Pneumonia due to Pneumocystis carinii is the most common life-threatening infection in patients with the acquired immunodeficiency syndrome (AIDS). It occurs at least once in some 60 percent of patients, and approximately one third of the pneumonic episodes are fatal. Despite an increasing awareness of other opportunistic infections in the syndrome, the proportion of patients who have had P carinii pneumonia by the time they are reported to the Centers for Disease Control has remained remarkably constant. As the incidence of AIDS is rising—notification rates are currently averaging 100 cases per week in the United States and ten per week in Europe—it is inevitable that an increasing number of chest physicians will be involved in the care of these patients.

Pneumocystis carinii has been recognized as a cause of pneumonia in immunosuppressed patients for approximately 40 years, and important advances have been made in the treatment and prophylaxis of the pneumonia, especially in patients receiving immunosuppressive therapy for malignant disease or organ transplantation. Patients with AIDS, however, present a special problem: diagnosis of Pneumocystis pneumonia in these patients is frequently delayed because the symptoms tend to develop gradually, often in previously healthy subjects, and treatment is complicated by an unusually high incidence of adverse reactions to specific therapeutic agents. Furthermore, these individuals have a very poor prognosis, irrespective of the treatment they receive: the median survival time of AIDS patients with P carinii pneumonia ranges from 35 weeks in patients with Pneumocystis pneumonia alone, to 44 weeks when there is coexistent Kaposi's sarcoma. The overriding priorities of management, therefore, are comfort and quality of life. It is especially important that all diagnostic and therapeutic decisions be tempered by compassion and attention to the individual patient's needs.

CLINICAL AND ROENTGENOGRAPHIC FEATURES

The clinical and roentgenographic features of Pneumocystis pneumonia are nonspecific, and diagnosis may require a high degree of suspicion. It is important to enquire about sexual preference, especially in men, and intravenous drug abuse, in any patient with unexpected respiratory symptoms or an unexplained abnormality on chest x-ray film. Symptoms often develop more gradually than in other immunosuppressed individuals with P carinii pneumonia, but it is worth remembering that the infection can present abruptly in these patients. Malaise, fever, nonproductive cough, and dyspnea are the usual symptoms, but chills and chest pain may also occur, and some patients do produce sputum. Oral candidiasis or generalized lymphadenopathy, though not always present, are useful clues to the diagnosis of AIDS, but physical signs in the chest are often unimpressive or absent. The chest roentgenogram typically shows diffuse bilateral pulmonary infiltrates, although the infiltrates may be confined to the upper or lower zones, and they are occasionally unilateral at the time of presentation. In up to 5 percent of cases, however, the lungs are roentgenographically clear, and this figure may well increase as patients are seen earlier in the disease. Enlarged hilar or mediastinal lymph nodes have been described in as many as one third of patients, but pleural effusions are uncommon and more suggestive of Kaposi's sarcoma.

