AIDS and the lung · 4

Series editors: D M Mitchell, A A Woodcock

Non-invasive investigation of pulmonary disease in patients positive for the human immunodeficiency virus

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The lung is the organ most frequently affected in patients with AIDS and, although *Pneumocystis carinii* pneumonia is the most common infection, the lung is often affected by other infections, and by neoplastic and infiltrative conditions.[1–8] Precise aetiological diagnosis of pulmonary disease in patients with AIDS has relied on examination of lung tissue or bronchial washings obtained at bronchoscopy as spontaneous sputum production is unusual, particularly in pneumocystis pneumonia.[1 2 9–13] More recently, some centres have developed a technique to obtain "induced sputum," the sputum induced by inhalation of nebulised hypertonic saline being examined for pathogens.[14–17] This technique will be discussed in detail in the next article in this series. As bronchoscopy is invasive, time consuming, expensive, and unpleasant for the patient and carries a small but important risk of complications[18] and as "induced sputum" requires some expertise to be effective, much effort has been devoted to the development and evaluation of non-invasive methods to assess both the severity and the specific cause of pulmonary disease in patients infected with HIV.

These non-invasive techniques include chest radiology,[1 2 11 13 19–22] arterial blood gas determination[1 2 11] or oximetry,[23] simple lung function tests,[24–26] gallium scanning,[27–29] and ^{99m}DTPA (technetium-99m diethylenetriamene pentacetic acid) scanning.[30–32] The ideal non-invasive investigation of pulmonary disease in HIV infected individuals would enable a specific diagnosis to be made and the therapeutic response to be monitored by a simple, quick, cheap, and universally available method. Unfortunately, none of these investigations fulfil these criteria but because they are non-invasive, and in some cases are quick and easy to perform and repeatable, they may be valuable in the following ways:

1 to determine the presence (or absence) of pulmonary disease in HIV antibody positive (HIV positive) patients with respiratory symptoms;

2 to assess disease severity—for example, hypoxaemia and the extent of respiratory failure;

3 to determine whether an invasive test is indicated to establish an aetiological diagnosis;

4 to monitor response to treatment.

The purpose of this review is to describe the value of non-invasive tests in the investigation of pulmonary disease in patients known to be HIV antibody positive or in patients thought to be at high risk of HIV infection.

Chest radiology

A chest radiograph is the initial investigation for known HIV positive patients and those at high risk who have respiratory symptoms and is a useful screening test.[1 2 11 13] In HIV positive symptomatic individuals any radiographic abnormality warrants further investigation. It is important, however, not to discount symptoms in patients with a normal radiograph as 5–14% of patients subsequently found to have respiratory disease had a normal chest radiograph at presentation.[13 20 23 26] Such a normal appearance may occur not only in pneumocystis pneumonia but also in *Mycobacterium avium-intracellulare* and cytomegalovirus infection.[33] In addition, the radiographic changes of pulmonary complications of AIDS are neither specific to any particular infection or neoplasm nor to AIDS itself. At presentation, however, the most frequent radiographic appearance of pneumocystis pneumonia is a bilateral perihilar haze, which in mild cases can be very subtle and easy to miss. In more severe cases diffuse interstitial perihilar shadows are obvious and late cases often show substantial alveolar filling with peripheral sparing at the bases and apices. These appearances may also be seen with pyogenic bacterial, mycobacterial, cytomegalovirus, and fungal infection in addition to Kaposi's sarcoma and lymphoid interstitial pneumonitis.[7 11 33–39] Severe cases of pneumocystis pneumonia frequently show extensive consolidation with air bronchograms and 5–10% of cases show atypical features, including cystic changes,[21] localised upper zone changes suggesting tuberculosis,[38] and, very rarely, hilar and mediastinal lymphadenopathy[39] or pleural effusion.[40] Radiographic changes may occur rapidly in pneumocystis pneumonia, so after being initially normal the radiograph may become grossly abnormal in a few days. By contrast, radiographic clearing on recovery tends to be slow, and indeed the radiograph

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may never return completely to normal, in keeping with the permanent lung function abnormalities that often remain after recovery.[41] The chest radiograph has been reported to have a sensitivity and specificity of 85% for the diagnosis of pneumocystis pneumonia.[21 22] When such typical radiographic features are present in patients with a "typical" clinical history and examination—that is, breathlessness, dry cough, normal findings on chest examination or basal crackles, and arterial hypoxaemia—then the sensitivity increases to 87% and the specificity to 90%.[42] This is perhaps not surprising as most pulmonary disease in AIDS is due to pneumocystis pneumonia. The reported sensitivity and specificity of chest radiography and other non-invasive investigations for the diagnosis of pneumocystis pneumonia are shown in the table.

