科技资料

# Mycoses in AIDS Patients

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# PREFACE

The World Health Organization estimates that at least five million people worldwide are infected with human immunodeficiency virus (HIV). Of these about 100,000 are in Asia and Oceania, 500,000 in Europe, 2 million in the Americas and 2.5 million in Africa (Mann, 1989). The acquired immunodeficiency syndrome is characterized by a derangement in cell-mediated immunity leading to opportunistic infections with for example *Mycobacterium* spp., *Candida* spp., *Cryptococcus neoformans*, *Pneumocystis carinii*, *Toxoplasma gondii* and *Cryptosporidium*.

The third symposium on "Topics in Mycology" brought together 265 experts from 32 countries to discuss the epidemiology, immmunological and pathogenetic aspects of AIDS and its opportunistic infections in general and fungal infections in particular.

*Pneumocystis carinii* pneumonia is by far the commonest opportunistic infection in AIDS patients. The nature and classification of *P. carinii* is still controversial. In search for its true taxonomic affinities an introductory paper formulates a number of key questions. Candidosis is another frequent opportunistic infection. A number of papers discuss the possibility that selective pressures may operate on *Candida albicans* within the AIDS population and influence its nature: this might have an impact on prophylaxis and curative and/or suppressive therapy.

AIDS has become the leading predisposing factor for cryptococcosis. Other infectious complications in AIDS patients include histoplasmosis and coccidioidomycosis. In contrast, paracoccidioidomycosis and blastomycosis are rare, as are aspergillosis and sporotrichosis. However, an unusual mycosis, penicilliosis (caused by *Penicillium marneffei*) has been proposed as indicative of AIDS. HIV infection and/or treatment may induce the appearance of other rare mycoses such as trichosporonosis, saccharomycosis and fusariosis. A great number of scientists of high international standing discuss the epidemiological, immmunological and clinical aspects of these mycoses and generate a number of questions that should stimulate further research.

These Proceedings, which are comprised of the papers presented at this symposium, contain a wealth of information on AIDS-indicative mycosis, dermatomycosis and rare mycoses encountered in some HIV positive patients, and provide up-to-date information on fungal models in immunocompromised animals, on pharmacokinetics and on the mode of action of antifungals of use in immunocompromised patients. The actual status and perspectives in the treatment of mycoses in patients with AIDS are highlighted.

The Symposium was organized in the "Institut Pasteur" (Paris), an institute that, since its founding in 1887, has contributed to the discovery of several pathogenic agents, a tradition renewed with the discovery of two viruses: HIV-1 and HIV-2.

The Symposium was sponsored jointly by the Janssen Research Foundation, the International Society for Human and Animal Mycology and the Mycology Unit of the Pasteur Institute.

The Editors

Mann, J., 1989, Global AIDS into the 1990's, World Health, October 1989: 6.

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# EPIDEMIOLOGY OF AIDS AND ITS OPPORTUNISTIC INFECTIONS

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The acquired immunodeficiency syndrome (AIDS), now known to be caused by a novel retrovirus known as the human immunodeficiency virus (HIV) (Barre-Sinoussi et al., 1983; Gallo et al., 1984), is characterized by a profound derangement in cell-mediated immunity leading to multiple opportunistic infections and unusual neoplasms. AIDS was first recognized in the spring of 1981 when *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma (KS) appeared in previously healthy homosexual men in California and New York (CDC, 1981a,b). It soon became apparent that other opportunistic diseases were present in addition to PCP and KS, and that groups other than homosexual men were also at risk including intravenous (IV) drug users, recipients of blood and blood products, and heterosexual contacts of persons at increased risk (CDC, 1981c; CDC, 1982a). By autumn of 1981, the CDC had created a task force to conduct epidemiologic, clinical and laboratory investigations on AIDS. For purposes of national surveillance, a case definition of AIDS was developed in 1982 that required the diagnosis of one or more of certain diseases at least moderately predictive of a defect in cell-mediated immunity in persons without underlying conditions known to cause immunodeficiency, but did not generally require laboratory confirmation of either immunodeficiency or infection with HIV (CDC, 1982b). Indicator diseases used in the initial CDC case definition, before HIV was identified as the causative agent of AIDS, are listed in Table 1. This original surveillance definition was subsequently modified in 1985 to include other severe manifestations such as disseminated histoplasmosis capsulati, bronchial or pulmonary candidiasis, chronic isosporiasis, and certain non-Hodgkin's lymphomas as knowledge about HIV infection increased (CDC, 1985). In 1987, the CDC case definition was revised and expanded for persons with laboratory evidence of HIV infection (e.g., positive HIV-antibody test or positive culture for HIV) to include a broader spectrum of diseases found in persons with HIV infection such as extrapulmonary tuberculosis, disseminated coccidioidomycosis, certain bacterial infections, HIV encephalopathy, and HIV wasting syndrome, and the presumptive diagnosis of selected diseases (see Table 2) (CDC, 1987).

