Severe Opportunistic Infections In AIDS Patients With Late-Stage Disease

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Background: **Clinicians caring for patients who have acquired immunodeficiency syndrome (AIDS) need to be aware of the wide variety of infectious diseases that can occur. Although *Pneumocystis carinii* pneumonia (PCP) is the most common AIDS-defining infection, other opportunistic infections associated with advanced immunodeficiency can develop after an initial diagnosis.**

Methods: **To ascertain AIDS-defining opportunistic infections that developed at the time of or after an AIDS diagnosis, an intensive chart review was conducted for 45 homosexual men with AIDS who died from 1990 through 1992. Time to death after first occurrence of these infections was also determined.**

Results: **The most common opportunistic infection occurring as the initial AIDS-defining illness was PCP (31 percent). The most common opportunistic infection occurring as a secondary disease was cytomegalovirus (CMV) disease (40 percent), followed by disseminated *Mycobacterium avium* complex (33 percent) and invasive candidiasis (31 percent). Each of these latter infections was associated with a poor prognosis (median time to death ≤8 months).**

Conclusions: **Diseases caused by CMV, disseminated *M. avium* complex, and invasive candidiasis were uncommon presenting manifestations of AIDS but were common secondary diseases that tended to be associated with limited survival. With increasing survival and a declining incidence of PCP as a result of medical therapy, other severe opportunistic infections might become increasingly recognized. (J Am Board Fam Pract 1994; 7:288-91.)**

Clinicians caring for patients with the acquired immunodeficiency syndrome (AIDS) need to be aware of the wide variety of serious opportunistic infections that might occur. Among AIDS patients from industrialized countries, the most common AIDS-defining opportunistic infection is typically *Pneumocystis carinii* pneumonia (PCP).[1-5] Researchers evaluating presenting manifestations of AIDS (including studies based on AIDS surveillance data) have reported a lower frequency of other serious opportunistic infections, such as cytomegalovirus (CMV) disease and disseminated *Mycobacterium avium* complex.[1-4] The most common AIDS-defining illness reported to the San Francisco Health Department through September 1993 was PCP (36 percent); each of the other AIDS-defining infections was reported less than 5 percent of the time as the initial AIDS-defining illness.[3] Because many of these other opportunistic infections tend to occur in persons with more advanced degrees of immunosuppression, however,[2,6] these diseases might be more likely to occur after the initial AIDS diagnosis.

In this analysis we were interested in learning which severe opportunistic infections occurred in patients with late-stage disease caused by the human immunodeficiency virus (HIV). To do so, we conducted an intensive review of records from a medical practice specializing in the care of HIV-infected individuals. We specifically chose records from persons who died of AIDS during the preceding 3 years and noted all AIDS-defining opportunistic infections that were reported at the time of or after an AIDS diagnosis.

Methods

This review was conducted at the office of a medical practice primarily devoted to the care of HIV-infected individuals. The senior physician in this

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practice has particular expertise in HIV-associated dermatologic conditions, including Kaposi sarcoma. Medical charts for patients cared for in this practice include records of all outpatient visits, summaries of inpatient hospitalizations, consultations, and results of laboratory testing and other diagnostic studies. Most HIV-infected persons in this practice (consistent with the distribution of AIDS in San Francisco cases) are homosexual and bisexual men.

We reviewed all records from adult men who had a diagnosis of AIDS according to the 1987 Centers for Disease Control case surveillance definition[7] and who had died during the period from 1990 through 1992. To ensure that complete histories were available, we reviewed only those records of patients who were seen from the initial AIDS diagnosis until the date of death. All medical records were initially searched to determine whether they met our inclusion criteria. Records meeting these criteria were then reviewed for demographic and risk history information, dates of AIDS diagnosis and death, first AIDS-defining disease, and evidence of any other infectious disease based on physical examination or laboratory studies. Median times to death for the major AIDS-defining infections were compared using the Wilcoxon rank sum test.

Results

We found 45 records that met our inclusion criteria. All records were from white homosexual or bisexual men; 1 man also reported a history of injection drug use. The median age at the time of AIDS diagnosis was 40 years (range=26–68 years). Of the men in this analysis, 1 (2 percent) had AIDS diagnosed in 1982, 7 (16 percent) during 1986–7, 16 (36 percent) during 1988–9, and 21 (47 percent) during 1990–1. Eight (18 percent) persons died in 1990, 29 (64 percent) in 1991, and 8 (18 percent) in 1992. The median time from the first diagnosis of AIDS until the date of death was 19 months (range=2–112 months).

Of the 45 men in this analysis, 15 (33 percent) had Kaposi sarcoma as their initial AIDS-defining disease. Fourteen (31 percent) had PCP, 10 (22 percent) had other AIDS-defining opportunistic infections, 3 (7 percent) had HIV wasting syndrome, 2 (4 percent) had a non-Hodgkin lymphoma, and 1 (2 percent) had HIV dementia.

The number of men with specific AIDS-defining infections at any time in their illness is shown in Table 1. This list includes those persons whose infection occurred as the initial manifestation of AIDS (primary diagnosis), as well as those whose infection first occurred after a diagnosis of AIDS had already been established (secondary diseases). This table presents only the first occurrence of an infection for each study subject; some individuals had a specific disease (such as PCP) on more than one occasion or had a disease caused by a specific infectious agent (such as CMV) affecting more than one organ system.

