Pneumocystis carinii: A review of an important opportunistic pathogen in AIDS

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MJ GILL, R READ. *Pneumocystis carinii*: A review of an important opportunistic pathogen in AIDS. Can J Infect Dis 1991;2(1):12-18. Since the first report of human infection with *Pneumocystis carinii* in 1942, cases of pneumonia due to this opportunistic pathogen have become increasingly common. Animal studies and clinical observations show that a significant depletion or dysfunction of T helper lymphocytes predisposes to clinical disease. Individuals with damaged T helper cells secondary to malignancies (eg, Hodgkin's lymphoma), drugs (eg, cyclosporine, steroids), or certain infections (eg, human immunodeficiency virus) are at particular risk. Serological studies suggest that disease is most often secondary to the reactivation of an asymptomatic infection, usually acquired during childhood. Increasing shortness of breath, a nonproductive cough and hypoxia often preceded by several weeks of lethargy, fever and weight loss are the classical features of *P carinii* pneumonia in acquired immune deficiency syndrome. Bronchoalveolar lavage is usually the optimal diagnostic test. Immunofluorescent staining on liquified sputum induced by nebulized saline appears to be a promising and noninvasive test. Early empiric therapy with trimethoprim-sulphamethoxazole (trimethoprim 5 mg-sulphamethoxazole 25 mg/kg/day every 6 h) or intravenous pentamidine (4 mg/kg/day) for 21 days is usually effective, but infection is not eradicated, and clinical disease is likely to recur. Prophylaxis using aerosolized pentamidine reduces the risk of pulmonary disease but can predispose to extrapulmonary infection. Improved in vitro and in vivo models of human pneumocystis infection would significantly increase understanding of the molecular biology of the organism, the pathogenesis of disease, and the optimal therapeutic regimens.

Key Words: *Immunosuppression*, Pneumocystis carinii, *Pneumonia*

Pneumocystis carinii: Aperçu d'un agent pathogène opportuniste important dans le syndrome d'immunodéficience acquise

RESUME: Depuis qu'on a rapporté le premier cas d'infection humaine à *Pneumocystis carinii* en 1942, les cas de pneumonie due à cet agent pathogène opportuniste se sont multipliés. Les études animales et les observations cliniques montrent qu'une diminution importante ou des anomalies fonctionnelles des cellules T prédispose à cette affection clinique. Les personnes dont les lymphocytes helper T ont été endommagés consécutivement à une affection maligne (ex: lymphome de Hodgkins), à des traitements médicamenteux (ex: ciclosporine, stéroïdes) ou à certaines infections (ex: virus d'immunodéficience humaine) sont surtout sensibles. Des études sérologiques suggèrent que la maladie est le plus souvent secondaire à la réactivation d'une infection asymptomatique habituellement acquise au cours de l'enfance. Une dyspnée croissante, une toux non productive et une hypoxie succédant souvent à plusieurs semaines de léthargie, de fièvre et de perte pondérale, constituent le tableau clinique classique de la

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pneumonie à *Pneumocystis carinii* dans le syndrome d'immunodéficience acquise. Le lavage bronchique est habituellement le test diagnostique optimal. La coloration immunofluorescente de l'expectoration liquéfiée provoquée par solution saline nébulisée semble être un test non invasif prometteur. Le traitement empirique précoce sous triméthoprime-sulfaméthoxazole à la dose de TMP 5 mg/SMX 25 mg/kg/j toutes les 6 heures ou sous pentamidine (4 mg/kg/j) pendant 21 jours est habituellement efficace, mais l'infection n'est pas éliminée et la maladie clinique récidivera probablement. Une aérosolthérapie prophylactique de pentamidine réduit les risques d'affection pulmonaire mais peut prédisposer à une infection extrapulmonaire. Une amélioration des modèles in vitro et in vivo de pneumocystose humaine contribuerait grandement à améliorer notre compréhension de la biologie moléculaire de l'organisme, de la pathogenèse de la maladie et des régimes thérapeutiques optimums.

