

Pneumocystis carinii pneumonia in HIV – investigate or just treat?

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Pneumocystis carinii pneumonia (PCP) is an extremely common manifestation of the acquired immunodeficiency syndrome (AIDS) resulting from infection with the human immunodeficiency virus (HIV). Most episodes present in a fairly typical manner with increased dyspnea and/or a non-productive cough, a diffuse interstitial pattern on chest radiograph and an elevated alveolar-arterial oxygen gradient. The pattern has been so typical of the disorder that empirical therapy without microbiological proof of disease is often initiated by primary care physicians. This strategy has not been tested in controlled clinical trials although decision analysis models have attempted to evaluate it. It is likely reasonable to choose empirical antimicrobial therapy in specific clinical settings such as: (a) typical radiographic picture in a person with dyspnea and/or nonproductive cough, presence of HIV and a CD4 count of less than 200 cells/mm³; (b) previous PCP, typical appearance and the patient is known to tolerate standard anti-PCP medications; and (c) high clinical suspicion in a patient who refuses bronchoscopy yet desires treatment or where bronchoscopy cannot be performed. However, early bronchoscopy should strongly be considered when the chest radiograph is not typical of *P. carinii* infection or if there is failure to respond after a predefined period.

Key Words: *Acquired immunodeficiency syndrome, Pneumocystis carinii, Pneumonia, Treatment*

Pneumonie à *Pneumocystis carinii* associée au VIH – Investiguer ou seulement traiter?

RÉSUMÉ : La pneumonie à *Pneumocystis carinii* (PPC) est une manifestation très courante du syndrome d'immunodéficience acquise (SIDA) et résulte de l'infection par le virus de l'immunodéficience humaine (VIH). La plupart des épisodes se présentent d'une manière plutôt typique: dyspnée progressive et/ou toux non productive, infiltrations interstitielles diffuses révélées par la radiographie pulmonaire et élévation du gradient alvéolo-artériel en oxygène. Ce tableau est si représentatif de l'affection que les omnipraticiens débutent souvent un traitement empirique sans preuve microbiologique de la maladie. Cette stratégie n'a jamais été validée par des essais cliniques contrôlés bien que des modèles analytiques décisionnels aient tenté de l'évaluer. Le choix d'administrer un traitement antimicrobien sur une base empirique est sûrement fondé dans certains contextes cliniques spécifiques tels que (a) image radiologique typique chez une personne présentant une dyspnée et/ou une toux non productive, présence du VIH et numération des CD4 inférieure à 200 cellules/mm³; (b) PPC antérieure, apparence typique et patient connu pour sa tolérance au traitement standard anti-PPC et (c) index de suspicion clinique élevé chez un patient qui refuse une bronchoscopie et demande un traitement ou lorsqu'il est impossible de pratiquer une bronchoscopie. Cependant, il est fortement recommandé de pratiquer rapidement une bronchoscopie lorsque la radiographie pulmonaire n'est pas caractéristique d'une infection à *P. carinii* ou si le patient ne répond pas au traitement après une période prédéterminée.

IT HAS BEEN ESTIMATED THAT THERE ARE APPROXIMATELY eight to 10 million cases of infection with the human immunodeficiency virus (HIV) in the world, of which over one million have progressed to the acquired immunodeficiency syndrome (AIDS) (1). Respiratory disease is the most common initial manifestation of AIDS, with *Pneumocystis carinii* pneumonia (PCP) accounting for the majority of respiratory presentations. As experience has increased over the years with what can be a fairly 'typical' presentation, the Centers for Disease Control and Prevention (CDC) has recognized that many patients are being treated for PCP without a confirmed diagnosis and have therefore revised the diagnostic criteria for the definition of AIDS for surveillance purposes. AIDS can be diagnosed on the basis of a presumptive diagnosis of PCP when the patient with HIV presents with the new onset of dyspnea on exertion or nonproductive cough, a diffuse interstitial pattern on chest radiograph, elevated alveolar-arterial oxygen gradient and no evidence of bacterial pneumonia (2). Despite the CDC accepting a presumed diagnosis of PCP for the categorization of AIDS, the CDC does not appear to endorse wholeheartedly empirical treatment.

In the early years of management of HIV infected patients, microbiological proof of infection with *P. carinii* was sought in virtually all patients. However, a strong argument can be made for empirical treatment based on clinical and radiographic suspicion of PCP. As well, there are investigations that can be initiated to raise or lower clinical suspicion given a history and chest radiograph compatible with PCP. The likelihood of PCP increases significantly when the CD4 count falls below 200 cells/mm³. The likelihood of PCP in the infected patient not receiving AZT (zidovudine) or pneumocystis prophylaxis given a compatible history and x-ray is approximately 65% if the CD4 count is less than 200 cells/mm³. However, with AZT and pneumocystis prophylaxis, that likelihood drops to perhaps 40% of all causes. The likelihood of PCP in the patient with a CD4 count from 200 to 500 cells/mm³ is approximately 25% without and 22% with antiviral and pneumocystis prophylaxis (3). With a CD4 count exceeding 500 cells/mm³, the chance of PCP is extremely low whether or not the patient receives other therapy. Examination of expectorated sputum is not helpful and should not be performed. Induced sputum has been successful in several centres equipped for appropriate induced sputum technique and evaluation. Yet experience in other centres has been variable. Certainly, the experience of many physicians in Canada has been less than ideal with this form of investigation. An elevated lactate dehydrogenase has been found to be a fairly reliable marker of PCP, but lactate dehydrogenase is not necessarily specific (4). Likewise, other investigative techniques studied, such as a low diffusion capacity, arterial oxygen desaturation with exercise and gallium scanning, are quite sensitive but nonspecific. One study has suggested that the presence of mouth lesions (hairy leukoplakia or oral candidiasis) and an elevated erythrocyte sedimentation rate may also raise clinical suspicion (5).

