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MINIREVIEW

Recent Advances in the Diagnosis, Treatment, and Prevention of *Pneumocystis carinii* Pneumonia

RICHARD T. DAVEY, JR.,[1]* AND HENRY MASUR[2]

Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases,[1] and Critical Care Medicine Department, Clinical Center, National Institutes of Health,[2] Bethesda, Maryland 20892

With the emergence of the acquired immunodeficiency syndrome (AIDS) in the early 1980s, understanding of the pathogenesis and therapy of *Pneumocystis carinii* pneumonia has broadened considerably. In previous decades, pneumocystis pneumonia was a rare infection occurring primarily in congenitally immunodeficient or nutritionally deprived children and in patients with advanced malignancy. In the 1960s and early 1970s, fewer than 100 cases per year were documented (43). Over the past 8 years, in contrast, approximately 80,000 AIDS patients have developed this infection at some point during their clinical illness (26). Recent projections are that up to 150,000 episodes of pneumocystis pneumonia could occur in the United States over the next 3 years (12), the vast majority of which would be in individuals currently already infected with human immunodeficiency virus type 1 (HIV-1). Although the precise effect that earlier, more widescale application of effective antiretroviral therapies and more aggressive antipneumocystis prophylactic regimens will have on the incidence of new episodes is difficult to predict, their adoption clearly strengthens the possibility that the incidence of new cases of symptomatic infection will drop dramatically despite a burgeoning number of HIV-1-infected patients. This review highlights some recent advances in the management of pneumocystis pneumonia which lend support to this optimism, particularly with reference to HIV-1-related disease.

THE ORGANISM

Although the role of *P. carinii* as a cause of pneumonia in the immunocompromised host has been known for over three decades, current efforts to better define the pathophysiology of infection with the strain(s) causing disease in humans are stymied by the inability to culture the organism reliably in vitro (45). Although both the cyst and trophozoite forms of *P. carinii* can be readily harvested from infected patients by methods such as bronchoalveolar lavage (BAL), efforts to propagate these specimens in long-term axenic culture have consistently failed. Similarly, inoculation of human-derived organisms into animals has failed to produce disease. As a consequence of this, there continues to be considerable interest in the development of appropriate animal models of infection with this organism. While rare instances have been reported in which host animals, such as rabbits, develop transient pneumocystis infection even in the absence of exogenously supplied immunosuppression (35), the most widely used models have been those involving corticosteroid-treated rats (9). These rodent models have proven quite useful both for harvesting organisms in bulk and for studying therapeutic and prophylactic agents. Currently, organisms derived from these models can be cultivated in vitro with modest growth for short periods, allowing limited drug susceptibility testing and immunologic studies (17).

Largely on the basis of morphological appearance, ultrastructural similarities, and antibiotic susceptibilities, *P. carinii* has traditionally been classified as a eucaryotic member of the *Protozoa*. This classification is tenuous, however, inasmuch as comparatively little is known about the life cycle of the organism, its metabolic requirements, and its natural reservoir(s). It is known, for example, that respiratory contact can often lead to pneumocystis infection in susceptible animals, as demonstrated when nude mice share a common air supply with wild-type rats in barrier cages (44). Yet, unlike those for most members of the *Protozoa*, the infective stage of the organism has never been identified, nor has symptomatic infection been successfully transmitted in the laboratory setting from one host animal to another by direct inoculation of isolated cysts or trophozoites. The latter findings are especially atypical for members of the *Protozoa* (in which growth within the definitive host is usually required for development of the infectious stage of the organism) and argue strongly for the existence of at least the infective stage of *P. carinii* being outside the mammalian host. Recently, refinements in nucleic acid sequence analysis have cast even further doubt upon the taxonomy of *P. carinii*. Using small-subunit rRNA (16S-like rRNA) comparisons, there are now data to suggest that this organism has a much stronger phylogenetic link with members of the *Fungi* (7, 39).

DIAGNOSIS

The initial step in the diagnosis of *P. carinii* pneumonia is the recognition of which patient populations are at high risk for development of this disease. Patients receiving intensive cytotoxic chemotherapy for malignancies, transplant recipients undergoing immunosuppression (especially those receiving cyclosporine), patients with adult T-cell leukemia as a consequence of infection with human T-cell leukemia virus type 1, and HIV-1-infected individuals are all groups which have been found to have a particularly high susceptibility to pneumocystis pneumonia. In many cases the period of maximal susceptibility to this infection can be predicted with reasonable accuracy. For example, children with acute lymphocytic leukemia are most prone to this infection during early intensive maintenance chemotherapy (rather than during induction). Similarly, the median time of onset of this infection in adult bone marrow transplant recipients is 9 weeks after transplant (25).