Localised radiographic changes in the lung tend to suggest pathogens other than pneumocystis pneumonia. Focal consolidation is more likely to be due to bacterial pneumonia but may occur with pneumocystis pneumonia or mycobacterial disease.[1 19 35 38 40] Upper zone shadowing with or without pleural effusions is more suggestive of tuberculosis, though atypical presentations of this disease are particularly common in patients with AIDS.[34] Nodular shadowing is usually a feature of Kaposi's sarcoma.[7 40] Hilar or mediastinal lymphadenopathy with or without pleural effusions suggest the presence of tuberculosis, lymphoma or Kaposi's sarcoma.[7 8 34 39] Other radiographic techniques, such as computed tomography, have been used to evaluate AIDS related lung disease.[43 44] Computed tomography may be particularly useful for patients with respiratory symptoms and a normal chest radiograph. In a preliminary study of 14 such patients all seven with an abnormal computed tomogram were subsequently found to have lung disease, whereas no pathogens were detected in the seven patients with a normal scan.[44]

Arterial blood gases and oximetry

Measurement of arterial oxygenation is necessary to determine the presence and extent of respiratory failure. This is particularly important in the detection and treatment of the rapidly progressive and potentially fatal hypoxaemia which characterises severe pneumocystis pneumonia.[1 2 23] Arterial puncture to estimate blood gas tensions has the advantage that hypocarbia (indicating hyperventilation) may be detected when the oxygen saturation is still relatively normal, and the alveolar-arterial oxygen gradient may be calculated. Only 8% of patients with pneumocystis pneumonia have a normal alveolar-arterial (A–a) oxygen gradient at rest.[1 2] Hypoxaemia and an abnormal A–a oxygen gradient are therefore sensitive indices for pneumocystis pneumonia, but they are non-specific and are seen with many of the other pulmonary complications of AIDS.

The use of an oxygen saturation meter to monitor respiratory failure in AIDS patients has obvious advantages for patients and staff as repeated arterial puncture is avoided. Users of such equipment should, however, be familiar with the sigmoid shape of the oxygen dissociation curve and be aware that high values for oxygen saturation do not always mean that all is well. Exercise induced arterial desaturation detected by oximetry may be a sensitive index for pneumocystis pneumonia. Thirty five of 40 patients with biopsy proved pneumocystis pneumonia who were able to exercise for 10 minutes developed an oxygen saturation of less than 90%; none of 12 healthy volunteers showed such a fall.[23] Twenty of the 24 patients with pneumocystis pneumonia and normal arterial blood gas tensions developed oxygen desaturation on exercise. By contrast, in a group of 19 patients with other AIDS related respiratory problems in the same study only two showed a fall in oxygen saturation.[23] This preliminary study suggests that looking for oxygen desaturation with exercise is a useful method of screening for pneumocystis infection, but comparisons with other screening methods are required.

Pulmonary function tests

Routine pulmonary function tests provide a convenient way of screening HIV positive patients to detect pulmonary disease: they are readily available in most hospitals, inexpensive, and quick to perform and repeat, and blood does not need to be drawn. Reduced values for single breath carbon monoxide transfer factor (TLCO), transfer coefficient (KCO), total lung capacity (TLC), vital capacity (VC), and forced vital capacity (FVC) have been reported in patients with pneumocystis pneumonia,

Comparison of the specificity and sensitivity of non-invasive investigations for pneumocystis pneumonia in HIV positive patients

First author	*Investigation*	*Specificity (%)*	*Sensitivity (%)*
Murray[1]	Radiography	90	[No data]
Suster[20]	Radiography (diffuse parenchymal infiltrates)	56	64
De Lorenzo[21]	Radiography (diffuse parenchymal shadowing)	86	No data
Millar[42]	History, examination blood gas analysis, and radiography	87	90
Smith[23]	Oximetry	90	79
Shaw[26]	TLCO < 70% predicted	72	92
Coleman[24]	TLCO < 80% predicted	86	[No data]
Curtis[25]	VC, TLC, TLCO < 80% predicted	85	52
		71	64
		90	23
Coleman[27]	Gallium scanning	100	20 (90% if includes only grade 3 or 4 scans)
Kramer[29]	Gallium scanning	>90	51 (83% if only diffuse pattern regarded as positive)
O'Doherty[31 32]	^{99m}Tc DTPA	>90	>90
Rosso[30]	^{99m}Tc DTPA	>90	>90

