Eur Respir J
1993, 6, 166–168

EDITORIAL

Rational approach to the diagnosis *of Pneumocystis carinii* pneumonia (PCP)

H. Lode*, T. Schaberg

Pneumocystis carinii pneumonia remains the most common and serious pulmonary complication of human immunodeficiency virus (HIV) infection, with 5–30% of patients developing respiratory failure [1–3]. Consequently, prophylactic regimens, using orally-administered trimethoprim-sulphamethoxazole and aerosolized pentamidine, have been developed in an attempt to decrease the morbidity from *P. carinii* pneumonia in HIV-infected patients [4, 5]. Although recent data have suggested that trimethoprim-sulphamethoxazole may be more efficacious than aerosolized pentamidine, many patients will continue to receive aerosolized pentamidine because of sulphamethoxazole intolerance, or personal preference on the part of the patient or the health care provider.

The diagnostic evaluation of HIV-infected adult and paediatric patients with suspected *Pneumocystis carinii* pneumonia commonly includes an initial induced sputum examination, which, if negative, is followed by fibreoptic bronchoscopy and bronchoalveolar lavage (BAL) [6, 7]. The diagnostic sensitivity both of BAL and of induced sputum examination has exceeded 90% in patients with acquired immunodeficiency syndrome (AIDS) who did not receive prior anti-pneumocystis chemoprophylaxis [8–12]. However conflicting results have been reported as to whether *Pneumocystis carinii* pneumonia (PCP) in patients with a history of pentamidine prophylaxis ("breakthrough PCP") is clinically less severe, or is more difficult to diagnose, than patients with no history of pentamidine prophylaxis ("non-breakthrough PCP") [13–15]. In the first study [13] from New York, no difference in markers of clinical severity, or in length of hospital stay, in patients with breakthrough PCP and non-breakthrough PCP, was reported, but the authors found that the sensitivity of BAL for the diagnosis of PCP was much reduced in patients with breakthrough PCP. In contrast, METERSKY and CATANZARO [14] found that patients with breakthrough PCP were less severely ill, as assessed by mean alveolar-arterial oxygen difference ($A\text{-}aPo_2$) at presentation, and rate of admission to the hospital, but found the sensitivity of sputum induction for the diagnosis of PCP to be no different in breakthrough and in non-breakthrough PCP. In a third study examining similar issues, LEVINE *et al.* [15] found that induced sputum was less sensitive for the diagnosis of PCP in patients with breakthrough PCP but did not find decreased disease severity in this group [15].

Several reasons could explain the different findings reported by these groups. These factors could be patient selection, number of prior episodes of PCP, and risk factor for HIV infection. Based on these considerations and attempting to interpret these conflicting results, some recently published contributions are of great interest.

A retrospective matched cohort comparison study [16] of patients admitted to San Francisco General Hospital with PCP from 1 August 1989, to 30 June, 1990, was undertaken to determine whether the use of aerosolized pentamidine prophylaxis decreased the clinical severity or the sensitivity of diagnostic tests for PCP. Patients who had received pentamidine prophylaxis during at least two months prior to the diagnosis of PCP were matched with patients who had not received the drug. Matching was based on the number of prior episodes of PCP, sex, age, and risk factors for HIV infection. As markers of clinical severity, alveolar-arterial oxygen difference, serum lactate dehydrogenase levels, out-patient *versus* in-patient treatment, length of hospitalization, length of intravenous antipneumocystis treatment, development of respiratory failure, in-hospital mortality, and chest radiographic appearance were determined. Of the 27 matched pairs identified, significantly fewer of the pentamidine cohort were treated as in-patients, and significantly more of this cohort had upper lobe dominant diseases on chest radiography, but the authors found no other significant differences between markers of clinical severity for the cohorts. In addition, they found no significant differences in the rate of induced sputum or BAL sensitivity for *P. carinii* between the two cohorts. They concluded that aerosolized pentamidine prophylaxis did not decrease the clinical severity or sensitivities of sputum induction or BAL as diagnostic tests for PCP [16]. In another recently published study from Bethesda and Los Angeles [17], the authors again assessed the yields of both induced sputum and BAL in the diagnostic process for breakthrough episodes of PCP. This study determined especially whether the yield of single middle or lower lobe BAL could be increased by the utilization of two techniques: 1) indirect immunofluorescent staining with a combination of two murine monoclonal anti-pneumocystis antibodies, in addition

