

The spectrum of pulmonary disease in patients with HIV infection

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JSG MONTANER, L SPOUR, C ZALA. The spectrum of pulmonary disease in patients with HIV infection. Can J Infect Dis 1994;5(Suppl E):34E-39E. *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma were the harbingers of the HIV epidemic more than 10 years ago. Since then, the spectrum of pulmonary disease associated with HIV infection has become better understood. Although most of these conditions are infectious in nature, neoplastic and inflammatory processes also occur with increased frequency. The most common infectious pulmonary diseases include PCP, *Mycobacterium tuberculosis* infection and pyogenic bacterial pneumonia secondary to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Staphylococcus aureus*. Among the noninfectious causes of pulmonary disease, the most common are Kaposi's sarcoma, airways hyper-reactive disease (asthma) and emphysema. Respiratory involvement in HIV-infected individuals is not always related to the HIV infection. These patients often present with pulmonary disorders that are common in the general population. Differential diagnosis of respiratory conditions is significantly facilitated by the prior knowledge of the degree of immunodeficiency present as measured by the CD4 count. In particular, most episodes of PCP occur in patients with absolute CD4 counts below 200 cells/mm³. On the other hand, bacterial pneumonias and tuberculosis tend to occur at any time during the natural history of HIV disease. History and physical examination can help in the differential diagnosis; however, they are relatively nonspecific in this setting. The same can be said of radiographic findings as well as laboratory and physiological abnormalities. Of note, the lactate dehydrogenase (LDH) serum level has proved to be extremely useful in ruling out PCP. Even mild PCP is usually accompanied by a significant elevation of LDH. Furthermore, the degree of LDH elevation generally correlates with the severity of the PCP episode. Also, changes in LDH parallel the clinical course of the underlying PCP. Often LDH level has been useful in discriminating worsening PCP following the initiation of therapy from worsening respiratory symptoms due to superimposed disease. It must be emphasized, however, that LDH level, although a very sensitive marker for PCP, is also nonspecific. Of note, hemolysis, lymphomas, pulmonary embolism, liver disease and dapsone therapy can be associated with elevated LDH in the context of HIV disease. Given the high frequency of respiratory involvement in this patient population, it is generally recommended that preventive therapies be used whenever possible. Current recommendations stress the need for pneumococcal vaccine, yearly 'flu vaccination and routine screening with tuberculin skin test (PPD). HIV-infected individuals with a PPD skin test reaction of 5 mm of induration or greater using 5 tuberculin units will be considered candidates for one year of isoniazid prophylaxis. PCP prophylaxis has been shown to be extremely useful in this setting either as primary or secondary prophylaxis. Recently, rifabutin at doses of 300 mg daily has been shown to decrease significantly the frequency of *Mycobacterium avium* complex infection in patients with CD4 counts below 100/mm³. (Pour résumé, voir page 35E)

Key Words: Human immunodeficiency virus, Lung, *Mycobacterium tuberculosis*, *Pneumocystis carinii* pneumonia

Éventail des maladies pulmonaires chez les patients atteints d'une infection au VIH