OVER THE PAST DECADE THE INCIDENCE OF *Pneumocystis carinii* pneumonia has increased dramatically (1,2). This changing epidemiology has principally been secondary to the epidemic of human immunodeficiency virus (HIV) infection causing the acquired immune deficiency syndrome (AIDS). In this review of *P carinii* infection the authors will outline the current understanding of the host factors related to disease, the biology of the organism, the pathogenesis of infection, the clinical features of disease, and the recent developments in both diagnosis and therapy.

BACKGROUND

Chagas (3) originally described *P carinii* in the lungs of guinea pigs in 1909. In a 1912 review of the works of Chagas and Carini (4), the term '*Pneumocystis carinii*', was first used for this organism. The first association of *P carinii* infection with human illness was noted in 1942 when the organism was found in malnourished debilitated children suffering from what was called 'interstitial plasma cell pneumonia' (5,6). By the late 1960s occasional cases of *P carinii* pneumonia were seen in adults who were immunocompromised from either immunosuppressive therapy or an underlying disease (1). However, as a result of the epidemic of HIV infection the number of cases of *P carinii* pneumonia has increased dramatically in the past decade, and is likely to continue to increase in the foreseeable future (2,7). *P carinii* pneumonia is the initial manifestation of AIDS in 60% of cases in North America, and ultimately occurs in 85% of AIDS patients (8). It is fatal in 5 to 10% of initial episodes, and has been a major contributor to death in 25% of AIDS cases.

HOST SUSCEPTIBILITY

Animal models and clinical observations have clearly defined that the single most critical factor in determining host susceptibility to *P carinii* infection is T cell function. Models such as the severe combined immunodeficiency mouse model, the hydrocortisone-treated rat model and the nude rat model, with their varying immunodeficiencies, clearly show that the one shared critical immunodeficiency predisposing to *P carinii* infection is impaired T cell function (9-11). The benefit of adoptive transfer of T lymphocytes to nude mice in preventing *P carinii* pneumonia, and the absence of prophylactic or therapeutic benefit from passive immunization, further support the critical role of T cell function (12,13). These findings are supported by the clinical observation that individuals either having malignancies causing T cell dysfunction or receiving immunosuppressive drugs depressing T cell function, along with individuals with selective depletion of T cells (eg, AIDS patients), have the greatest predisposition to *P carinii* infection (14-16).

The recent epidemic of HIV infection, in which T cell function is relatively selectively destroyed, has provided some quantitative information on the T helper threshold for reactivation of *P carinii* infection. In a large prospective study of the natural history of HIV infection among homosexual men, the incidence of *P carinii* pneumonia was strongly associated with both the absolute T helper lymphocyte cell number and the relative T helper cell percentage. During the study, 13%, 24% and 39% of individuals with a T helper number of less than 200/mm^3 developed *P carinii* pneumonia by six, 12 and 36 months, respectively (17). Such information is of value both in determining the most appropriate time for intervention with prophylaxis against *P carinii* pneumonia and in determining more likely diagnoses (18).

TAXONOMY

In the original description of *P carinii*, Chagas (3) thought the organism was a variant of a trypanosome. However, since 1912 it has been traditionally viewed as a protozoa, due to its failure to grow on fungal media and its response to antiprotozoan drugs such as pentamidine. More recently it has been proposed that it should be classified as a fungus (19). The initial evidence to support this proposal was based on its affinity for

fungal stains, its presumed airborne mode of spread, and its ultrastructural characteristics. More recent convincing evidence has also classified *P carinii* as a fungus by analysis of the RNA component of the small ribosomal subunit, which is accepted as a strong marker of phylogenetic affiliations. The close affinity of the ribosomal RNA to that of fungi suggests that *P carinii* should be classified within the fungal group (19). Such information on the likely molecular biology of the organism may be of great value in determining potential targets for antimicrobial therapy.