DIAGNOSIS

Choice of Procedure

Diagnosis of P carinii pneumonia rests on identification of the organism in lung tissue or respiratory secretions. There are no serologic tests for identifying patients with active disease. A number of studies have demonstrated the value of fiberoptic bronchoscopy as a method of obtaining suitable specimens. In the series from a recent workshop of the National Heart,
Lung and Blood Institute (NHLBI), a retrospective study of the pulmonary complications of AIDS in six centers over a three-year period, bronchoscopy was performed in 368 episodes of Pneumocystis pneumonia and the diagnosis was established in 348 (95 percent) of them. Fixed tissue specimens and touch imprints of tissue, both obtained by transbronchial biopsy, had diagnostic yields of more than 95 percent; bronchoalveolar lavage fluid alone had a yield of 79 percent; and although the yield with brush biopsies was only 37 percent, there were four instances in which these provided the only positive specimen. In a number of smaller published studies, the results with bronchoalveolar lavage have been even more impressive, with yields comparable to those of transbronchial biopsy, possibly because the NHLBI analysis did not distinguish true bronchoalveolar lavage, in which the bronchoscope is wedged into a subsegmental bronchus before instilling and withdrawing fluid, from bronchial washings, in which only the proximal large airways are irrigated. The relatively low diagnostic yield from bronchial brushing, a feature of most studies, probably reflects the mainly intraalveolar localization of P carinii. Bronchoscopic procedures are effective for diagnosing the other pulmonary complications of AIDS, with the exception of Kaposi's sarcoma, and they are also relatively safe in these patients. Transbronchial biopsy carries the usual 5 to 8 percent risk of pneumothorax, but significant hemoptysis is rare, and there have been no deaths. Fiberoptic bronchoscopy is therefore the diagnostic procedure of choice in all patients with AIDS or suspected AIDS who are thought to have P carinii pneumonia. In patients with bleeding disorders and patients undergoing mechanical ventilation, the procedure should be restricted to bronchoalveolar lavage, but in all other subjects, the bronchoscopy should probably include transbronchial biopsy as well, with touch imprints of tissue in addition to fixed tissue specimens. Ideally, bronchial brush biopsies should be obtained at the same time, but brushing ought not to be performed alone. Open lung biopsy should be considered only in patients who have had a nondiagnostic bronchoscopy, and even then it is often preferable to repeat the bronchoscopy first.

**Indications for Bronchoscopy**

Although fiberoptic bronchoscopy provides a safe and highly effective means of obtaining pulmonary specimens in patients with AIDS and Pneumocystis pneumonia, there are a number of issues regarding its use which need to be clarified by further study.

The first issue concerns previously healthy subjects from high risk groups for AIDS who present with pulmonary symptoms but have a normal chest roentgenogram. Which of these patients should undergo bronchoscopy? A variety of noninvasive studies have been performed in an attempt to select the patients most likely to have Pneumocystis pneumonia. The arterial oxygen tension is a relatively insensitive screening test, as it is normal (>80 mm Hg) in approximately 20 percent of patients with Pneumocystis pneumonia and AIDS. The alveolar minus arterial partial pressure of oxygen (P[A-a]O₂) may be more sensitive, but it is still unclear whether the measurement must be made on exercise in order to be useful. The diffusing capacity for carbon monoxide (Dco) is less than 70 percent of the predicted value in almost all patients with AIDS and P carinii pneumonia, but low values are also seen in high risk patients without AIDS. The gallium scan is another highly sensitive method for detecting *Pneumocystis* pneumonia: when read in the conventional way, it also has a low specificity, but in a recent study of 22 AIDS patients, the specificity was increased to 90 percent, while retaining 100 percent sensitivity, by using a graded scoring system for pulmonary uptake of the nuclide. Gallium scanning is expensive, and takes one to three days to complete, but these findings are encouraging and justify further assessment of the technique.

The second issue concerns patients who have had a previous episode of Pneumocystis pneumonia. Patients with AIDS who have clinically recovered from *P carinii* pneumonia sometimes fail to eliminate the organisms from their lungs. Three to six weeks after starting specific therapy, 25 to 67 percent of AIDS patients still have *P carinii* detectable in pulmonary tissue or lavage specimens. There are insufficient data to know how much longer the organisms persist, and it is unclear whether the persistent forms observed are all viable and pathogenic. However, they may complicate the interpretation of subsequent diagnostic procedures. The identification of *P carinii* during a second pneumonic episode, therefore, is of unknown significance, and it is particularly important to attempt to exclude other causes of pulmonary infiltrate before concluding that there is a recurrence of Pneumocystis pneumonia.

A third issue is whether bronchoscopy could be replaced by an even simpler procedure in some patients. One technique under investigation is the collection of pulmonary lavage fluid with a disposable catheter introduced through the mouth, while the preliminary findings of another study indicate that most cases of *P carinii* pneumonia in AIDS can even be diagnosed from induced sputum. The effectiveness of these techniques for diagnosing other infections, and their value in patients with normal chest roentgenograms, have not been determined, but the procedures are safe and inexpensive, and they promise to be useful as screening tests, especially in centers with
larger numbers of AIDS patients.