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Table 1. Diseases used in the initial (1982) CDC case definition of AIDS, before HIV was identified, and considered at least moderately indicative of underlying immunodeficiency

| |
|---|
| **A. Viral infections (noncongenital)** |
| Chronic (>1 month) mucocutaneous herpes simplex infection |
| Histologically evident cytomegalovirus infection of an organ other than liver or lymph node |
| Progressive multifocal leukoencephalopathy caused by papovavirus (JC virus) |
| **B. Bacterial infections** |
| Disseminated *Mycobacterium avium* complex or *M. kansasii* infection |
| **C. Fungal infections** |
| Candidal esophagitis |
| Cryptococcal meningitis or disseminated infection |
| **D. Protozoan and helminthic infections** |
| *Pneumocystis carinii* pneumonia |
| *Toxoplasma gondii* encephalitis or disseminated infection (noncongenital) |
| Chronic (>1 month) *Cryptosporidium* enteritis |
| Strongyloidiasis (pneumonitis, encephalitis, or disseminated infection beyond the gastrointestinal tract) |
| **E. Neoplasms** |
| Kaposi's sarcoma in a person <60 years of age |
| Primary lymphoma limited to the central nervous system |

As of January 1989, 139,886 AIDS cases had been reported from 142 of 177 countries or territories throughout the world participating in the Global Programme on AIDS of the World Health Organization (WHO)*,** (Berkelman.et al., 1989) . The USA had the most reported cases followed by France, Uganda, and Brazil. According to WHO, which coordinates worldwide surveillance for AIDS, the present number of AIDS cases is markedly underestimated; underreporting ranges from 10% to 80% by country. WHO estimates that the actual number of AIDS cases worldwide is approximately 377,000. It is now well-recognized that AIDS is only part of the clinical spectrum of HIV infection. Infection by HIV invariably causes a variety of milder clinical manifestations that precede AIDS, and these in turn are usually preceded by a long asymptomatic incubation period. As many as 5 million persons are estimated to be infected with HIV worldwide** (Berkelman et al., 1989).

* Heyward, W.L., AIDS Program, Center for Infectious Diseases, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia, Personal communication.

** World Health Organization, January 31, 1989, Update, AIDS cases reported to the Global Programme on AIDS.

As of January 1, 1989, a total of 82,764 AIDS cases had been reported to CDC from the USA (CDC, 1989c). The number of AIDS cases reported each year continues to increase; however, the rate of increase has steadily declined, except in 1987, when the expansion of the CDC case definition resulted in an abrupt increase in reported cases. Of the AIDS cases reported from the USA, 90% were in males ≥13 years of age, and the mean age at the time of diagnosis was 37 years. Groups at increased risk for AIDS, and the percentages of the total number of patients in each group, included those with histories of homosexual/bisexual contact without IV-drug use (68%), IV-drug users without homosexual/bisexual contact (17%), and those with both homosexual/bisexual contact and IV-drug use (8%). Another 2% had histories of blood transfusion, 1% had hemophilia or other coagulation disorder, 1% had heterosexual contact with sex partners at increased risk for or known to be infected with HIV, 1% were born in countries with predominantly heterosexual transmission of HIV (CDC, 1988b), and 3% had undetermined means of infection.

Eight percent of the AIDS cases from the USA have been reported among women ≥13 years of age. Fifty-two percent had histories of IV-drug use, 18% had sex partners with histories of IV-drug use, 7% had sex partners otherwise at increased risk for or known to be infected with HIV, 11% had histories of blood transfusion, 4% were born in countries with predominantly heterosexual transmission of HIV (CDC, 1988b), and 8% had undetermined means of infection.