RÉSUMÉ : La pneumonie à *Pneumocystis carinii* (PPC) et le sarcome de Kaposi ont été décrits comme entités distinctives de l'épidémie de VIH, il y a plus de 10 ans. Depuis lors, les différentes manifestations pulmonaires associées à l'infection au VIH ont été mieux comprises. Bien que la plupart de ces affections soient de nature infectieuse, les processus néoplasiques et inflammatoires se produisent aussi avec une fréquence accrue. Les maladies pulmonaires infectieuses les plus fréquentes sont la PPC, l'infection à *Mycobacterium tuberculosis*, et la pneumonie bactérienne pyogène secondaire à *Streptococcus pneumoniae*, *Haemophilus influenzae* ou *Staphylococcus aureus*. Parmi les causes non infectieuses de la maladie pulmonaire, la plus fréquente est le sarcome de Kaposi, l'hyperréactivité bronchique (asthme) et l'emphysème. L'atteinte respiratoire chez les sujets infectés au VIH n'est pas toujours liée à l'infection au VIH. Ces patients présentent souvent les mêmes troubles pulmonaires répandus que la population générale. Le diagnostic différentiel des maladies respiratoires est considérablement facilité par une connaissance préalable du degré d'immuno-déficience, mesuré par la numération des CD4. En particulier, la plupart des épisodes de PPC surviennent chez des patients dont la numération des CD4 absolue est sous les 200 cellules/mm³. D'autre part, les pneumonies bactériennes et la tuberculose tendent à se produire en tout temps durant l'évolution naturelle de la maladie au VIH. L'anamnèse et l'examen physique peuvent aider au diagnostic différentiel; toutefois, ils ne sont pas spécifiques dans ce contexte. On peut dire la même chose des observations radiographiques et des rapports d'analyses de laboratoire ou des examens physiologiques. Il faut noter que les taux sériques de lactate déshydrogénase (LDH) se sont révélés très utiles pour écarter le diagnostic de PPC. Même la PPC légère est habituellement accompagnée d'une élévation significative du LDH. De plus, le degré d'élévation du LDH est généralement en corrélation avec la gravité de l'épisode de PPC. Également, les changements du LDH concordent avec l'évolution clinique de la PPC sous-jacente. Le taux de LDH a même été utile pour distinguer une aggravation de la PPC suite à l'amorce d'un traitement d'une aggravation des symptômes respiratoires attribuables à une maladie surimposée. Il faut souligner toutefois que le taux de LDH, bien qu'il soit un marqueur très sensible de la PPC, est également non spécifique. Notons que l'hémolyse, les lymphomes, l'embolie pulmonaire, la maladie hépatique et le traitement au dapsonne sont associés à une élévation du LDH dans le contexte de la maladie au VIH. Étant donné la grande fréquence des atteintes respiratoires chez cette population de patients, il est en général recommandé de traiter préventivement autant que possible. Les recommandations actuelles soulignent la nécessité d'un vaccin pneumococcique, d'une vaccination annuelle contre l'influenza et d'un dépistage de routine à l'aide d'un test cutané à la tuberculine (PPD). Les sujets infectés au VIH qui manifestent une réaction cutanée avec induration de 5 mm ou plus après l'administration de 5 unités de tuberculine seront considérés des candidats au traitement prophylactique par isoniazide d'une durée d'un an. La prophylaxie de la PPC s'est révélée extrêmement utile dans ce contexte, soit à titre de prophylaxie primaire ou secondaire. Récemment, la rifabutine à des doses de 300 mg par jour s'est révélée apte à diminuer significativement la fréquence de l'infection au complexe *Mycobacterium avium* chez des patients dont la numération des CD4 était inférieure à 100/mm³.

PNEUMOCYSTIS CARINII PNEUMONIA (PCP) AND KAPOSI'S sarcoma were the harbingers of the HIV epidemic more than 10 years ago. Since then, the spectrum of pulmonary disease has become better understood. Although the majority of these conditions is infectious in nature, neoplastic and inflammatory processes also occur with increased frequency among individuals infected with HIV, the causative agent of AIDS (1).

The infectious causes of pulmonary disease among HIV-infected individuals are shown in Table 1. PCP, *Mycobacterium tuberculosis* and pyogenic bacterial pneumonia secondary to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Staphylococcus aureus* infection are the most frequently encountered complications. Less frequently, a variety of fungi and viruses can give rise to pulmonary infection. Cytomegalovirus pneumonitis, once felt to be extremely frequent in this population, is now most often regarded as a contaminant in pulmonary secretions. Although *Mycobacterium avium* intracellulare (MAI or MAC) is a frequent late complication of AIDS, respiratory disease secondary to MAI is distinctly uncommon (2).

The noninfectious causes of pulmonary disease among HIV-infected individuals are listed in Table 2.

TABLE 1
Infectious pulmonary diseases in HIV/AIDS

Most common

Pneumocystis carinii pneumonia
Pyogenic bacterial pneumonia
Mycobacterium tuberculosis

Less common

Aspergillosis
Cryptococcosis
Coccidioidomycosis
Histoplasmosis
Cytomegalovirus
Mycobacterium avium intracellulare
Nocardia
Rhodococcus equi
Cryptosporidium
Toxoplasmosis

Among them, Kaposi's sarcoma is particularly frequent (3). More recently, an increased frequency of airways hyperreactivity and emphysema has been described in AIDS patients (4,5). Less frequently, lymphocytic interstitial pneumonitis, nonspecific interstitial pneumonitis lymphoma and drug radiation-related pneumonitis can be seen (2).