Stains for P carinii

The results of stains for P carinii should be available to the clinician within a few hours, so that treatment can be started promptly. It should be appreciated that the classic stain for the organism, Gomori's methenamine silver stain, performed on fixed tissue, demands time and expertise, and many laboratories are unable to provide a report on the same day as bronchoscopy. More rapid results can be obtained from fresh tissue or frozen sections and by using other stains. The toluidine blue-O stain and rapid silver stains are reliable methods for identifying the cyst, while the Giemsa and Gram-Weigert methods will also stain the sporozoites and trophozoites. Recent reports attest to the value of the standard Gram stain for identifying both the cyst wall and the internal sporozoites; although this method may be insufficiently sensitive to rely on its use alone, it is simple and often permits identification of the organism within a few minutes.

TREATMENT

The treatment of P carinii pneumonia in AIDS has proved to be unexpectedly frustrating. Anti-Pneumocystis drugs form the mainstay of therapy, but supportive measures, including mechanical ventilation and treatment of coexistent infections, are important in individual patients. There is general agreement that empiric therapy should not be initiated unless specific diagnosis is delayed, since the anti-Pneumocystis drugs in use are potentially hazardous in AIDS patients. Furthermore, although Pneumocystis pneumonia is the most common complication of the syndrome, the differential diagnosis of pulmonary infiltrates in patients with AIDS is wide, and it is common for other opportunistic infections, and/or Kaposi's sarcoma, to coexist with P carinii. In the NHLBI series, 228 (48 percent) of 441 patients with lung involvement had other opportunistic infections, approximately half with and half without P carinii, and 36 (8 percent) had Kaposi's sarcoma of the lung in addition to P carinii.

Choice of Anti-Pneumocystis Drug

To date, most patients with AIDS and Pneumocystis pneumonia have been treated initially with high doses of intravenous trimethoprim-sulfamethoxazole, as this is clearly the regimen of choice in non-AIDS patients with P carinii infection. Fewer than half (approximately 45 percent in each of the two largest series*) of AIDS patients treated in this way, however, have completed their course of trimethoprim-sulfamethoxazole successfully. The other patients have either failed to respond or have experienced adverse reactions to the drug combination. Leukopenia, skin rashes, drug fever, hepatotoxicity, and thrombocytopenia have been sufficiently severe to prompt a change of treatment in 18 to 50 percent of patients.** These findings are in sharp contrast to cure rates of 64 to 87 percent, with a very low incidence of serious side-effects reported for other immunosuppressed patients treated in the same way. The other drug approved for use in P carinii pneumonia is pentamidine. This was the first agent shown to be effective in Pneumocystis pneumonia, but it was displaced as the drug of choice in the pre-AIDS era, when trimethoprim-sulfamethoxazole was found to have fewer adverse effects. For this reason, the use of pentamidine in AIDS has, until recently, usually been reserved for patients intolerant of, or unresponsive to, trimethoprim-sulfamethoxazole. A prospective comparison of the two drugs as first-line therapy is currently in progress.7 Preliminary results suggest that the incidence of adverse effects is the same irrespective of the drug used initially and that pentamidine may be more efficacious than trimethoprim-sulfamethoxazole. It is possible, therefore, that pentamidine may be superior to trimethoprim-sulfamethoxazole for the initial treatment of pneumocystosis in AIDS, but data from additional comparative trials are needed before a firm recommendation can be made. For the time being, neither agent is clearly superior, but there are certain patients for whom one or the other may be preferable. Trimethoprim-sulfamethoxazole should be avoided in patients who have a history of allergy to either of its components, and also in patients on fluid restriction since its intravenous administration requires at least 1,200 ml fluid daily. It is the preferred agent in patients with chronic renal failure, however, as pentamidine is a more frequent cause of renal dysfunction.** Intravenous pentamidine is probably the drug of choice when there is pretreatment thrombocytopenia, but there is no clear choice in AIDS patients with a low white cell count prior to treatment, since both drugs can cause leukopenia.7,11

