP: Pneumocystis carinii pneumonia; HIV: human immunodeficiency virus.

(biphasic, $T_{\text{p}}<3$ min) DTPA scan. However, in four of these 12 patients the chest radiograph was normal (1) or focally abnormal (3) at presentation, becoming diffusely abnormal during the course of the illness. In two patients with a persistently normal chest radiograph, the diagnosis of PCP was based on respiratory symptoms and an abnormal DTPA scan alone. The 14 unconfirmed cases responded appropriately to high dose co-trimoxazole.

Two deaths occurred during the study. In both patients PCP was confirmed and treated. No other infective agent was found in sputum, bronchoscopic washings or transbronchial biopsies and serology did not suggest co-infection. Post mortem examinations were not performed.

The DTPA scan was abnormal in 34 of the 36 patients (94%) considered or proven to have PCP (table 2). In nine of the 14 unconfirmed cases of PCP the DTPA scan was repeated at 6 wks and in each case the clearance curves had reverted to normal. Thirty eight patients had a normal DTPA scan but this was falsely negative in two (5.4%). In one patient with a diffusely abnormal chest radiograph, the induced sputum and transbronchial biopsies confirmed PCP. In the other, the radiograph was focally abnormal, induced sputum confirmed PCP and transbronchial biopsies revealed histological evidence of both Kaposi sarcoma and PCP. A third patient with a normal DTPA scan and a normal chest radiograph but a positive induced sputum recovered without treatment and has not developed PCP at three months follow-up (falsely positive induced sputum).

At presentation the chest radiograph was diffusely abnormal in 21 of the 34 cases (62%) with an abnormal DTPA scan (table 1). In the remaining 13 cases (38%) the chest radiograph was focally abnormal in seven and normal in six. Of these 13 patients, initially considered to have PCP on the basis of the DTPA scan, the diagnosis was confirmed in seven cases (four focally abnormal and three normal radiographs at presentation) either by bronchoscopy (2) or induced sputum examination (5). The chest radiograph became diffusely abnormal consistent with PCP during the course of the illness in five of these seven confirmed cases with an atypical radiograph at presentation. The remaining six patients with unproven PCP and an atypical chest radiograph at presentation, either developed a diffusely abnormal chest radiograph characteristic of PCP (4) or
other infections. In one case with a normal chest radiograph, four patients who were subsequently proven to have PCP, in whom induced sputum was considered to have PCP, in whom induced sputum was obtained and the remaining three (abnormal DTPA scan, diffusely abnormal chest radiograph) rapidly recovered with treatment for PCP resulted in a rapid recovery. True negative induced sputums occurred in the remaining seven patients in whom other infections were confirmed. One patient with an abnormal DTPA scan was unable to produce a sputum sample but the diagnosis of PCP was confirmed at bronchoscopy when the initiation of treatment failure required this to be performed.

Table 2. – The DTPA scan in the initial assessment of fever and breathlessness in 72 HIV positive patients

<table>
<thead>
<tr>
<th>DTPA scan Result</th>
<th>Proven PCP</th>
<th>Unconfirmed PCP</th>
<th>Other infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTPA scan abnormal (T_{50} &lt;3 min)</td>
<td>20</td>
<td>14*</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>DTPA scan normal (T_{50} &gt;3 min)</td>
<td>2</td>
<td>0</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>14</td>
<td>36</td>
<td>72</td>
</tr>
</tbody>
</table>

*: in 12 cases the chest radiograph was diffusely abnormal consistent with PCP. In the remaining 2 patients the chest radiograph was persistently normal. For definitions see legend to table 1.

responded to treatment without an alternative cause for respiratory illness (2). The DTPA scan may have been falsely positive in the two cases (5.4%) in which the diagnosis was based on respiratory symptoms and an abnormal DTPA scan alone in the presence of a persistently normal chest radiograph.

Eighteen patients with a normal DTPA scan had a focally abnormal chest radiograph at presentation (table 1). In one patient the DTPA scan was falsely negative as bronchoscopy demonstrated the co-existence of PCP and Kaposi sarcoma. In the remaining 17 patients a definitive cause for the pneumonia was established in the majority (Mycobacterium tuberculosis (5), Haemophilus influenzae (4), Streptococcus pneumoniae (4), Aspergillus fumigatus (1)). Nineteen patients had a normal DTPA scan and a normal chest radiograph. Respiratory infection was confirmed in five and treated appropriately, seven were treated with broad spectrum antibiotics and recovered without a microbiological diagnosis, five recovered without treatment and two were diagnosed as non Hodgkin's lymphoma. None of these patients (who were not on prophylaxis for PCP) developed PCP on follow-up.

