

Is There Anything New in *Pneumocystis jirovecii* Pneumonia? Changes in *P. jirovecii* Pneumonia over the Course of the AIDS Epidemic

Alison Morris

Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

(See the article by Walzer et al. on pages 625–33)

The epidemiological characteristics and outcome of HIV-associated *Pneumocystis jirovecii* pneumonia (PCP) have shifted multiple times over the course of the AIDS epidemic. Despite the availability of HAART, PCP remains a leading cause of morbidity and mortality. The article by Walzer et al. [1] in this issue of *Clinical Infectious Diseases* summarizes the experience with HIV-associated PCP over a 21-year period in a single center. The authors examine several distinct eras of HIV and PCP care, including (1) before the use of adjunctive corticosteroids for PCP (1985–1989), (2) after the introduction of adjunctive corticosteroids but before availability of HAART (1990 through June 1996), and (3) after the introduction of HAART (July 1996 through 2006). This work provides a valuable perspective on factors influencing outcome in PCP and on changes in the disease over several phases of HIV and PCP care. It is, to our knowledge, the largest single-series experience

to date, with 494 patients and 547 episodes of laboratory-documented PCP, making an important and unique contribution to this field.

Walzer et al. [1] found that the demographic characteristics of patients with PCP changed over time, reflecting changes in the HIV infection epidemic. Before 1996, subjects with PCP were more likely to be men whose risk factor for HIV infection was sex with other men. After 1996, there was an increase in the number of heterosexual men and women with PCP. Subjects in the post-HAART period were also more likely to have their hospital admission for PCP represent the first time that they learned of their HIV infection status. In fact, more than one-half of the PCP cases were diagnosed in patients who were unaware that they were infected with HIV. These patients may have waited longer than others to seek care for their respiratory symptoms, because they had a lower partial pressure of oxygen at hospital admission than did patients in the previous eras and were more likely to require intensive care unit (ICU) admission and mechanical ventilation. Subjects were also unlikely to have received PCP prophylaxis. Although we do not know how many of these patients were eligible for prophylaxis, a recent report from the Adult/Adolescent Spectrum of HIV project found

that the proportion of eligible patients in the United States who actually receive primary prophylaxis for PCP decreased during the period 1994–2003, largely as the result of an increase in the number of patients who did not restart prophylaxis when their CD4⁺ cell count decreased following a previously good response to HAART [2]. These data highlight the need to diagnose and treat HIV infection in at-risk populations to decrease morbidity and mortality and to prevent spread of HIV. Emphasis also needs to be placed on offering appropriate and timely PCP prophylaxis. It is unlikely that we will see a decrease in future hospital admissions for PCP without improvements in implementing these preventive measures.

Somewhat surprisingly, there was little change in mortality at this center over the past 20 years. Mortality in the pre-HAART, precorticosteroid therapy period was essentially identical to that in the post-HAART, postcorticosteroid therapy period. There was an increase in mortality that was not statistically significant during the pre-HAART, postcorticosteroid period that was perhaps secondary to more-aggressive ICU care of patients with PCP. It is also possible that mortality has improved in the HAART era, but the study did not have sufficient power to detect this difference.

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Reprints or correspondence: Dr. Alison Morris, Dept. of Medicine, Div. of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, 628 NW MUH, 3459 Fifth Ave., Pittsburgh, PA 15213 (morrisa@upmc.edu).

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Despite the difficulties involved in comparing results from different centers with different patient populations, other studies have found mortality in the post-HAART era to be remarkably similar to that reported by Walzer et al. [1]. Although the studies included a short period before HAART availability, 2 large multicenter cohorts reported PCP mortality ranging from 8.2% to 11.5% in the HAART era [3, 4]. In a review of patients from a county hospital in Los Angeles, California, for the period 2000–2003, my colleagues and I also found a mortality of 11.6% (A.M., unpublished data). The consistency of these findings suggests that perhaps we have reached a threshold in the care of HIV-infected patients with PCP and that further improvements will require discovery of new therapies or changes in other aspects of care.

Predictors of mortality were consistent throughout the course of the study. The authors identified increasing age, low hemoglobin level, low partial pressure of oxygen at hospital admission, experiencing a second or third episode of PCP, the presence of a medical comorbidity, and pulmonary Kaposi sarcoma as indicators of increased risk for mortality throughout the various time periods. Many of these predictors are similar to those found in other cohorts [5–7], but the presence of pulmonary Kaposi sarcoma as a mortality risk factor is a novel finding. The authors speculate that impaired gas exchange from the combination of pulmonary Kaposi sarcoma and PCP might explain the increased mortality. It is also possible that the finding represents a tendency to perform bronchoscopic examinations for patients who are more severely ill or have more-advanced immunocompromise.

One of the major controversies in the care of HIV-infected patients with PCP is the impact of HAART administration during the acute episode. The question is 2-fold: first, do patients who have been receiving HAART before development of PCP have improved outcome, compared with those who have not? Second, should

patients initiate HAART while being treated for PCP? An early study, conducted before the HAART era, found that patients who received antiretroviral therapy during hospitalization for PCP had improved mortality in univariate analysis [7]. A study performed after the availability of HAART found that ICU mortality for patients with PCP was substantially lower among those who continued or initiated HAART during hospitalization [8]. A study of ICU patients by Miller et al. [9] that was performed at the same center as the current study [1] found that mortality improved in ICU patients with PCP in the HAART era, despite the fact that none of their patients were receiving HAART, which suggests that changes in ICU care might have been driving the improvements. Recently, my group has found that subjects at a county hospital in Los Angeles who continued or initiated HAART during hospitalization for PCP, both in ICUs and outside of ICUs, did not differ with respect to mortality from those who did not receive therapy (A.M., unpublished data). The current study [1] cannot speak directly to this issue, because there were no patients who were receiving HAART during the 2 months before hospitalization or during PCP treatment. There are no large-scale, prospective studies of HAART and PCP, and the question of initiating HAART in patients with acute PCP remains unanswered. Potential problems with starting HAART in this population include development of the immune reconstitution inflammatory syndrome, difficulties with administration of antiretroviral medications in hospitalized patients who may have other organ system compromise or difficulty with oral medications and absorption, the potential for the development of drug-resistant strains of HIV if drugs need to be stopped and started during hospitalization, and issues of compliance after hospital discharge.

It is often difficult to compare studies of the epidemiological characteristics and outcomes of PCP, because they are usually

performed in different periods and at different centers that may have varying levels of expertise in HIV care, different philosophies towards utility of care, and diverse patient populations. The current study overcomes these limitations by examining outcomes of PCP at a single center throughout the course of the AIDS epidemic. Despite major strides in caring for patients with HIV infection during the past quarter of a century, not much has really changed in the prognosis or predictors of mortality for patients with PCP. Although previous studies from these authors and others indicate that ICU mortality due to PCP has improved, overall mortality at this center has not changed significantly, and clinical signs associated with mortality were fairly constant during the course of the study. What has changed in both this series and others is that more cases of PCP now result from failure to diagnose HIV infection, rather than from the inevitable progression of AIDS seen before the availability of current antiretroviral therapies. This finding should prompt continued efforts to identify patients who are at risk for HIV infection and to bring them into care. Until we achieve this goal, there will likely not be any more good news concerning this disease.

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