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole is usually administered intravenously in a dose of 20 mg/kg of trimethoprim and 100 mg/kg of sulfamethoxazole daily, divided into four doses. It can also be given orally, at the same dosage, and there is evidence that this is effective in AIDS,8 but most physicians prefer the intravenous route because failures attributed to poor absorption of the oral preparation have been reported in other immunosuppressed patients. Parenteral therapy also eliminates problems of compliance, which may be especially important in drug abusers. Compliant patients who have responded well to intravenous therapy may be changed to the oral drug after 10 to 14 days, and managed as an outpatient, but discharge before the end of that time is inadvisable as most
adverse reactions to trimethoprim-sulfamethoxazole in these patients occur during the second week of treatment. 2,3 Although blood levels of trimethoprim and sulfamethoxazole correlate with clinical efficacy in Pneumocystis pneumonia, it is unnecessary to make these measurements in clinical practice. Folinic acid should not be given routinely to patients receiving trimethoprim-sulfamethoxazole, for there is no evidence that the vitamin prevents or reverses the cytopenias observed with this agent in AIDS patients, and there is a small risk that it could impair the efficacy of the antibiotic. The cytopenias which occur with trimethoprim-sulfamethoxazole in AIDS patients appear usually to have an immunologic rather than a metabolic basis, but there may be exceptions to this: a recent report of megaloblastosis in four of five AIDS patients who developed leukopenia while receiving trimethoprim-sulfamethoxazole4 suggests that it is probably still prudent to prescribe folicin acid in this context if the white cell count is actually falling. Although trimethoprim-sulfamethoxazole and pentamidine can both cause leukopenia, the mechanism is probably different with the two agents, for experience has shown that it is safe to change to pentamidine in patients who become leukopenic while receiving trimethoprim-sulfamethoxazole.4 Other indications for changing to pentamidine include progressive or severe thrombocytopenia, worsening hepatic function, severe skin rashes, significant drug fever, and rarely, renal toxicity.

It would be helpful to know whether the adverse effects associated with trimethoprim-sulfamethoxazole in AIDS are dose-related and whether such high doses are necessary. The current recommendations are based on the results of a study of pneumocystis in leukemic children, in which the high dosage regimen now used was more efficacious than a fourfold smaller dose. The value of the high dose given intravenously has been confirmed in other patients, but there has been little work with intermediate doses. Perhaps it is time to define the optimal dosage and scheduling of trimethoprim-sulfamethoxazole when treating P. carinii pneumonia in AIDS patients.

Pentamidine

Pentamidine is available in two forms. The isethionate salt, available commercially, is given in a dose of 4 mg of the salt/kg/day. The dose of the methanesulfonate salt, available from the Centers for Disease Control, is usually expressed as the weight of pentamidine base only—the recommended daily dose is 2.3 mg of pentamidine base/kg. Both salts can be given intramuscularly, but this is associated with a risk of sterile abscesses at the injection sites, and we prefer slow intravenous injection. Intravenous administration carries a risk of severe hypotension, but this can be avoided by infusing the drug over a period of at least 60 minutes, with frequent measurements of blood pressure. Other adverse effects of pentamidine include neutropenia, renal impairment, hepatic dysfunction, and hypoglycemia,4,11 followed rarely by sustained hyperglycemia.

Response to Treatment

Patients with AIDS exhibit a slower clinical and roentgenographic response to treatment than other patients with P. carinii pneumonia.1,10 This is important when assessing the response to either trimethoprim-sulfamethoxazole or pentamidine: each agent should be given a trial of at least four days before considering a change of treatment. Furthermore, the assessment must be largely clinical: serial pulmonary function tests do not appear to correlate with short-term clinical improvement, and chest roentgenograms do not often change before seven to ten days.1 If treatment with the first drug has failed, it should be discontinued. There is no evidence that simultaneous treatment with trimethoprim-sulfamethoxazole and pentamidine will prolong survival,10 and their toxicities could be additive.