TABLE 2
Noninfectious pulmonary diseases in HIV/AIDS

Common
Kaposi's sarcoma
Airways hyperreactivity (asthma)
Emphysema
Less common
Lymphocytic interstitial pneumonitis
Nonspecific interstitial pneumonitis
Lymphoma
Drug-related pneumonitis
Radiation-related pneumonitis
Pulmonary hypertension
Pneumothorax (usually related to <i>Pneumocystis carinii</i> pneumonia)
Pulmonary emboli

It is important to highlight that not all lung disease in patients with HIV infection or even AIDS is necessarily related to the HIV infection. These patients often present with pulmonary disorders that are common in the general population. As mentioned above, asthma, emphysema and bacterial pneumonia are frequent non-HIV specific conditions in these patients.

The relative frequency of HIV-associated complications is continuously changing as new effective preventive and/or suppressive therapies and antiretrovirals continue to alter the natural history of the disease. As shown in Table 3, PCP represented the leading AIDS index diagnosis in Canada up to January 1987. At that time, PCP alone was the index disease in 52% of cases. As of January 1993, PCP alone represented 38% of the AIDS index diagnoses, while 33% were attributed to other opportunistic infections. Although the frequency of PCP as the AIDS index disease has decreased somewhat since the advent of PCP prophylaxis, PCP remains the single most frequent AIDS index disease (6,7).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis will be influenced by prior knowledge of the degree of immunosuppression present. In the absence of signs or symptoms, this can be readily assessed using the CD4 cell count. In general, AIDS-defining illnesses are uncommon if the CD4 count is above 300/mm³. In particular, most episodes of PCP occur in patients with absolute CD4 counts below 200/mm³. On the other hand, bacterial pneumonias or tuberculosis tend to occur at any time during the natural history of HIV disease (8).

Historical data or behavioural factors will also influence the differential diagnosis. As such, the frequency of bacterial pneumonias is particularly high among HIV-infected individuals who use intravenous drugs for recreational purposes (9,10). The prior knowledge of the PPD (Mantoux or tuberculin test) status in an HIV-infected individual is also important. The chances of reactivation of tuberculous infection among HIV-infected individuals with a

TABLE 3
AIDS index diseases in Canada

	January 1987 (%)	January 1993 (%)
PCP alone	52	38
PCP ± Kaposi's sarcoma	61	43
Other opportunistic infections	20	33

PCP *Pneumocystis carinii pneumonia*

positive tuberculin reaction (**induration 5 mm or greater**) is extremely high (11-14).

Although not frequent, respiratory disease in the context of HIV infection can at times lead to acute respiratory failure. This is in fact the leading cause of intensive care unit (ICU) admission among HIV-infected individuals. Of the causes of ICU admission related to HIV infection, acute respiratory failure secondary to PCP is by far the most important due to its high frequency and its potentially high mortality. In a recent review of the causes for admission to ICU in HIV-infected individuals at St Pauls Hospital in Vancouver, between the years 1985 and 1990, PCP was diagnosed in 92% of the ICU cases, cerebral toxoplasmosis in 3%, Kaposi's sarcoma in 3% and bacterial pneumonia, gastrointestinal bleeding, lymphoma and cardiomyopathy in 2% each of the cases (15). Note that more than one condition could be present in a given patient.

It is useful to keep in mind that the natural history of HIV/AIDS is continuously being altered by state-of-the-art therapy. Also, the so-called 'prophylaxis' against the various opportunistic infections encountered is usually not true prophylaxis but rather suppressive therapy. It is important to consider that not all respiratory disease in HIV-infected individuals is necessarily an opportunistic infection or AIDS-related disease, but often these represent non-HIV specific pathology. Finally, contrary to most other areas of medicine, the search for a single diagnosis when dealing with AIDS may be fruitless, since multiple pathological processes often occur simultaneously in this disease (16).