* Klinik Heckeshorn/City Hospital Berlin, Zehlendorf, Dept of Chest and Infectious Diseases, affiliated Freie Universität, Berlin, Zum Heckeshorn, 33, D-1000 Berlin 39, Germany.

to routine total toluidine blue O and cytopathological staining; and 2) the performance of multiple lobe, site-directed BAL (*i.e.* both upper lobe and middle or lower lobe lavage, including the lobe with the greatest radiographic abnormality). Results of 252 fibreoptic bronchoscopies, performed at the two different institutions, were analysed. *P. carinii* pneumonia was documented in 21 episodes in patients who did not receive prior anti-pneumocystis chemoprophylaxis, and in 41 episodes of patients who received aerosolized pentamidine. Monoclonal antibody staining in multiple lobe site-directed BAL resulted in similar diagnostic yields for *P. carinii* in the non-prophylaxis (100%) and aerosolized pentamidine (98%) groups. If BAL had been performed without monoclonal antibody staining and multiple lobe, site-directed lavage, then the yield would have decreased to 95% in the non-prophylaxis group and to 80% in the aerosolized pentamidine group. If the yields for single, middle or lower lobe BAL without monoclonal antibody staining and multiple lobe site-directed BAL with monoclonal antibody staining were compared in patients receiving aerosolized pentamidine, the sensitivity was significantly improved when both supplemental techniques were used (98 *versus* 80%). These data suggest that the use of both immunofluorescent and monoclonal antibody staining and multiple lobe, site directed BAL, in addition to middle and lower lobe lavage and conventional staining techniques, can maintain the high positive yield of BAL for *P. carinii* in patients receiving aerosolized pentamidine prophylaxis.

In this edition of the journal CHOUAID *et al.* [18] report on a comparison of systematic BAL *versus* BAL only after negative induced sputum, in 138 HIV-infected patients with suspected PCP, over a ten month period in Paris. Forty seven patients were receiving PCP-prophylaxis with pentamidine aerosols (n=37), or sulphamethoxazole-trimethoprim (n=10). Twenty seven patients were receiving secondary prophylaxis (pentamidine isothionate aerosols, 300 mg every four weeks (n=21), or sulphomethoxazole-trimethoprim, one tablet *q.d.* (n=6)). Sputum induction technique was based on inhalation of an aerosolized 3% saline solution for 15 min, using an ultrasound device; induced sputum and BAL specimens were processed immediately, two stains (Giemsa and silver) were used for each sample; in addition a specific monoclonal antibody for *P. carinii* was used. The induced sputum technique was either not feasible or unsuccessful in 40 of the 138 patients (29%). All of these patients underwent BAL, and PCP was diagnosed in 13% (32%). Both induced sputum technique and BAL were successfully performed in 98 of the 138 patients (71%). The sensitivity of induced sputum, using conventional and immunofluorescent staining, was 0.27 and 0.56 respectively. The economic analysis showed that the two strategies were equivalent in cost terms, when the induced sputum to BAL cost ratio is equal to the product of the prevalence of PCP and the sensitivity of induced sputum procedure. The authors [18] concluded that immunofluorescent tests should be the reference technique for induced sputum samples, whilst conventional stains are more reasonable for BAL samples.

In summary, considering the recently published data on this issue and taking into account the different health cost systems in Europe as well as patient comfort in most institutions, the sputum induction technique will be the first diagnostic procedure in patients with suspected PCP. After an initial negative induced sputum examination for PCP in HIV-infected patients, especially in those receiving aerosolized pentamidine chemoprophylaxis, a multiple lobe site-directed BAL with immunofluorescent monoclonal antibody staining should be performed.