It is generally recommended that treatment with either pentamidine or trimethoprim-sulfamethoxazole be continued at least 14 to 21 days. The optimal duration of therapy for AIDS patients is uncertain, however, for it is not yet clear what constitutes a cure of P. carinii infection in these patients. The relapse rate of Pneumocystis pneumonia in AIDS patients has been 20 percent to 30 percent,10,12 and the presence of P. carinii on repeat pulmonary lavage or biopsy correlates poorly with clinical progress. There is evidence from one study that prolonging therapy up to 35 days reduces the number of patients with persistent P. carinii in pulmonary tissue or washings,5 but it is not known whether such patients are at reduced risk of recurrent clinical disease, and there are no studies in which P. carinii has been eradicated from every patient. Until the goal of treatment has been defined, it will be impossible to determine the optimal duration of therapy.

Despite the difficult and prolonged course of P. carinii pneumonia in AIDS, the overall prognosis for each pneumonic episode is similar to that in other immunosuppressed patients.10 Failure to respond to trimethoprim-sulfamethoxazole,2,10 the need for mechanical ventilation,5 and second episodes of Pneumocystis pneumonia10 are all associated with a poor prognosis. The use of corticosteroids in critically-ill patients is controversial.

Prevention

Can Pneumocystis pneumonia be prevented in AIDS? There have been no controlled studies of long-term prophylaxis with anti-Pneumocystis drugs in the syndrome. Trimethoprim-sulfamethoxazole, at low
Dosage, has been effective in preventing overt pneumocystis infection in other immunosuppressed subjects, but in AIDS, the risk of adverse reactions probably outweighs potential benefits for most patients. Promising results have been obtained with an alternative preventive agent, pyrimethamine-sulfadoxine (Fansidar), given in a dose of one tablet weekly, but these must be tempered by recent reports to the Centers for Disease Control of six deaths attributed to this drug combination in otherwise healthy subjects who were using it for antimalarial prophylaxis.

The Future

Trimethoprim-sulfamethoxazole and pentamidine are the only anti-Pneumocystis agents which have been studied in controlled trials, but other agents warrant further study. Alpha-difluoromethylornithine, an inhibitor of polyamine biosynthesis, has been used with success in six AIDS patients intolerant of, or unresponsive to, conventional therapy; a small number of patients receiving immunosuppressive therapy have been treated successfully with a combination of pyrimethamine and sulfadiazine, but there are no reports of use of this drug combination in AIDS; and recent studies in animals suggest that diamodophenylsulphone (Dapsone) may be effective against P carinii. Intravenous gamma-globulin has recently been reported to prolong survival in AIDS patients with Pneumocystis pneumonia, possibly by inhibiting proliferation of B-lymphocytes and thereby limiting the severity of lymphocytic pulmonary infiltrates, but an insufficient number of patients have been studied to permit a clear appraisal of its efficacy.

When considering treatment and prevention of pneumocystosis in AIDS, it is sobering to remember how little we know about the organism itself or the pathogenesis of the pneumonia. Until now, detailed studies of P carinii have been limited by our inability to propagate the organism routinely in vitro. A recent report of successful culture in a lung-derived cell line may offer hope for new investigative approaches, but the reliability of this system needs to be assessed by further study. Experiments in animals indicate that P carinii is acquired by the air-borne route, and many hospitals recommend that masks be worn by coughing AIDS patients whenever they leave their room, and by personnel in direct and sustained contact with such patients. Serologic studies, however, suggest that asymptomatic Pneumocystis infection is common in the general population. Overt pneumonia in AIDS is believed to represent activation of latent infection, but proof of this is lacking.

Pneumocystis pneumonia was the first infection described in AIDS and it remains a common presentation of the syndrome. It is also a major cause of morbidity and mortality in these patients. Whatever foreseeable advances are made in our understanding of AIDS, the management of individual patients will still require careful attention to the specific therapy of opportunistic infections, especially P carinii pneumonia. For the time being, the treatment of these infections remains the only hope for patients with AIDS.

References


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PCP in Patient with AIDS (Catteral, Pottsman, Remington)