* Corresponding author.

The advent of the AIDS pandemic has provided considerable insight into the factors governing host susceptibility. Measurement of the peripheral CD4+ cell count has been shown to have substantial value in predicting the cause of pneumonia in an HIV-1-infected individual, with pneumocystis pneumonia occurring almost exclusively in those patients whose CD4+ counts are below 200 cells per mm^3 and particularly in those whose counts are less than 100 cells per mm^3 (5, 24). Indeed, within this patient group as a whole, the CD4+ count has proven useful on epidemiologic grounds for assessing relative risk over time for development of pneumocystis pneumonia when patients are stratified according to initial CD4+ counts. For example, on average an HIV-1-infected individual with a CD4+ count greater than 700 cells per mm^3 has only a 3.8% chance of developing pneumocystis pneumonia within a 3-year period, whereas in a patient whose CD4+ count is in the range of 201 to 350 cells per mm^3, this risk rises to 22.9% over the same 3-year period (5). It should be cautioned that the value of CD4+ counts in predicting the period of increased susceptibility to this pneumonia may not be valid for other forms of immunosuppression; their utility in transplant recipients or cancer patients, for example, remains to be determined.

Pneumocystis pneumonia may be manifested differently in HIV-1-infected patients and those with other forms of immunodeficiency (19). In oncology patients undergoing chemotherapy, for example, its presentation is typically that of a rapidly progressive disease, with severe hypoxia and dyspnea developing within 5 to 10 days of initial manifestations. In AIDS patients, in contrast, the onset of symptoms is usually more insidious and prolonged than in non-AIDS patients, with nonspecific symptoms such as low-grade fever, mild cough, dyspnea on exertion, fatigue, and weight loss often being present weeks to months before the pulmonary symptoms become sufficiently severe to prompt diagnostic intervention. A delay in diagnosis in these cases affects the prognosis unfavorably, in that experience has shown that early and accurate diagnosis of pneumocystis pneumonia has beneficial consequences upon outcome and can minimize toxicity associated with therapy. Increasing recognition of this altered presentation of disease, by prompting earlier adoption of appropriate therapeutic strategies, may reduce the incidence of severe or secondary complications of the infection.

Considerable insight has been gained in our understanding of which factors are of value in predicting the clinical course of AIDS-related pneumocystis pneumonia. The presence of severe abnormalities on the initial chest radiograph and an alveolar-arterial oxygen gradient ($AaPO_2$) greater than 30 mm Hg at the start of therapy are both associated with higher mortality during the period of acute treatment for this infection (3). In addition, the severity of interstitial edema on transbronchial biopsy, the presence of an elevated $AaPO_2$ at the time of diagnosis, and persistence of pneumocystis cysts after 3 weeks of therapy all correlate with decreased long-term survival in these patients. Some investigators have found that elevated lactate dehydrogenase levels correlate with the presence of *P. carinii*, the severity of clinical disease, and survival (15, 46). The prognostic value of these findings in an individual episode is uncertain, however, and hence clinical monitoring of this factor in a given patient must be interpreted with caution.

The method(s) of choice to diagnose pneumocystis pneumonia has undergone considerable evolution during the past decade. Prior to the first description of the use of BAL for the diagnosis of this infection in 1978 (16), open-lung biopsy was considered the diagnostic procedure of choice in susceptible patients. Because of its almost 100% sensitivity for this disease, as well as the occasional failure of more recently introduced methods to establish a definitive diagnosis in some cases, open-lung biopsy continues to have a role today (32). However, because of the morbidity associated with the procedure, as well as the recently documented effectiveness of BAL in establishing a diagnosis in most cases, open-lung biopsy must now be considered a procedure of last resort to be used when other, less invasive methods have failed or are contraindicated. Improvements in fiber-optic bronschoscopy have allowed BAL, with or without transbronchial biopsy, to emerge as a leading diagnostic technique in the evaluation of pulmonary disease in both AIDS and non-AIDS patients (4, 10, 38). The presence of pneumocystis organisms in a BAL specimen from an untreated patient is highly suggestive of clinical infection and therefore almost always merits active therapy (30). The sensitivity of BAL alone in the diagnosis of pneumocystis pneumonia ranges from 86 to 97% (31). When combined with transbronchial biopsy (which has an independent sensitivity of between 88 and 97% for this disease), the sensitivity of this procedure for detecting *P. carinii* approaches 100% (4).