References

1. Murray JF, Mills J. – Pulmonary infectious complications of human immunodeficiency virus infection. *Am Rev Respir Dis* 1990; 141: 1582–1598.
2. Kovacs JA. – Advances in the diagnosis of *Pneumocystis carinii* pneumonia. *In*: Volberding P, Jacobson MA, eds. AIDS clinical review. New York, Marcel Dekker, 1990; pp. 129–147.
3. The National Institutes of Health. – University of California Expert Panel for Corticosteroids as Adjunctive Therapy of Pneumocystis Pneumonia. Consensus statement of the use of corticosteroids as adjunctive therapy for Pneumocystis pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med* 1991; 323: 1500–1504.
4. Fischl MA, Dickinson GM, La Voie L. – Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *J Am Med Assoc* 1988; 259: 1185–1189.
5. Monataner JSG, Lawson LM, Gervais A, *et al.* – Aerosol pentamidine for secondary prophylaxis of AIDS-related *Pneumocystis carinii* pneumonia: a randomized, placebo-controlled study. *Ann Intern Med* 1991; 114: 948–953.
6. Murray JF, Garay SM, Hopewell PC, *et al.* – Pulmonary complications of the acquired immunodeficiency syndrome: an update report of the second National Heart, Lung and Blood Institute Workshop. *Am Rev Respir Dis* 1987; 135: 504–509.
7. Ognibene FP, Gill VJ, Pizzo PA, *et al.* – Induced sputum to diagnose *Pneumocystis carinii* pneumonia in immunosuppressed pediatric patients. *J Pediatr* 1989; 115: 430–433.
8. Broaddus C, Dake MD, Stulbarg MS, *et al.* – Bronchoalveolar lavage and transbronchial biopsy for the diagnosis of pulmonary infections in the acquired immunodeficiency syndrome. *Ann Intern Med* 1985; 102: 747–752.
9. Venet A, Clavel F, Israel-Biet D, *et al.* – Lung in acquired immune deficiency syndrome: infectious and immunologic status assessed by bronchoalveolar lavage. *Bull Eur Physiopathol Respir* 1985; 21: 535–543.
10. Golden JA, Hollander H, Stulbarg MS, Gamsu G. – Bronchoalveolar lavage as the exclusive diagnostic modality for *Pneumocystis carinii* pneumonia: a prospective study among patients with acquired immunodeficiency syndrome. *Chest* 1986; 90: 18–22.
11. Kovacs JA, Ng Vl, Masur H, *et al.* – Diagnosis of *Pneumocystis carinii* pneumonia: improved detection in sputum with use of monoclonal antibodies. *N Engl J Med* 1988; 318: 589–593.

12. Leigh TR, Hume C, Gazzard B, *et al.* – Sputum induction for diagnosis of *Pneumocystis carinii* pneumonia. *Lancet* 1989; 2: 205–206.
13. Jules-Elysee KM, Stover D, Zaman MB, Bernard EM, White DA. – Aerosolized pentamidine: effect on diagnosis and presentation of *Pneumocystis carinii* pneumonia. *Ann Intern Med* 1990; 112: 750–757.
14. Metersky ML, Catanzaro A. – Diagnostic approach to *Pneumocystis carinii* pneumonia in the setting of prophylactic aerosolized pentamidine. *Chest* 1991; 100: 1345–1349.
15. Levine SJ, Masur H, Gill VJ, *et al.* – Effect of aerosolized pentamidine prophylaxis on the diagnosis of *Pneumocystis carinii* pneumonia by induced sputum examination in patients with the human immunodeficiency virus. *Am Rev Respir Dis* 1991; 144: 760–764
16. Fahy JV, Daniel P, Chin P, *et al.* – Effect of aerosolized pentamidine prophylaxis on the clinical severity and diagnosis of *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis* 1992; 146: 844–848.
17. Levine SJ, Kennedy D, James H, *et al.* – Diagnosis of *Pneumocystis carinii* pneumonia by multiple lobe, site-directed bronchoalveolar lavage with immunofluorescent monoclonal antibody staining in human immunodeficiency virus-infected patients receiving aerosolized pentamidine chemoprophylaxis. *Am Rev Respir Dis* 1992; 146: 838–843.
18. Chouaid C, Housset B, Poirot JL, Roux P, Lebean B. – Cost effectiveness of the induced sputum technique for the diagnosis of *Pneumocystis carinii* pneumonia (PCP) in HIV-infected patients. *Eur Respir J* 1993; 6: 248–252.