The remaining 2% of AIDS cases reported to CDC from the USA have been <13 years of age; 55% were male. Eighty-two percent of pediatric cases were <5 years of age at diagnosis, and 40% were <1 year of age. Seventy-eight percent had mothers at increased risk for or known to be infected with HIV, 13% had received a blood transfusion, 6% had received blood products used to treat hemophilia, and 4% had undetermined means of exposure to HIV.

In the USA, the cumulative incidence of AIDS cases is disproportionately higher in blacks (3.2 to 1) and Hispanics (2.8 to 1) when compared with whites (CDC, 1989b; Selik et al., 1988). The higher rate of IV-drug use among black and Hispanic groups resulting in greater risk of HIV exposure appears to be a contributing factor to this racial disproportion.

Among all AIDS patients from the USA, 59% are reported to have died. However, the median survival time is about one year, and by 7 years after diagnosis, at least 80% have died; the actual case-fatality rate is higher because of incomplete reporting of deaths. AIDS incidence continues to be highest in the most populous metropolitan areas in the USA, and the states of California, Florida, New Jersey, New York, and Texas account for 65% of all cases.

Projections of the number of AIDS cases that will be diagnosed and reported to the CDC in the future have been made using mathematical and statistical models (CDC, 1989a; Morgan and Curran, 1986). Using an extrapolation model, the CDC estimated in May 1988 that 365,000 cumulative AIDS cases will have been diagnosed in the USA by the end of 1992 (CDC, 1989a). Of these 365,000 cases, 263,000 cumulative deaths are predicted by the end of 1992. Projections also indicate that a total of 172,000 AIDS patients in the USA will require medical care during 1992 at a cost expected to range from $ 5 - 13 billion. The above figures are probably underestimates of HIV-related morbidity, since many clinical manifestations of HIV infection are not diagnosed or reported to CDC, even with the revised and expanded 1987 case definition. It has been estimated by mortality studies that only 70% to 90% of HIV-related deaths are identified through USA surveillance of AIDS (Buehler et al., 1989)

In Europe and the eastern Mediterranean region, 19,094 AIDS cases had been reported from 45 countries as of January 1989. Most of these cases

occurred in homosexual men or in persons using IV drugs. Countries reporting the most cases included France (5,655), Italy (3,008), the Federal Republic of Germany (2,779), Spain (2,165), and the United Kingdom (1,982). However, the highest rates for AIDS (number of cumulative cases per million population) were reported from Switzerland (66.5), France (65.3), and Denmark (51.4) (WHO, 1988).

In the Americas (excluding the United States), 13,595 cases of AIDS had been reported as of January 1989. Leading countries reporting AIDS cases were Brazil (4,709), Canada (2,196), Haiti (1,661), and Mexico (1,642). In the Caribbean, the absolute numbers of reported AIDS cases are miniscule when compared to other regions, but the incidence rates are reported to be among the highest in the world (Berkelman et al., 1989). In some Caribbean countries, the number of heterosexually transmitted AIDS cases is greater than the total number of cases acquired by homosexual transmission and IV drug use (Berkelman et al., 1989; Pape et al., 1986); the male:female ratio among AIDS cases is reported to range from 4:1 to 1:1, depending on the country.

Fifty-two African countries had reported a total of 21,213 AIDS cases at the beginning of 1989, with 7 countries reporting more than 1,000 cases: Uganda (5,508), Tanzania (3,055), Kenya (2,732), Malawi (2,586), Burundi (1,408), Zambia (1,296), and Congo (1,250). The male:female ratio among AIDS cases reported from Africa was approximately 1:1, and the number of cases attributed to heterosexual transmission exceeded 90% in some regions (Berkelman et al., 1989). However, in Africa, AIDS patients have clinical features and immunologic derangements similar to those reported in patients from the USA and Europe.

As of January 1989, 1,460 AIDS cases had been reported from 18 of 35 countries in Asia and the Pacific basin. The majority of cases (1,168) were reported from Australia. On this continent, the epidemiology of HIV infection parallels that of the United States and western Europe.