Diagnosis by expectorated sputum examination is another technique that has undergone considerable refinement over the last several years. While colorimetric staining (e.g., Gomori methenamine silver nitrate, toluidine blue O, and Giemsa stains) of expectorated sputum alone has a comparatively poor yield, several groups have found that the sensitivity of this procedure can be markedly increased when sputum specimens are obtained by hypertonic saline nebulization (2, 33). Estimates of up to 55% sensitivity have been described using sputum induced by the nebulization technique, which can be further improved to 78% by addition of a sputum liquefication step using reducing agents such as dithiothreitol (47). Immunofluorescence staining of sputum specimens using monoclonal antibodies against surface antigens of *P. carinii* augments the diagnostic sensitivity of these noninvasive techniques even further (18). The monoclonal antibody staining procedure, commercially available in kit form as either a direct or indirect fluorescent-antibody technique, is comparatively simple to perform, decreases the processing time of a specimen, and also markedly improves the specificity of staining seen over that with colorimetric dyes. In a recent trial comparing conventional staining and immunofluorescence staining of sputum samples from documented cases of infection, use of the monoclonal antibody increased the sensitivity of the procedure to over 90% from approximately 80% for the colorimetric techniques (20).

Overall, the lack of patient morbidity associated with specimen recovery, the relative ease with which specimens can be obtained and processed, the additional discrimination afforded by newer methods of staining such as immunofluorescence, and the markedly reduced cost have combined to make induced sputum examination an especially attractive alternative to bronchoscopic methods. It has supplanted BAL as the first-line approach to diagnosis of uncomplicated pneumocystis pneumonia at many centers and is rapidly becoming the procedure of choice in the initial evaluation of pulmonary infiltrates on the part of many clinicians dealing with immunosuppressed patients (29).

Several other modalities have also been evaluated for their utility in the diagnosis of pneumocystis pneumonia, although most suffer from diminished sensitivity relative to the techniques discussed above. Pulmonary function testing (37) or gallium (^{67}Ga) citrate radioisotope scanning (41), for exam-

ple, may show abnormal findings relatively early in the course of disease, but the overall utility of each is limited by the nonspecific nature of the results, their cost, and, in some cases, by the time expended in performing them. Their proper role, if any, remains undefined.

THERAPY

In initiating therapy for pneumocystis pneumonia once the diagnosis has been established, the clinician has the choice between two antibiotic regimens which have proven efficacy in this infection, namely trimethoprim-sulfamethoxazole and parenteral pentamidine isethionate. These agents have been shown to be of comparable efficacies in the treatment of this disease in patients with non-AIDS malignancies, although trimethoprim-sulfamethoxazole is preferable because of a lower incidence of severe side effects (13). The efficacies of these two regimens in the therapy of AIDS-associated pneumocystis pneumonia appear to be generally comparable as well, although one recent study revealed that survival without mechanical ventilatory support was significantly higher in patients treated with trimethoprim-sulfamethoxazole (86%) than in patients treated with pentamidine (61%) (34).