Cyto-immunological examination of induced sputum was not performed in the early months of this study. Sputum induction was subsequently attempted in 39 patients. Adequate specimens could not be obtained in three cases despite repeated attempts. The results for the 36 patients in whom induced sputum was obtained are summarized in table 3. In the first six months of its use induced sputum was examined in 19 patients. It provided the definitive diagnosis in 50% of those patients otherwise considered to have PCP (7 of 14). In two cases the initial sample was negative and became positive on repeat examination. Four of the seven patients considered to have PCP, in whom induced sputum was negative, had the diagnosis confirmed at bronchoscopy and the remaining three (abnormal DTPA scan, diffusely abnormal chest radiograph) rapidly recovered with treatment. True negative induced sputums occurred in four patients who were subsequently proven to have other infections. In one case with a normal chest radiograph and DTPA scan, induced sputum was falsely positive and the patient recovered without treatment. Confirmation of the diagnosis with induced sputum avoided the need for bronchoscopy in two patients. In the final six months, induced sputum was examined in 17 patients and was positive in 7 of 10 cases considered to have PCP (70%). The chest radiograph was diffusely abnormal in the three patients with a negative induced sputum and treatment for PCP resulted in a rapid recovery. True negative induced sputums occurred in the remaining seven patients in whom other infections were confirmed. One patient with an abnormal DTPA scan was unable to produce a sputum sample but the diagnosis of PCP was confirmed at bronchoscopy when initial treatment failure required this to be performed.

Table 3. – Cyto-immunological examination of induced sputum in the initial assessment of fever and breathlessness in 36 HIV positive patients

<table>
<thead>
<tr>
<th>Induced sputum Result</th>
<th>PCP</th>
<th>Other infection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced sputum positive</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Induced sputum negative</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>12</td>
<td>36</td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus; PCP: Pneumocystis carinii pneumonia.

During the 18 months of this study, bronchoscopy was performed in 16 cases. Twelve patients with suspected PCP required bronchoscopy because of rapid deterioration or treatment failure. The diagnosis of PCP was confirmed in all 12 cases. In a further two patients the DTPA scan was falsely normal and PCP was confirmed at bronchoscopy. In the first bronchoscopy was performed because the chest radiograph was diffusely abnormal in the presence of a normal DTPA scan. In the second, the chest radiograph was focally abnormal, and a bronchoscopy was performed because the patient deteriorated despite treatment with broad spectrum antibiotics. Transbronchial biopsies revealed histological evidence of both Kaposi sarcoma and PCP. In two patients with both a normal chest radiograph and a normal DTPA scan, bronchoscopy for progressive deterioration revealed non-Hodgkin's lymphoma. Bronchoscopy was performed in nine cases in the 6 mths prior to the introduction of sputum induction, six cases in the second 6 mths and one patient in the final 6 mth period of the study.

Serological examination for Legionella pneumophila, Mycoplasma pneumoniae, Toxoplasma and CMV was performed in all patients. Raised titres of IgG suggestive of previous CMV or toxoplasma infection were frequent. Elevated IgM titres were not detected suggesting that there were no active cases. In two patients CMV was isolated from bronchial washings using the DEAFF test but Pneumocystis carinii was
also isolated. In neither case was there histological evidence of viral pneumonia. Serology for *Legionella pneumophila* and *Mycoplasma pneumoniae* was negative in all cases.

**Discussion**

*Pneumocystis carinii* pneumonia is the most frequent cause of respiratory illness in AIDS [2, 18]. In the present study, 36 of 72 patients (50%) with confirmed HIV infection presenting with fever and breathlessness were considered to have PCP. The diagnosis was confirmed histologically or cytologically in 22 cases. In 12 of the 14 unconfirmed cases, PCP was diagnosed on the basis of a typical clinical picture, an abnormal DTPA scan and a diffusely abnormal chest radiograph (although in four patients the radiograph was either focally abnormal (3) or normal (1) at presentation and became diffusely abnormal during the course of the illness). Histological or cytological confirmation was omitted in these cases because it has been demonstrated that PCP would be confirmed at bronchoscopy in 95% of patients with a diffusely abnormal chest radiograph and a typical clinical picture [8]. In two cases PCP was diagnosed on the basis of a typical clinical picture and an abnormal DTPA scan in the presence of a persistently normal chest radiograph. In both cases the response to treatment was consistent with early PCP. The results of this study suggest that in the initial evaluation of patients presenting with fever and breathlessness, a management strategy incorporating the technique of DTPA scanning is effective and reliable.

The early symptoms of PCP precede the radiological changes. It is in these mild, early infections which frequently present in the out-patient clinic that the DTPA scan is particularly useful. In this situation an abnormal DTPA scan (biphasic, T<sub>50</sub>&lt;3 min) may precede the diffusely abnormal chest radiograph characteristic of PCP by up to 1 wk. Irrespective of a patient's smoking history, the DTPA scan is sensitive and specific with no clear difference from normal or from most other causes of pneumonia. Atypical chest radiographs occur in a significant proportion of patients with PCP. This study demonstrates that the DTPA scan will effectively distinguish between focally abnormal chest radiographs due to PCP and those due to other infections. In the study by Miller et al. [8], seven patients (15%) with focally abnormal chest radiographs (and accordingly not considered to have PCP) had pneumocystis demonstrated at bronchoscopy. In the present study, 13 cases (38%) considered to have PCP had either a normal or focally abnormal radiograph at presentation although in nine the typical diffuse bilateral changes developed during treatment. The greater sensitivity of DTPA scanning, when compared with plain radiography, would be expected since it measures epithelial permeability which will change before the chest radiograph becomes abnormal. This explains its usefulness in the assessment of patients with early disease in whom the diagnosis would not otherwise be considered.