Worldwide, HIV infection via sexual contact, blood and body fluids, and mother to child continue to be the predominant modes of transmission. Berkelman et al. 1989, emphasized that the differences in the epidemiologic patterns of HIV infection and AIDS in specific countries or regions are primarily due to differences in the proportions of the modes of transmission. They further pointed out that all areas of the world have shown large rates of increase of AIDS, and that the areas only differ according to the time in which HIV infection was introduced.

Although active surveillance for AIDS did not begin until 1982, the epidemic of AIDS appears to have arisen in the USA, central Africa, and Haiti at about the same time in the late 1970's. Retrospective studies have revealed that persons fitting the 1982 CDC case definition for AIDS were present in New York City as early as 1977 (Bigger, 1988). These findings were followed by similar reports of persons fitting the CDC case definition in Haiti (Pape et al., 1983) as well as central Africa (Clumeck et al., 1984). The oldest stored blood sample that has been found to be positive for antibodies to HIV-1 by western blot assay was collected in 1959 in Zaire (Nahmias et al., 1986) The oldest clinical specimen from which HIV-1 has been isolated was a serum sample taken in 1976 also from a patient in Zaire (Getchell et al., 1987). The geographic origin of HIV-1 remains unknown.

A new AIDS virus, HIV-2, was discovered in 1985 (Clavel et al., 1987; Horsburg and Holmberg, 1988). This virus, which has been found predominantly in west Africans, can produce clinical manifestations indistinguishable from those caused by HIV-1 (Clavel et al., 1987; CDC, 1988a; CDC, 1989b). Like HIV-1, sexual contact is the most important route of transmission of HIV-2, and it may have a long incubation period.

Isolated cases of HIV-2 infection have been reported in several countries, including France (Brücker et al., 1987;), Italy (Ferroni et al., 1987), Brazil (Veronesi et al., 1987), the Federal Republic of Germany (Marquart et al., 1988) and the USA (CDC, 1989b). However, unlike HIV-1, HIV-2 is generally restricted to west Africa at present.

## OPPORTUNISTIC INFECTIONS

Opportunistic diseases are the predominant causes of morbidity and mortality in AIDS, and their clinical and pathologic features are well described (Gold, 1985; Gold, 1988; Gal et al., 1988; Selik et al., 1987). Although PCP is by far the most commonly reported opportunistic infection in AIDS patients, 24 other infectious and neoplastic diseases used as indicators of AIDS in the 1987 revision of the CDC case definition are also encountered (CDC, 1987). The percentages of AIDS cases reported with various AIDS-indicative diseases among cases diagnosed since the 1987 revision of the CDC case definition and reported through 1988 in the USA are given in Table 2. Retrospective reviews of autopsy reports and medical records have demonstrated that the cumulative incidence of some opportunistic diseases in AIDS patients is much greater than the frequencies reported to CDC based on surveillance data (Reichert et al., 1983; Welch et al., 1984). Estimates of the cumulative incidence based on surveillance alone are generally lower than the true values because most diseases that occur in AIDS patients after the patients have initially been reported are not reported to CDC.

Protozoa most often encountered in AIDS are *P. carinii*, *Toxoplasma gondii*, *Cryptosporidium* spp., and Isospora *belli*. Based on clinical and autopsy findings, approximately 85% of AIDS patients develop PCP during their illness (Mills, 1986). AIDS patients may also develop neurologic manifestations because of toxoplasmic encephalitis, and *T. gondii* is the most common cause of central nervous system (CNS) mass lesions in AIDS. The prevalence of toxoplasmic encephalitis in AIDS patients has been estimated to be as high as 25% in San Francisco and 12% in New York City (Wong et al., 1984). The clinical course of cryptosporidiosis caused by *Cryptosporidium* spp. in AIDS is characterized by severe, protracted , watery diarrhea. The coccidian *Isospora belli* also causes chronic diarrhea in AIDS. It is usually restricted to the epithelial cells of the small intestine, but disseminated extraintestinal isosporiasis in an AIDS patient has recently been reported (Restrepo et al., 1987).