EPIDEMIOLOGY

Some early serological studies looking for human antibodies against *P carinii* infection used an indirect immunofluorescent assay against intact organisms isolated from either human or rodent specimens. Other studies used an enzyme-linked immunosorbent assay (ELISA) and solubilized murine *P carinii* antigens. These studies failed to provide a consistent, convincing picture of the epidemiology of human infection (20,21). Subsequent studies have shown that human- and rat-derived strains of *P carinii* have significant antigenic differences, which may account for some of the discrepancies. More recent studies using human-specific *P carinii* antigens suggested that the vast majority of adults have already been infected with *P carinii* (22,23). Such findings support the concept that disease from *P carinii* is due to reactivation of a latent organism.

CLINICAL FEATURES

The symptoms and signs of *P carinii* pneumonia are relatively nonspecific. Chronic but increasingly severe symptoms such as fever, shortness of breath and a nonproductive or mildly productive cough associated with malaise and weight loss, are common findings in *P carinii* pneumonia (24). Characteristically symptoms have progressed over a period of several weeks to months. However, the duration of symptoms does not correlate with either the severity of the disease or the prognosis (25). The presentation of *P carinii* pneumonia in AIDS differs significantly from that in other immunocompromised patients. AIDS patients have a significantly longer median duration of symptoms prior to presentation (28 versus five days), a lower mean respiratory rate, and a higher mean room air arterial oxygen tension (25).

Physical examination of the chest is usually surprisingly unremarkable, with only occasional nonspecific bilateral crackles found. In advanced disease, respiratory distress, cyanosis and tachypnea are common. This nonspecific presentation may be even more subtle in patients known to be HIV positive and receiving prophylaxis against *P carinii* infection (26). For patients who have no apparent risk of HIV infection, the presence of oral candidiasis, lymphadenopathy, hairy leukoplakia, or cutaneous lesions of Kaposi's sarcoma should alert the physician to the possible diagnosis of *P carinii* pneumonia. In those known to be HIV infected, a T helper lymphocyte count of less than $200/mm^3$ also makes the diagnosis of *P carinii* pneumonia more likely (27). However, this marker appears not to be as useful an indicator of *P carinii* pneumonia in children seropositive for HIV (28).

LABORATORY INVESTIGATIONS

The radiological picture of *P carinii* pneumonia is most often that of diffuse interstitial infiltrates involving all portions of the lung. Diffuse and focal airspace consolidation, cystic changes and pneumatoceles, along with cavitation, can occasionally be seen. Lobar consolidation, pneumothorax and pleural effusions have also occasionally been associated with *P carinii* pneumonia. Approximately 5 to 25% of patients with proven *P carinii* pneumonia have absolutely normal chest x-rays at presentation (25,29,30). The use of aerosolized pentamidine to prevent *P carinii* pneumonia has been shown to alter the radiographic pattern if *P carinii* pneumonia should develop. Such patients are less likely to have diffuse infiltrates and more likely to have predominant infiltrates of the upper lobe (26).

Nonspecific abnormalities in pulmonary function tests are present with *P carinii* pneumonia. Reductions in vital capacity, total lung capacity, and single breath diffusing capacity of carbon monoxide are relatively common. An increased alveolar-arterial oxygen gradient, particularly marked on exercise, is also a common finding at presentation (31). The use of radioisotope scanning (gallium-67) has been shown to be a sensitive but nonspecific diagnostic test for *P carinii* pneumonia (32). However, due to cost and the inherent slow nature of the test, it is seldom appropriate as a first-line diagnostic test.