PCP was the most common opportunistic infection, as well as the most common AIDS-defining infection at the time of an AIDS diagnosis. Disease caused by CMV, disseminated *Mycobacterium avium* complex, and *Candida* of the esophagus or lungs were uncommon presenting manifestations of AIDS but were often seen after the initial AIDS diagnoses. These other infections also tended to be associated with a poorer prognosis. The median time to death after the first diagnosis of PCP was 19.5 months (range=0–61 months). The median time to death after first diagnosis of CMV disease (5.5 months, range=0–25) was significantly shorter than for PCP (P=0.008). The median time to death after first diagnosis

Table 1. Number of Persons with AIDS-defining Infections by First Occurrence of Disease (n=45).

Opportunistic Infection	As Primary AIDS Diagnosis	As Secondary Disease	Total No. (%)
Pneumocystis carinii pneumonia	14	10	24 (53)
Cytomegalovirus*	0	18	18 (40)
Mycobacterium avium complex†	2	15	17 (38)
Candida of esophagus or lungs	2	14	16 (36)
Toxoplasmosis	2	4	6 (13)
Cryptococcosis	2	2	4 (9)
Cryptosporidiosis	1	3	4 (9)
Extrapulmonary tuberculosis	1	1	2 (4)
Isosporiasis	0	1	1 (2)

*Disseminated, visceral (e.g., retinitis).
†Disseminated, bacteremia.

of disseminated *M. avium* complex (5 months, range=0–15) was also significantly shorter than for PCP ($P=0.002$). The median time to death after first diagnosis of *Candida* of the esophagus or lungs was 8 months (range=0–54); differences in time to death with PCP were of borderline significance ($P=0.06$).

Discussion

As previously suggested, PCP was the most common initial AIDS-defining infection, although a number of men also developed PCP as a secondary disease. CMV disease, disseminated *M. avium* complex, and *Candida* of the esophagus or lungs were uncommon presenting manifestations of AIDS, but common secondary diseases. These late manifestations of AIDS tended to be associated with limited survival, consistent with these infections developing at a more severe degree of immunosuppression.

The infections reported in this study were based on our review of medical records. Additional infections could have occurred but were not detected. For example, disseminated disease caused by *M. avium* complex or CMV might have occurred as a preterminal condition in some patients for whom a definitive diagnosis was never made. One comparative study of clinical and autopsy diagnoses for AIDS patients who died found that CMV disease was the most common AIDS-defining disease diagnosed at autopsy; however, this condition was often not recognized prior to death.[8] It is therefore likely that infectious diseases were even more common than we described.

Specific diagnoses for this analysis were derived from either clinical or laboratory reports. In some cases presumptive diagnoses of conditions, such as CMV retinitis or PCP, were based on clinical presentation and response to empiric therapy. When laboratory confirmation was available, however, it typically supported the initial clinical diagnosis.

Generalizing our results to other HIV-infected individuals must be done with caution. By design this analysis was conducted on a subset of men who had died of AIDS and therefore reflects those with the most severe degree of HIV-induced immunodeficiency. In addition, this was a study of San Francisco homosexual and bisexual men. The distribution of infections in other demographic or risk groups might differ. One study of HIV-infected persons from New York City found that injection drug users, when compared with homosexual men, were less likely to have CMV disease or cryptosporidiosis and more likely to have PCP, esophageal candidiasis, and extrapulmonary tuberculosis.[9]

The CDC has recently expanded the AIDS case definition to include HIV-infected persons with pulmonary tuberculosis, recurrent pneumonia, invasive cervical cancer, or a CD4+ lymphocyte count <200 cells/μL or <14 percent.[10] For some individuals this revised definition will result in a diagnosis of AIDS earlier in the course of their HIV infection. This expanded definition, however, would not affect our conclusions concerning late manifestations of AIDS and the poor prognosis associated with them.

Although our review focused on AIDS-defining opportunistic infections, HIV-infected patients (particularly those with advanced immunodeficiency) are also susceptible to many other infectious conditions, including a wide variety of complications, such as bacterial sepsis, oral candidiasis, and candidal vaginitis.[11]

With improved survival as a result of antiretroviral therapy and increased use of PCP prophylaxis, we should expect that the proportion of AIDS patients with opportunistic infections besides PCP will increase. For example, one study of PCP prophylaxis reported a number of patients developing disease resulting from disseminated CMV or *M. avium* complex.[12] Another large observational study found that HIV-infected men who received PCP prophylaxis before an AIDS diagnosis were more likely to develop disease due to *M. avium* complex, CMV, or esophageal candidiasis.[4] Several studies indicate a decline in PCP as an AIDS-defining illness or an increase in other serious opportunistic infections.[2,4,5,13] Future disease trends could be affected by additional modifications in prophylactic therapy. Use of therapies, such as trimethoprim-sulfamethoxazole for PCP prophylaxis, might decrease the occurrence of other infections, such as cerebral toxoplasmosis.[14] Recent guidelines have also addressed the use of rifabutin as prophylaxis against *M. avium* complex.[15] Widespread use of these prophylactic therapies could further modify the spectrum of opportunistic infections, with diseases caused by such organisms as CMV becoming increasingly evident.

Summary

AIDS patients are susceptible to a variety of serious opportunistic infections as late manifestations of AIDS, including CMV disease, disseminated *M. avium* complex, and invasive candidiasis. Clinicians caring for those with HIV disease need to be aware of the current distribution of infectious complications so they can diagnose and treat these conditions as accurately and promptly as possible.

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