DTPA scanning offers significant advantages over alternative nonspecific tests, such as desaturation on exercise [19] or the measurement of carbon monoxide transfer coefficient [20]. In particular, it is highly sensitive to early disease and is more specific. In this study the sensitivity was 94% and the specificity at least 94%. There were no false positive tests in smokers. Furthermore, as an out-patient screening test, DTPA scanning is acceptable, convenient and cheap. It is potentially available in all hospitals with a gamma camera or scintillation probe and could be widely adopted.

Despite these advantages it remains a nonspecific test. CMV pneumonitis, *L. pneumoniae* and other interstitial diseases may mimic the appearance of PCP on the DTPA scan [12]. Previous clinical reviews suggest that the prevalence of CMV pneumonitis [21] and *L. pneumoniae* [22] is low. Although subclinical *P. carinii* and CMV colonization of the lungs is frequent [3], our previous studies suggest that an abnormal DTPA scan does not occur in these circumstances [12].

The examination of induced sputum has been proposed as an alternative to bronchoscopy when investigating potential PCP. Although specific, the sensitivity of induced sputum for PCP is variable [9, 10]. With both the Grocot and the newer immuno-fluorescent staining techniques there is a "learning curve" before reliable results are obtained and success may also depend on the severity of the pneumonia. In early disease, the patient may be unable to produce a sputum sample despite attention to the details of the technique. Clinically obvious PCP is invariably induced sputum positive [10] whilst data from experienced centres suggest that in early disease induced sputum may be negative when BAL is positive [23]. Cases of falsely positive induced sputum following the introduction of the monoclonal antibody staining technique have been reported [24] and occurred in one case in the present study. The clinical relevance of occasional pneumocystis in induced sputum or BAL remains to be determined. An important aspect of the introduction of induced sputum and cyto-immunological examination has been that we have progressively carried out fewer bronchoscopies.

In an HIV positive patient the confirmation of PCP at bronchoscopy produces unequivocal evidence of the onset of AIDS. However, the necessity for histological confirmation of PCP in a typical patient with a diffusely abnormal chest radiograph has been questioned [8] and will not be practical in the future. In the present study bronchoscopy was performed in 12 patients with suspected PCP because of rapid deterioration or treatment failure in whom it was felt necessary to obtain histological confirmation. This did not lead to an alternative or additional diagnosis (PCP was confirmed in 12) in any individual but it justified the use of second line drug therapy with pentamidine or trimetrexate. Microbiological serology was unhelpful in diagnosis or management of the patients. The low prevalence of *Legionella pneumoniae*, mycoplasma pneumonia and CMV pneumonia [21, 22] suggests that the routine use of these tests is unnecessary.
During the 18 mths of the study there were two deaths. Both occurred in the initial 6 mths. In the last 6 mth period, PCP was diagnosed earlier as measured by clinical features, severity of hypoxaemia and degree of abnormality of the chest radiograph. The use of the DTPA scan and the technique of induced sputum in a management strategy aimed at early diagnosis and outpatient treatment has resulted in a progressive reduction in the admission rate (overall 66%), a reduced need for bronchoscopy, a low case fatality (5.4%) and significant financial savings. The convenience and sensitivity of DTPA scanning has made a major contribution to the success of this management scheme.

In a recent review of indirect tests used in the detection of lung infections in the acquired immunodefiency syndrome (AIDS) [11], this study answers many of the uncertainties and demonstrates the effectiveness of DTPA scanning for the early detection of PCP in HIV positive patients presenting with fever and breathlessness.

References


RÉSUMÉ: Au cours d’une étude prospective de 72 patients VIH positifs consultant pour de la fièvre et de la dyspnée, un protocole de mise au point non invasif, incluant une technique de scanning faisant appel à la DTPA marquée par radio-isotopes et à l’expectoration provoquée, s’est avéré
hautement sensible et spécifique pour la détection précoce de la pneumonie à *Pneumocystis carinii* (PCP). Lors de la consultation, le scan DTPA s'avère anormal chez 34 des 36 cas de PCP (94%) quelle que soit l'histoire tabagique, alors que le cliché radiographique présente des anomalies diffuses chez 21 patients (62%). L'expectoration provoquée a permis d'identifier 7 des 14 patients (50%) atteints de PCP au cours des six premiers mois de son utilisation, et 7 des 10 patients (70%) au cours des six derniers mois. Le scanner pulmonaire DTPA et l'examen de l'expectoration provoquée sont des techniques non invasives qui peuvent être utilisées pour l'exploration de patients externes. En combinaison, elles ont détecté tous les cas de PCP lors de la consultation, ont réduit les indications de bronchoscopie, ont entraîné une létalité très basse (5.4%), et réduit les besoins d'hospitalisation. *Eur Respir J.*, 1991, 4, 19-25.