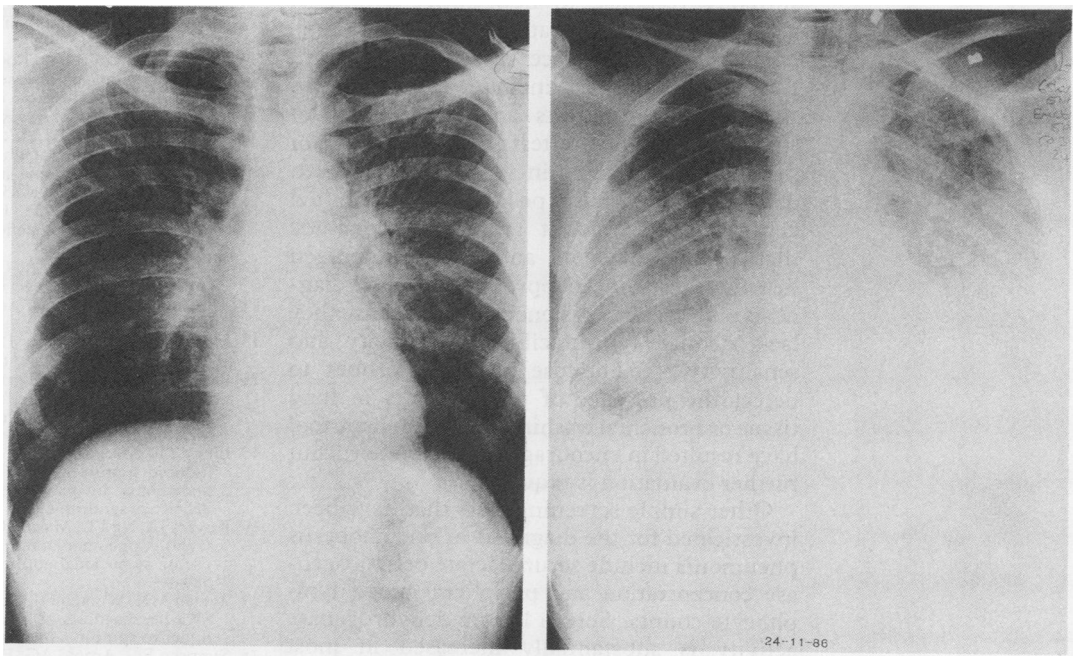
TLCO—transfer factor for carbon monoxide; VC—vital capacity; TLC—total lung capacity; ^{99m}Tc DTPA—technetium labelled diethylenetriamine pentacetic acid.

whereas other simple measures of airway function (peak expiratory flow, forced expiratory volume in one second, maximum expiratory flow rate at 50% of vital capacity) are often normal.[24-26] A reduction in TLCO is the most sensitive of these indices for pneumocystis pneumonia[26] (table) and may correspond with the extent of histological abnormality in the lung.[45] A reduced TLCO value, however, lacks specificity and values of 70% predicted or less are detected in many AIDS related lung disorders (for example, Kaposi's sarcoma and mycobacterial infection) and also in some HIV positive patients without overt lung disease.[26 45] The explanation for this last finding is not clear. The reduced TLCO does not appear to be related to smoking or intravenous drug abuse[46]; it may be due to lung damage induced directly by HIV itself as non-specific interstitial pneumonitis is being increasingly recognised in these patients.[4] Despite these potential pitfalls, the TLCO remains a useful screening test, particularly when sequential measurements can be made. A sudden fall in TLCO associated with new respiratory symptoms nearly always represents pulmonary disease. In one study 12 of 13 patients with pneumocystis pneumonia had a TLCO less than 70% predicted with a mean value of 50% predicted, which improved to 63% predicted on recovery.[26] By contrast, the mean TLCO (% predicted) for patients with the AIDS related complex was 77%, for patients with non-pulmonary Kaposi's sarcoma 70%, and for those with AIDS without overt lung disease 70%.[26] Widespread use of lung function testing has been limited by fears of cross infection—both by HIV, which may be present in saliva,[47] and by mycobacteria.[48] The use of disposable one way valves for spirometry and saliva absorbing bacteriostatic filters for gas transfer testing circumvents this problem.[26] Further simple and inexpensive modifications to conventional lung function equipment have recently been described, which if generally adopted should remove the risk of infection completely.[48]