Even with the information gained from a combination of

history, physical examination, radiology and any of the other noninvasive investigations mentioned, one must also be aware that there are a variety of disease states, both infectious and noninfectious, that will result in dyspnea, bilateral infiltrates and disturbances in gas exchange. These disorders include bacterial, atypical and fungal infections, tuberculosis, other mycobacteria, Kaposi's sarcoma, lymphocytic interstitial pneumonia, pulmonary fibrosis, neoplastic disorders and congestive heart failure. As well, atypical manifestations of PCP may occur. For example, an upper lobe pattern of interstitial disease in patients who have received aerosolized pentamidine may occur.

BRONCHOSCOPY VERSUS EMPIRICAL THERAPY

The most direct method for obtaining an adequate sample is fiberoptic bronchoscopy with bronchoalveolar lavage. The sensitivity of bronchoscopy with bronchoalveolar lavage exceeds 90% in virtually all studies. The specificity is obviously excellent. Transbronchial biopsies add potential morbidity with little gain in sensitivity. The advantages of early fiberoptic bronchoscopy include the ability to find other potential infective agents that could be treated, and not subjecting a patient to the potential and frequent side effects of antimicrobial therapy for PCP. Furthermore, when the use of trimethoprim-sulphamethoxazole is limited due to previous adverse side effects, the alternative agents (eg, pentamidine or the combination of clindamycin and primaquine) do not carry the broad antibacterial spectrum of trimethoprim-sulphamethoxazole. An incorrectly diagnosed episode of PCP may lead to misdiagnosing someone as having AIDS rather than simply carrying HIV. The diagnosis of AIDS carries a great psychological burden as well as the potential addition of therapy with toxic and often unproven agents. Finally, it would be far simpler, with less morbidity, to conduct bronchoscopy on a patient with mild disturbances in gas exchange rather than attempting bronchoscopy in the patient who has developed severe respiratory distress following failure of anti-PCP agents.

The advantage of foregoing bronchoscopy and initiating empirical therapy include a significant cost saving, eliminating discomfort related to bronchoscopy and not subjecting medical personnel to the risk of contamination with infected body fluids.

A recent publication approached the question of bronchoscopy versus empirical therapy using the technique of decision analysis (6). The model was based on a patient not receiving pneumocystis prophylaxis presenting with criteria satisfactory for the CDC diagnosis of presumed PCP. Early bronchoscopy with treatment based on the bronchoscopy results was compared with empirical treatment for PCP (trimethoprim-sulfamethoxazole or pentamidine, and steroids) and delayed bronchoscopy in those not responding to five days of treatment. There was essentially no difference in the expected one-month survival rates comparing both management strategies. Therefore, it was concluded that empirical treatment would be a superior strategy in that specific

scenario, given that early bronchoscopy did not offer any additional survival benefit and was associated with additional costs and discomfort with possible morbidity to the patient. Unfortunately, the study used bronchoscopy with bronchoalveolar lavage and transbronchial biopsies. One could argue that transbronchial biopsies are not necessary, and therefore not using them would decrease morbidity. As well, the study did not use a model in which patients received pneumocystis prophylaxis, which would lower the estimated prior probability of PCP. It could be argued that with aggressive use of trimethoprim-sulphamethoxazole prophylaxis and the knowledge that it is a better prophylactic agent than aerosolized pentamidine, empirical therapy should not be initiated in those patients tolerating trimethoprim-sulphamethoxazole prophylaxis even when the clinical scenario is highly suggestive of PCP. Nevertheless, the study is extremely useful and provides objective information for empirical treatment initially, with bronchoscopy reserved for those who fail to respond appropriately within five days.

Systemic corticosteroids are now accepted as part of standard therapy for patients with PCP and a PaO_2 of less than 70 mmHg (7). If empirical therapy is instituted in such a scenario it behooves the physician to also prescribe corticosteroids. The advantages have been adequately documented in several trials when the diagnosis is certain (8-10). While the study by Tu and colleagues (6) included steroid therapy, they did not factor in potential morbidity. Generally, a limited course of corticosteroids is well tolerated but the potential exists for acceleration of respiratory illness when the cause of the disorder is an infecting organism other than

P. carinii. As well, a history of glucose intolerance will likely influence the prescription of empirical therapy and corticosteroids.

This entire debate may be somewhat irrelevant as empirical therapy is the standard of care for many physicians. A survey of 463 respirologists in the United Kingdom questioned management strategies in patients with HIV. Two hundred and sixty-six physicians responded, with two-thirds choosing empirical treatment of PCP over immediate fibre-optic bronchoscopy (11).

While each case should be individualized, empirical treatment with antibiotics against *P. carinii* is a reasonable option under the following scenarios:

- Typical radiographic picture in a person with dyspnea and/or nonproductive cough, HIV and a CD4 count less than 200 cells/mm³, whether or not the person is receiving antiretroviral therapy or PCP prophylaxis.
- Previous PCP, typical appearance and the patient is known to tolerate standard anti-PCP medications.
- High clinical suspicion in a patient who refuses bronchoscopy yet desires treatment, or where bronchoscopy cannot be performed.

Empirical therapy alone should not be initiated when the chest radiograph is normal or demonstrates atypical findings such as nodules, masses, effusions or adenopathy. Finally, predefined criteria should be established as to when empirical treatment is classified as a failure (eg, five days). Bronchoscopy or other definitive investigations should then be conducted accordingly.

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