HISTORY AND PHYSICAL EXAMINATION

As in any other setting, pulmonary involvement in patients with HIV infection generally produces nonspecific signs and symptoms. Fever, malaise and weight loss for several weeks to months before the onset of pulmonary symptoms are not infrequent. In a group of patients with AIDS and pulmonary involvement, Stover *et al* (17) reported that cough was the most frequent symptom, present in 89% of patients. Dyspnea was present in 64%, productive cough in 39%, pleuritic pain in 20% and hemoptysis in 3% of patients. Acute symptoms were characteristically present among patients with bacterial pneumonias who were more likely to present with shaking chills. Symptoms in patients with opportunistic infections such as PCP were usually more

indolent, although in some instances they were also rapidly progressive (17).

Physical examination may be useful in establishing the diagnosis of AIDS or AIDS-related complex, but is not usually helpful in establishing the etiology of the pulmonary involvement. Pulmonary findings during physical examination are more useful in suggesting that the respiratory symptoms in a given high risk patient are not caused by an AIDS-related opportunistic infection. Diffuse wheezing would suggest the diagnosis of asthma; consolidation of the lung would be suggestive of an acute bacterial pneumonia; and a large pleural effusion, particularly if it is accompanied by characteristic skin or mucosal lesions, would be suggestive of Kaposi's sarcoma.

RADIOGRAPHIC FINDINGS

The chest radiograph is usually the first tool in the assessment of an HIV-infected individual with respiratory symptoms. Only rarely does the chest x-ray yield a firm diagnostic clue; however, findings are often helpful in guiding the next steps in the evaluation.

A diffuse interstitial pattern is most commonly caused by PCP. It must be recognized, however, that PCP can present with a wide variety of radiological patterns, from a normal x-ray to airspace disease, and from cavitory lesions to pneumothoraces. The interstitial pattern may be limited to the upper lung fields, particularly among patients who develop PCP while receiving aerosolized pentamidine for PCP prophylaxis. A diffuse interstitial pattern may also occur with *M tuberculosis*, MAI, histoplasmosis and coccidioidomycosis. Malignancies are infrequent causes of diffuse interstitial patterns. A diffuse airspace pattern can be essentially attributable to any of the infections described above. In addition, malignancies can also cause diffuse airspace consolidation. Such a radiological appearance, in the context of PCP, is often associated with significant respiratory distress. Focal airspace consolidation is most often attributable to bacterial pneumonia, but may also be caused by *Mycoplasma pneumoniae* or viruses. PCP and mycobacterial infections have also led to focal airspace consolidation in the past. Nodular lesions are often seen with Kaposi's sarcoma. They can also occur with mycobacterial and fungal infections as well as PCP. Cavitory lesions are relatively uncommon among patients with HIV disease. They have been described in the context of PCP, *M tuberculosis*, *M avium*, bacterial pneumonias and fungal infections.

Pleural effusions, particularly if they are large, are likely related to Kaposi's sarcoma. Smaller effusion can be seen in association with any of the above mentioned infectious processes. Intrathoracic adenopathy is frequently seen in the context of malignancies (Kaposi's sarcoma or lymphoma) or infectious processes, particularly tuberculosis. Pneumothoraces have been noted in association with PCP, particularly among those receiv-

ing aerosol pentamidine for PCP prophylaxis. Finally, it must be emphasized that a normal chest film does not rule out significant pulmonary involvement by any of the above mentioned conditions in patients with HIV infection. Of note, it has been demonstrated that a full two-thirds of HIV-infected individuals with advanced immunodeficiency may have unsuspected lung lesions on examination with high resolution computed tomography of the chest. Destructive lung lesions, from isolated lung cysts to widespread emphysema, were particularly frequent in these individuals (5,18).

OTHER LABORATORY TESTS

Numerous other laboratory tests are often useful in the assessment of HIV-infected individuals presenting with respiratory complaints. Obviously, this greatly varies depending on the specific nature of their complaints. In general, the serum level of lactate dehydrogenase (LDH) has proven extremely useful in this setting to rule out PCP. Even mild PCP is usually accompanied by a significant elevation of LDH, to one and a half to two times the upper limit of normal. The degree of LDH elevation generally correlates with the severity of the PCP episode. Furthermore, changes in LDH parallel the clinical course of the underlying disease. This is a useful aid in discriminating worsening PCP following the initiation of therapy from worsening respiratory symptoms due to a superimposed process.