DIAGNOSIS

A definitive diagnosis of *P carinii* pneumonia can be made by the identification of the trophozoites or cysts of *P carinii* on respiratory specimens. Traditionally, open lung biopsy or transbronchial biopsy have been the diagnostic procedures of choice for patients with *P carinii* pneumonia (25). However, it was soon appreciated that, due to the higher parasite load often present in AIDS patients, bronchoalveolar lavage could be highly sensitive in achieving a diagnosis. The clinical specimen is often examined using a

methanamine silver stain for *P carinii* cysts. More recently, examination of sputum induced by nebulized 3% saline and then liquified with dithiothreitol has proved promising as a noninvasive test (33-35). The use of monoclonal antibodies has enhanced the sensitivity of this test beyond that achieved with the traditional Diff-Quik and toluidine blue 0 stains (34). In one study there were no false positive immunofluorescent stains, and a sensitivity of 92% was achieved (34). However, in patients receiving aerosolized pentamidine, one study suggested that the parasite load may be so low that transbronchial biopsy is necessary for diagnosis (26).

PROGNOSTIC MARKERS

Severe abnormalities on initial chest radiography and alveolar-arterial oxygen differences greater than 30 mmHg have been associated with a higher mortality during the acute episode of *P carinii* pneumonia (36). Decreased long term survival after the diagnosis of pneumonia also correlated with severity of interstitial edema on the initial biopsy, and an elevated alveolar-arterial oxygen difference. One recent study has suggested that neutrophilia greater than 5% on bronchoalveolar lavage is also a poor prognostic marker (37). The persistence of pneumocystis cysts after three weeks of therapy has also been associated with decreased long term survival (36).

THERAPY

In the treatment of acute *P carinii* pneumonia in AIDS, 21 day regimens of either trimethoprim-sulphamethoxazole (trimethoprim 5 mg/sulphamethoxazole 25 mg/kg/day every 6 h) or intravenous pentamidine (4 mg/kg/day) have approximately equal efficacy (38). One study, however, has suggested that survival in patients treated with trimethoprim-sulphamethoxazole may be superior to that in those treated with pentamidine (86% versus 61%, respectively) (39). Unfortunately, both pentamidine and trimethoprim-sulphamethoxazole have significant side effects, particularly in AIDS patients. The incidence of these side effects can be as high as 60%. Rash, anemia, leukopenia, thrombocytopenia, nausea and vomiting occur and are seen most commonly with trimethoprim-sulphamethoxazole. With pentamidine, nephrotoxicity, hypotension, cardiac dysrhythmias and hypoglycemia are the most frequent problems (38,39). Although significant, the toxicity associated with these standard regimens is rarely life threatening and can often be diminished by dose reduction, allowing the drug to be continued (39). Attempts to circumvent the toxicity of intravenous pentamidine by delivering treatment doses by inhalation have been disappointing, especially in moderate to severe *P carinii* pneumonia (40,41).

Due to the limitations of these two treatments, other therapeutic regimens have been investigated. The combination of dapsone 100 mg/day plus 25 mg/kg every 6 h of oral trimethroprim for 21 days has been shown to be effective and well tolerated in patients with mild *P carinii* pneumonia (42). The main adverse effects encountered were methemoglobinemia and anemia. A comparative trial of trimethoprim-sulphamethoxazole and trimethoprim-dapsone for treatment of mild to moderate *P carinii* pneumonia has shown equal efficacy, with fewer adverse effects in the trimethoprim-dapsone arm (43). One open uncontrolled study has evaluated trimetrexate 30 mg/m^2/day for 21 days in the treatment of patients with *P carinii* pneumonia who could either not tolerate, or had failed to respond to, standard drug regimens (44). This preliminary study suggested that the combination of trimetrexate with leucovorin rescue 20 mg/m^2 every 6 h for 23 days was safe and effective for the treatment of such patients (44). Eflornithine, an experimental drug which inhibits polyamine synthesis, has also shown early promise as therapy for patients failing conventional therapy for *P carinii* pneumonia (45). One further uncontrolled study has suggested that clindamycin (300 to 450 mg every 6 h) and daily primaquine (15 mg base) may be effective for treatment of *P carinii* pneumonia with few side effects (46,47).