For AIDS-associated pneumocystis pneumonia, the incidence of side effects due to either drug is quite high, in excess of 60% in most series. Trimethoprim-sulfamethoxazole has the potential advantage of inhibiting the organism at two different stages in the folate pathway, namely inhibition of dihydropteroate synthetase (sulfamethoxazole) and inhibition of dihydrofolate reductase (trimethoprim). The major side effects of this combination are mild-to-severe rash (the cause of which is unknown), leukopenia, thrombocytopenia, nausea, vomiting, and renal impairment. In moderate-to-severe disease, the drug should usually be given intravenously (in divided doses) at a total daily dose of 20 mg of trimethoprim and 100 mg of sulfamethoxazole per kg of body weight; in more mild cases, some clinicians prefer to administer the drug orally. It may be prudent to monitor peak sulfamethoxazole levels periodically, especially when the drug is given orally, to ensure adequate levels in serum (100 to 150 μg of sulfamethoxazole per ml); there are also data demonstrating that keeping the sulfamethoxazole level below 200 μg/ml may reduce the frequency of adverse reactions (I. W. Fong, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1226, 1988). Lower doses of trimethoprim (15 mg/kg per day) and sulfamethoxazole (75 mg/kg per day) may also be associated with fewer side effects without any compromise in efficacy (23, 34). These lower doses may permit a greater percentage of patients to complete a full 21 days of therapy. It should be remembered that the appropriate duration of treatment with this combination or any other agent has not been established conclusively. It has been suggested that the frequent persistence of recoverable cysts in the lung tissues of treated AIDS patients, coupled with the high relapse rate, argues for a somewhat longer course of therapy than in non-AIDS infections. Most clinicians prefer to treat episodes of AIDS-associated pneumocystis pneumonia for 21 days rather than the usual 14 days recommended for non-AIDS cases, although clinical data supporting increased efficacy with the longer course are lacking.

While the incidence of adverse reactions with trimethoprim-sulfamethoxazole in AIDS patients is high, it is generally preferred over parenteral pentamidine because toxicities of the latter drug tend to be more severe. These toxicities include significant azotemia, pancreatitis, hypoglycemia followed by hyperglycemia, leukopenia, thrombocytopenia, nausea, vomiting, orthostatic hypotension, and a bitter taste that can severely affect caloric intake. While many of these side effects are reversible with discontinuation of the drug, some (such as pancreatic dysfunction and dysglycemia) may be permanent and severe. The incidence of glucose intolerance during pentamidine administration correlates with the degree of drug-induced renal impairment (36). The precise mechanism of action of this drug is unknown. It should be given once daily by slow intravenous infusion (60 to 90 min in 100 ml of 5% glucose) at a dose of 4 mg/kg; intramuscular administration causes sterile abscess formation and is no longer routinely recommended. There is also evidence to suggest that in AIDS patients lower doses of pentamidine (3 mg/kg) may be as effective as 4 mg/kg and have fewer side effects (6).

Although many patients improve progressively during therapy, some patients have a transient clinical and radiographic worsening of their disease during the first 3 to 5 days after initiation of treatment regardless of which agent is chosen as first-line therapy. This may be caused by an inflammatory response to dead or dying organisms. This worsening usually improves by day 7 to 10 of therapy. Thus, switching agents on the basis of this interim deterioration may be premature and could merely result in replacing one set of potential drug toxicities with another.

Largely because of its success in the rodent model of pneumocystis pneumonia, dapsone is another antifolate that has been investigated for its potential therapeutic value. In one study, the rate of response to dapsone (100 mg/day) alone was significant (61%) but was still substantially lower than that to either conventional therapy (85%) or the combination of dapsone plus trimethoprim (100%) (27). In another study, dapsone (100 mg/day) plus trimethoprim (20 mg/kg per day) was evaluated in AIDS patients experiencing their first episode of pneumocystis pneumonia and was found to be as effective, better tolerated, and associated with fewer serious side effects than conventional agents given to previous patients (21). Dapsone plus trimethoprim may therefore be an acceptable alternative to either trimethoprim-sulfamethoxazole or pentamidine in some patients, especially those with mild-to-moderate disease. Toxicities of dapsone include a hypersensitivity rash that does not necessarily require discontinuation of therapy, hemolytic anemia, methemoglobinemia, and gastrointestinal upset.

In addition to the three regimens described above, several other drugs are being evaluated in the treatment of pneumocystis pneumonia. One of the most promising is trimetrexate, an inhibitor of dihydrofolate reductase which is 1,000-fold more potent than trimethoprim in in vitro assays of activity against this enzyme. When given to AIDS patients at daily doses of either 30 or 45 mg/m^2 by intravenous infusion, the response rate has ranged from 77 to 92%, respectively (1, 23). The role of trimetrexate as primary therapy for pneumocystis pneumonia awaits completion of a multicenter trial comparing this agent with trimethoprim-sulfamethoxazole in patients with moderately severe disease. A major drawback of trimetrexate therapy thus far, however, has been the high relapse rate (up to 60%) seen when the drug has been used as a single agent. Combinations of this drug with other agents and/or prompt institution of antipneumocystis prophylaxis after completion of acute therapy are among the proposed strategies for reducing this high relapse rate, although none has yet been validated in a controlled clinical trial. Toxicities of this drug include granulocytopenia, thrombocytopenia, elevated hepatic transaminases, and, rarely, rash; these

toxicities are generally mild and dose dependent. Bone marrow suppression caused by the drug is due to its antifolate activity and usually can be readily ameliorated by concomitant administration of leucovorin at 20 mg/kg every 6 h intravenously or orally.