It must be emphasized, however, that LDH, although a very sensitive marker of PCP, is also nonspecific. Elevations in the level of LDH can be seen in hemolytic processes, lymphomas, pulmonary embolisms and liver disease, among other conditions occurring not infrequently among HIV-infected individuals. Of particular note, in this context, is the fact that dapsone therapy can lead to the development of methemoglobinemia, which in turn leads to hemolytic anemia and an elevation in LDH. Because this is a dose-related phenomenon, it is most likely to be encountered among patients who are receiving treatment with full doses of dapsone for an episode of PCP rather than those receiving low dose intermittent dapsone for PCP prophylaxis (19-23).

Numerous other tests have been used with various degrees of success in the assessment of patients with respiratory involvement in the context of HIV infection. These include: pulmonary function test before and after bronchodilators; methacholine challenge; carbon monoxide diffusing capacity of the lungs; oxygen saturation while breathing air at rest and during exercise; and arterial blood gases. If pulmonary function tests are normal, a gallium lung scan is often performed. Increased uptake in the lungs would suggest direct pulmonary involvement and would warrant further evaluation to establish a definitive diagnosis (2).

All of the these tests, while very sensitive indicators of lung dysfunction, have a relatively low specificity. As such, etiological confirmation of pulmonary involve-

ment must be obtained from pulmonary secretions, as dictated by signs and symptoms. This is most often done using sputum, sputum induction or bronchoalveolar lavage. In all instances, respiratory secretions should be examined thoroughly, considering the wide variety of organisms that can lead to respiratory involvement in these patients.

PREVENTION OF RESPIRATORY DISEASE AMONG HIV-INFECTED INDIVIDUALS

Given the very high frequency of respiratory involvement in this patient population, it is generally recommended that an aggressive preventive strategy be initiated immediately upon diagnosis of HIV infection. All HIV-infected individuals should receive pneumococcal vaccine. It has now been demonstrated that this is a cost effective intervention that should be implemented as soon as possible following the diagnosis of HIV to maximize the chances of an adequate humoral response. Yearly 'flu vaccination during the appropriate time of the year is also recommended for all HIV-infected individuals. The cost effectiveness of this is less well documented (2).

A PPD skin test will allow identification of individuals at high risk for the development of tuberculosis. A 5 mm or greater induration following a 5 tuberculin unit (TU) PPD will require one year of isoniazid (INH) prophylaxis. PPD skin testing should ideally be repeated on a yearly basis. The predictive value of this test is likely to be compromised as the immunodeficiency progresses (2,11-14).

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PCP prophylaxis should be initiated in all HIV-infected individuals who have any of: CD4 count below 200/mm³; fraction CD4 count below 15%; unexplained fever; oral candidiasis; or a prior episode of PCP. The preferred prophylactic regimen is trimethoprim-sulfamethoxazole (TMP-SMX) 1 double-strength tablet once daily, for life. Adverse reactions to TMP-SMX are frequent and at times severe among HIV-infected individuals. Patients should be warned that the drug must be discontinued if generalized rash or fever develops. Alternative prophylactic regimens include dapsone at a dose of 100 mg by mouth three times weekly or aerosol pentamidine intermittently. Aerosol pentamidine can be taken in doses of 60 mg every second day for five doses followed by one dose every two weeks via a Fisoneb ultrasonic nebulizer (Fisons, New York); alternatively, 300 mg monthly can be delivered via a Respirgard tube jet nebulizer (Marquest, Colorado). It should be noted that the aerosol pentamidine doses are nebulizer-specific (2,6,8).

Recently it has been demonstrated that rifabutin at doses of 300 mg daily can significantly decrease the frequency of MAI in patients with advanced immunodeficiency. This prophylactic intervention is recommended for patients who have CD4 counts below 100/mm³ (24).

Despite the availability of preventive therapies, we must recognize that they are only partially effective. Furthermore, issues of acceptability, tolerability and compliance, among others, will continue to jeopardize our ability to eradicate definitively some of these often serious respiratory complications of HIV/AIDS (2-5).

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