Although AIDS or HIV-infected patients are susceptible to all the mycoses, their profound cellular immunodeficiency makes them extraordinarily susceptible to certain opportunistic fungi of normally low pathogenicity (Chandler, 1985; Holmberg and Meyer, 1986). The most frequently encountered agents are *Candida albicans*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* var. *capsulatum*. The percentage of AIDS patients with mycoses caused by these agents based on 3,170 cases reported to CDC between May 1983 and June 1984 included candidal oropharyngitis (41.8%), candidal esophagitis (9.4%), cryptococcal meningitis or disseminated infection (5.9%), and disseminated histoplasmosis capsulati (0.51%) (Chandler, 1985). With the revised and expanded 1987 AIDS case definition, there have been slight to moderate increases in the reported frequencies of occurrence of these mycoses in AIDS patients (see Table 2). However, these percentages are still underestimates because follow up information is seldom available or obtained on opportunistic infections that occur after the initial report of an AIDS case to CDC.

Retrospective surveys have revealed that 58% to 81% of AIDS or HIV-infected patients develop one or more fungal infections at some time during their illness (Reichert et al., 1983; Welch et al., 1984) . Oropharyngeal

Table 2. Percentages of AIDS cases reported with various AIDS indicative diseases among cases diagnosed since the 1987 revision of the CDC case definition and reported through 1988 in the USA

| AIDS-Indicative Disease | Percent* (N=28,920) |
|---|---|
| *Pneumocystis carinii* pneumonia: definitive diagnosis | 45 |
| presumptive diagnosis | 11 |
| HIV wasting syndrome | 14 |
| Kaposi's sarcoma: definitive diagnosis | 8.2 |
| presumptive diagnosis | 1.6 |
| Candidiasis of esophagus: definitive diagnosis | 6.7 |
| presumptive diagnosis | 5.2 |
| HIV encephalopathy (dementia) | 5.8 |
| Cryptococcosis, extrapulmonary | 5.7 |
| Herpes simplex, causing esophagitis, pneumonitis, or chronic mucocutaneous ulcers | 3.2 |
| Candidiasis of bronchi, trachea, or lungs | 3.0 |
| Cytomegalovirus disease other than retinitis | 3.0 |
| *Mycobacterium avium* complex or *M. kansasii* disease, disseminated or extrapulmonary: definitive diagnosis | 2.5 |
| presumptive diagnosis | 0.2 |
| Lymphoma, immunoblastic or equivalent (other than brain) | 1.7 |
| Cryptosporidiosis, causing chronic diarrhea | 1.6 |
| *Mycobacterium tuberculosis*, extrapulmonary disease definitive diagnosis | 1.6 |
| presumptive diagnosis | 0.3 |
| Cytomegalovirus retinitis: presumptive or definitive | 1.4 |
| Toxoplasmosis of CNS: definitive diagnosis | 1.2 |
| presumptive diagnosis | 2.5 |
| Mycobacterial disease caused by other or unidentified species, disseminated or extrapulmonary: definitive diagnosis | 0.9 |
| presumptive diagnosis | 0.3 |
| Histoplasmosis capsulati, disseminated or extrapulmonary | 0.9 |
| Lymphoma, Burkitt's or equivalent (other than in brain) | 0.7 |
| Progressive multifocal leukoencephalopathy | 0.6 |
| Salmonella septicemia, recurrent (counted separately in adults only) | 0.5 |
| Lymphoma, primary in brain | 0.4 |
| Bacterial infections, multiple or recurrent, serious pyogenic (counted in children only) | 0.3 |
| Coccidioidomycosis, disseminated or extrapulmonary | 0.2 |
| Isosporiasis, causing chronic diarrhea | 0.2 |
| Lymphoid interstitial pneumonia (in children only) definitive diagnosis | 0.1 |
| presumptive diagnosis | 0.1 |

*The sum of percentages exceeds 100% because some cases had >1 disease reported.

candidiasis (thrush) occurs in most AIDS patients, but candidal esophagitis is less common; disseminated candidiasis is rare, even at autopsy. The incidence of cryptococcosis in AIDS patients ranges from 6% to 29% depending on the patient group selected for study (Pitchenik et al., 1983; Vandepitte et al., 1983; Kovacks et al., 1985; Zuger et al., 1986). Although candidiasis, cryptococcosis, histoplasmosis capsulati, and coccidioidomycosis are the mycotic indicators in the current (1987) CDC case definition for AIDS, a review of the literature and our laboratory