Most patients on these regimens improve progressively during therapy, but some experience radiographic and clinical deterioration about five days after starting treatment. This is believed to be caused by an inflammatory response to dead or dying organisms, and usually resolves by days 7 to 10 of therapy. Switching agents on the basis of this deterioration is not advocated (48).

For patients with moderate to severe *P carinii* pneumonia (arterial-alveolar gradient greater than 35 mmHg or a partial pressure of oxygen less than 70 mmHg on room air), a consensus panel has recommended the early adjunctive use of systemic corticosteroids to reduce the likelihood of death, respiratory failure and deterioration in oxygenation (49). A dose of prednisone 40 mg bid (days 1 to 5), reduced to 20 mg bid (days 6 to 10), and finally stopping after a dose of 20 mg daily between days 11 and 21, was used in the largest study supporting the use of steroids (50). Other studies also support the early use of steroids in seriously ill patients (51,52). However, the potential value of steroids in patients failing conventional therapy after 12 h is unknown, and ongoing

clinical surveillance for adverse effects in patients receiving steroids is recommended (50).

PROPHYLAXIS

Despite receiving antiviral therapy such as zidovudine, approximately 60% of AIDS patients suffer from a relapse of *P carinii* pneumonia within the first year after diagnosis (18). This high attack rate has caused a variety of different drugs to be studied for use as secondary prophylaxis to prevent relapse of *P carinii* pneumonia, as well as primary prophylaxis for patients at highest risk of *P carinii* pneumonia (T helper count less than 200/mm^3 or less than 20%).

Primary prophylaxis with trimethoprim-sulphamethoxazole (160 mg trimethoprim/800 mg sulphamethoxazole) administered twice daily with leucovorin rescue (5 mg daily) successfully prevented *P carinii* disease in a placebo controlled trial of AIDS patients with Kaposi's sarcoma (53). Unfortunately, 17% of patients had to discontinue therapy due to unacceptable side effects, and 50% had some form of adverse effect. Other drugs such as pyrimethamine-sulphadoxine, dapsone or dapsone-trimethoprim have been proposed as prophylactic agents, but await proper evaluation in controlled trials (54,55).

Aerosolized pentamidine has been accepted as providing both primary and secondary prophylaxis against *P carinii* pneumonia, and has been licensed for use in the United States (18). One approved dose is 300 mg every four weeks administered by a nebulizer meeting a certain set of standards (usually a Respirgard II Jet Nebuliser [Marquest, Colorado]); this recommendation has been supported by a recent randomized controlled trial comparing 30 mg every two weeks, 150 mg every two weeks, and 300 mg once monthly (56). In Canada, for secondary prophylaxis after a large Canadian multicentre trial, a second approved dose of pentamidine (60 mg every other week after an induction period of 60 mg on five days during the first two weeks) administered by an ultrasonic nebulizer (FISONEB™) has been licensed for use (57).

At present the optimal dosage and form of prophylaxis is not yet determined, but prophylaxis in some form is currently recommended for all individuals with a T helper count less than 200 cells/mm^3 and/or 20% of total lymphocytes (18).

EXTRAPULMONARY DISEASE

P carinii can cause infections other than *P carinii* pneumonia in patients with impaired T cell function. *P carinii* has been shown to cause infections in the skin, liver, thyroid, bone marrow and retina (58-65). Many but not all such patients had received aerosolized pentamidine. This form of drug administration may achieve adequate drug concentrations in the lung, but subtherapeutic levels elsewhere. *P carinii* should be suspected in any HIV-infected individual who presents with unexplained multisystem disease, particularly if he or she is receiving aerosolized pentamidine.

SUMMARY

As the number of individuals with impaired immunity from HIV infection increases, it is inevitable that *P carinii* will become a common infection in clinical practice. Unfortunately, an inadequate understanding of the pathogenesis of infection and a limited ability to study the organism in vitro and in vivo have hindered the development of safe and effective measures for prophylaxis and therapy. However, improved diagnostic and therapeutic approaches are currently being developed which offer promise in the control of this disease.

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