Because of toxicities associated with parenteral administration of many of these agents, there has been substantial interest in developing alternative methods of targeting delivery of antipneumocystis drugs directly to the lung. Aerosolization of pentamidine is one such method of delivery that has particular promise in this regard because of the relative ease of administration, lack of significant side effects apart from occasional bronchospasm (especially in smokers), and ability to attain high intraalveolar drug levels with minimal systemic absorption. Proper nebulization of the drug, resulting in droplet particle sizes of between 2 and 3 μm, appears critical to ensure adequate delivery of pentamidine to the lower respiratory tract passages. In one pilot study of treatment of mild episodes of pneumocystis pneumonia in AIDS patients, 9 of 13 patients receiving aerosolized pentamidine (4 mg/kg per day, via Ultra Vent nebulizer) responded to therapy, compared with 9 of 10 patients receiving daily parenteral pentamidine at 3 mg/kg per day (6). In another study involving similar patients treated with 600 mg of aerosolized pentamidine (via Respirgard II jet nebulizer) daily for 21 days, 13 of 15 patients responded to therapy, side effects were minimal, and no relapses were seen (28). On the basis of these encouraging results, more extensive evaluation of the role of aerosolized pentamidine in treatment of this infection is under way. Recent reports of early relapses following aerosolized pentamidine therapy need to be carefully assessed to determine whether these occur more commonly than with other modes of therapy. Until the results of these evaluations are known, however, aerosolized pentamidine cannot be recommended for use as first-line therapy in acute disease outside of a controlled clinical trial.

Difluoromethylornithine, a specific inhibitor of ornithine decarboxylase, has some efficacy against AIDS-associated pneumocystis pneumonia, although published clinical experience with this drug to date has been limited to patients either refractory to or intolerant of more conventional agents (11). The combination of primaquine and clindamycin has substantial in vitro efficacy against the organism, and preliminary reports of its clinical use are promising (40). Piritrexim, an oral antifolate structurally similar to trimetrexate, has considerable promise because of both its oral formulation and its excellent in vitro potency against the organism. Phase I evaluation of this agent is under way.

In recent years, a number of investigators have looked at the role of high-dose corticosteroids in the treatment of AIDS-related pneumocystis infection (22, 42), both as primary therapy and in patients failing conventional agents. Most series have reported significant improvements in respiratory function with corticosteroids, although the effect on patient survival remains less certain. Formal evaluation of corticosteroids as adjuncts in the primary therapy of moderate-to-severe episodes is being conducted at several centers. The specific indications for when to administer corticosteroids, the type of patient most likely to benefit from their use, the optimal dose and duration of treatment with these drugs, and their potential side effects are questions that these studies will help answer.

Finally, in managing patients who fail to improve after 5 to 10 days of therapy with conventional agents or who experience progressive clinical deterioration during this time, few data exist to guide the appropriate choice of second-line therapy. Many clinicians prefer to substitute (or even combine) one conventional agent with another in this situation, although there is no evidence that this improves patient survival. Switching to "salvage" therapy with agents such as trimetrexate or difluoromethylornithine, or adding corticosteroids as discussed above, are other strategies that have proven successful in individual patients, but more controlled trials in this area are clearly needed.

PROPHYLAXIS

The urgency to develop effective strategies for prophylaxis against pneumocystis pneumonia is driven by the knowledge that approximately 60% of AIDS patients, despite receiving antiretroviral therapy in the form of zidovudine, are likely to relapse within 1 year of their first episode of pneumonia (5). Primary and secondary episodes of pneumocystis pneumonia thus constitute a major cause of morbidity and mortality in this disease, a reduction in which may serve to increase the potential life expectancy of patients with HIV-1 infection. Previous work with pediatric patients with acute leukemia and other childhood malignancies has documented the ability of a regular schedule of primary prophylaxis with an agent such as trimethoprim-sulfamethoxazole (trimethoprim, 150 mg/m^2; sulfamethoxazole, 750 mg/m^2, given either thrice weekly or daily) to eliminate the risk of pneumocystis pneumonia during periods of immunosuppression (14). Benefits of primary and secondary prophylaxis in susceptible HIV-1-infected patients are also clear, although the choice of prophylactic medications, the optimal route of delivery, and the frequency of administration remain areas of controversy.