Radionuclide scanning

Gallium-67 citrate scans detect pulmonary inflammation and have been used for some time as a screening test for AIDS related lung disease in several centres in the United States. Early reports suggested that diffuse uptake of gallium-67 by the lungs in an at risk patient was both highly specific and sensitive for pneumocystis pneumonia.[11 27] More recent studies have confirmed a high sensitivity, more than 90%, for pneumocystis pneumonia but showed low specificity, 51%.[29] This may reflect greater awareness of the possible significance of pulmonary symptoms by both physicians and patients in groups at high risk of HIV infection, who therefore present earlier in the course of their disease. Gallium-67 scans may also be useful in monitoring the response of pneumocystis pneumonia to treatment. This was shown in a study in which scans were graded 1–4 according to the intensity of gallium uptake; in 12 patients with pneumocystis pneumonia and scans initially graded 3 or 4, 10 reverted to grades 1 and 2 on recovery. Two further patients had persistent grade 4 changes after treatment of pneumocystis pneumonia and in both *P carinii* was still present on repeat bronchoscopy.[28] Another uptake pattern, focal gallium accumulation, has been associated with the presence of *Mycobacterium avium-intracellulare*. In one small study nine of 10 patients with *M avium-intracellulare* had such changes.[29]

In contrast to gallium-67, which is selectively taken up by inflammatory cells, the clearance of aerosolised ^{99m}TC DTPA from the lung is a measure of pulmonary epithelial permeability or "leakiness."[49] DTPA clearance from the lung is greatly increased in patients with pneumocystis pneumonia[31] and has been



Radiographic appearance of (a) early and (b) late stages of Pneumocystis carinii pneumonia.

advocated as a screening test for this disease. A major problem with this investigation is that clearance is also increased in smokers.[49] In patients with pneumocystis pneumonia, however, a biphasic clearance curve is seen, which differs from that seen in smokers or with other AIDS related respiratory problems.[30 31] Furthermore, after recovery from pneumocystis pneumonia this biphasic clearance curve reverts to a monophasic curve, allowing this technique to assess response to treatment.[32] A small comparative study of gallium-67 and ^{99m}Tc DTPA scanning in 11 patients suggests that the latter is more specific for pneumocystis pneumonia.[50] Both techniques, however, are time consuming and costly, and require the assistance of a nuclear medicine department. They are likely to be available only in large centres, and even there, in the context of HIV associated pulmonary disease, they may have little more to offer than the more simple screening tests.

Blood tests

The serodiagnosis of AIDS related pulmonary disease would have obvious advantages. The difficulty in isolating *P carinii* from clinical specimens and the need to obtain such specimens, usually by bronchoscopy, have stimulated particular interest in the possibility of serodiagnosis for these diseases. An early study suggested that a complement fixation test for pneumocystis pneumonia was useful in the epidemic childhood form of the illness as 90% of proved cases were seropositive, in contrast to only 3% of the control group.[51] Later studies, however, using immunofluorescent techniques showed that more than 75% of children were seropositive by the age of 4 years;[52] the presence of antibody to *P carinii* could not be taken to indicate active infection unless a fourfold increase in titre could be shown. Conversely, patients with AIDS, by virtue of their immune incompetence, may be unable to mount an antibody response to new antigens and so might remain seronegative for pneumocystis pneumonia in the face of active infection. Further problems include difficulty in standardising the tests and the sources of antigen. Evaluation of tests for the presence of pneumocystis antigen in serum has also been disappointing;[51] false positives have limited clinical utility.[53] Most authorities conclude that, at present, both antibody and antigen detection tests are inappropriate for the diagnosis of pneumocystis pneumonia because they lack adequate reproducibility, specificity, and sensitivity.[54 55] The use of DNA probes to detect the presence of pneumocysts in lung tissue or bronchial washings as a diagnostic tool have resulted in encouraging initial reports but further evaluation is required.[56]

Other simple screening tests that have been investigated for the diagnosis of pneumocystis pneumonia include serum lactate dehydrogenase concentration and peripheral blood lymphocyte counts. Serum lactate dehydrogenase activity is substantially increased in most patients with pneumocystis pneumonia,[57 58] but this enzyme is also increased to a lesser extent in HIV positive patients with other pulmonary disease, again raising the problem of specificity in particular. Similar problems arise with the use of peripheral blood lymphopenia or reduced CD4 lymphocyte counts for the diagnosis of pneumocystis pneumonia, even though most cases of pneumocystis pneumonia and of other opportunist infections in HIV positive patients will be associated with low CD4 counts.[59]

Conclusion

There are many different causes of pulmonary disease in patients with AIDS, for most of which there is specific and effective treatment. It is clear from this brief review of non-invasive investigations that a specific diagnosis cannot be made by these methods, with the exception of induced sputum. The non-invasive tests discussed still have important roles, however, in establishing the presence of pulmonary disease in HIV positive patients, in assessing the severity of established disease, and in monitoring the response to treatment.

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