Prophylactic use of trimethoprim-sulfamethoxazole has been among the most commonly used regimens thus far in AIDS patients and remains the standard against which most other regimens have been compared. In one study, 60 AIDS patients with Kaposi's sarcoma and no history of pneumocystis pneumonia were randomized to receive either 800 mg of sulfamethoxazole and 160 mg of trimethoprim twice daily (plus 5 mg of oral leucovorin daily) or placebo; none of the 30 patients receiving active drug as primary prophylaxis, versus 16 of 30 (53%) receiving placebo, developed pneumocystis pneumonia over a 2-year follow-up period (8). Side effects occurred in 15 of 30 patients (50%) on the antifolate combination, however, and 17% had reactions severe enough to require discontinuation of the drug. Regimens involving this combination given on a less frequent basis have also been devised, although efficacy data for HIV-1-infected patients are lacking. Similarly, data regarding its role in secondary prophylaxis remain incomplete.

Other drugs which have been proposed for use in prophylaxis include dapsone (either alone or in combination with another agent such as pyrimethamine or trimethoprim) on a daily or weekly basis, weekly pyrimethamine-sulfadoxine (Fansidar), intermittent parenteral pentamidine, and aerosolized pentamidine. The latter agent has been evaluated in a number of unblinded trials and appears to be quite effective in preventing recurrences of pneumocystis pneumonia; data regarding its role in prevention of primary episodes are still preliminary. One of the largest trials involved 14 community treatment centers in San Francisco, Calif., and began in 1987 (5). In that study, patients were randomized to receive either 30 mg of aerosolized pentamidine every 2 weeks, 150 mg every 2 weeks, or 300 mg every 4 weeks. Interim analysis at 1 year showed that the frequency of recurrent pneumocystis disease dropped from 24% in the 30-mg group to only 13%

when the 300-mg dose was used. Toxicities of the drug were minimal and identical to those previously seen with use of the drug for treatment of active disease. On the basis of these and other data, the U.S. Food and Drug Administration recently approved the use of aerosolized pentamidine for primary and secondary prophylaxis in HIV-1-infected patients; the approved dose is 300 mg once every 4 weeks, to be administered by a nebulizer meeting the performance standards of the type used in the San Francisco study (the Respirgard II jet nebulizer). As the drug has become more widely used in clinical practice, disturbing reports of both upper lobe disease and extrapulmonary dissemination of *P. carinii* in patients receiving aerosolized pentamidine prophylaxis have appeared, but the extent of this problem remains uncertain.

In June 1989, the Public Health Service Task Force on Anti-Pneumocystis Prophylaxis published recommendations for the prevention of pneumocystis pneumonia in HIV-1-infected individuals (5). This panel concluded that the CD4+ cell count (and/or CD4+ percentage of total lymphocytes) constitutes a reliable indicator of an HIV-1-infected individual's relative risk of acquiring pneumocystis pneumonia in the near future and recommended that routine monitoring (every 3 to 6 months) of these parameters be implemented as a means of determining when prophylaxis should be used (5). A fall in the CD4+ count below 200 cells per mm^3 (and/or 20% of total lymphocytes) was suggested as the point at which primary antipneumocystis prophylaxis generally should begin, using either trimethoprim-sulfamethoxazole or aerosolized pentamidine as described above according to clinical preference and compatibility with concomitant medications. Secondary prophylaxis was recommended for all patients with a history of pneumocystis pneumonia regardless of CD4+ cell count.

SUMMARY

In summary, recent advances in our ability to diagnose, treat, and prevent recurrences of pneumocystis pneumonia have significantly improved the clinical management of this infection, especially in HIV-1-infected individuals. As current investigations allow our therapeutic armamentarium in this disease to be strengthened even further, it is likely that pneumocystis pneumonia will pose a diminishing threat to those patients currently most susceptible to this infection.

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