Trends in Mortality Due to Invasive Mycotic Diseases in the United States, 1980–1997

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To determine national trends in mortality due to invasive mycoses, we analyzed National Center for Health Statistics multiple-cause-of-death record tapes for the years 1980 through 1997, with use of their specific codes in the International Classification of Diseases, Ninth Revision (ICD-9 codes 112.4–118 and 136.3). In the United States, of deaths in which an infectious disease was the underlying cause, those due to mycoses increased from the tenth most common in 1980 to the seventh most common in 1997. From 1980 through 1997, the annual number of deaths in which an invasive mycosis was listed on the death certificate (multiple-cause [MC] mortality) increased from 1557 to 6534. In addition, rates of MC mortality for the different mycoses varied markedly according to human immunodeficiency virus (HIV) status but were consistently higher among males, blacks, and persons ⩾65 years of age. These data highlight the public health importance of mycotic diseases and emphasize the need for continuing surveillance.

Several reports, including some based on data from hospital-based and population-based surveillance, have identified upward trends in the incidence of various mycotic infections [1–6]. In a report by Pinner et al. [7] that compared multiple-cause-of-death data for 1980 and 1992, the rate of deaths in which infectious disease was the underlying cause increased 58% (from 41 to 65 deaths per 100,000 population) in the United States, and mycoses increased from the tenth leading underlying cause of such deaths to seventh during the study period. In another report, Selik et al. [3] found that the epidemic of human immunodeficiency virus (HIV) had greatly increased mortality due to the opportunistic mycoses pneumocystosis, cryptococcosis, and histoplasmosis.

To determine national trends in mortality due to invasive mycoses, we analyzed National Center for Health Statistics multiple-cause-of-death record tapes for the years 1980 through 1997, using their specific codes in the International Classification of Diseases, 9th Revision (ICD-9 codes 112.4–118 and 136.3). We report the findings for the major systemic mycotic diseases.

METHODS

Multiple-cause-of-death record tapes from the National Center of Health Statistics for the years 1980 through 1997, the most recent year for which data are available, were analyzed. These tapes include information from all death certificates filed in the United States. In this database, a single underlying cause of death was reported for each death, and multiple nonunderlying causes (immediate, intermediate, or contributing causes) may have also been listed. Causes of death were recorded according to ICD-9 codes [8]. HIV infection

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Table 1. Ranking of underlying causes of deaths due to infectious diseases in the United States in 1980 and 1997.

	1980		1997	
Rank	Type of infection	No. of deaths	Type of infection	No. of deaths
1	Respiratory tract	56,966	Respiratory tract	87,181
2	Septicemia	9438	Septicemia	22,396
3	Kidney/UTI	8006	HIV/AIDS	16,524
4	Heart	2486	Kidney/UTI	13,413
5	Tuberculosis	2333	Heart	5577
6	Bacterial meningitis	1402	Hepatobiliary	4596
7	Gastrointestinal	1377	Mycoses	2370
8	Hepatobiliary	1277	Tuberculosis	1259
9	Perinatal	1035	Gastrointestinal	1053
10	Mycoses	828	Perinatal	820

NOTE. Categories of infectious diseases identified by anatomic site rather than by causative microorganism did not have any microorganism specified in the death-certificate data. UTI, urinary tract infection.

was specifically identified by supplemental codes (0.42–0.44) that were introduced in 1987 [9]; however, since ICD-9 code 279.1 (deficiency of cell-mediated immunity) served as a proxy for HIV infection before 1987, we used this code to extend our search for data from the years before the introduction of codes 0.42–0.44. The specific ICD-9 codes that we used for invasive mycoses were as follows: blastomycosis, codes 116.0–116.2; candidiasis, 112.4–112.9; coccidioidomycosis, 114.0–114.9; histoplasmosis, 115.0–115.9; and other mycoses (including allescheriasis, aspergillosis, chromoblastomycosis, cryptococcosis, mycotic mycetomas, phaeohyphomycosis, rhinosporidiosis, sporotrichosis, and zygomycosis), 117.0–118.0. For malignancy, we used codes 140–208 and 210.0–239.0.

We searched the database for deaths with any of the ICD codes for the mycotic diseases in any of the 20 "entity axis" data fields for multiple causes of death. In the context of this analysis, deaths "from" a particular mycotic disease include deaths for which there was any mention of the mycotic disease on the death certificate (regardless of whether the mycotic disease was the underlying cause or a nonunderlying cause, such as a contributing cause). Thus, any death due to multiple mycotic diseases that was listed contributed to the counts of death due to each mycotic disease. The word "from" is used even for nonunderlying causes of death because, according to the instructions for the United States Standard Death Certificate, every diagnosis recorded on the certificate must be a part of the causal chain of events leading to death or must have otherwise contributed to the death; no condition should be included that was merely an important cause of illness or disability and did not lead or contribute to death.

To calculate annual death rates, we used mid-year estimates of the US population, which are based on decennial census data (Population Estimates Program, Population Division, US Census Bureau, Washington, D.C.). To control for changes in the age distribution of the population, age-adjusted rates were calculated on the basis of age-specific data and using the age distribution of the 1990 US population as the standard. The sex and race rate ratios were computed with use of Poisson regression and data unadjusted by age. We used the SAS System for Windows, release 6.12 (SAS Institute), for our analysis.

We reviewed the contribution of all the mycoses as both underlying and multiple causes of death. With respect to the former, the numbers of deaths are largely underestimated because in this data set, a disease such as malignancy or AIDS listed anywhere on the death certificate is preferentially listed as the underlying cause of death. In addition, since there were relatively few deaths in which an invasive mycosis was reported to be the underlying cause of death, we limited our further review of trends in mortality due to these infections to the multiple-cause mortality data (i.e., the mycosis appeared anywhere on the patient's death certificate).

RESULTS

The underlying causes of infectious-disease mortality are ranked in table 1. In 1980 mycoses ranked tenth, but in 1997 they were seventh.

Multiple Causes of Death

All mycoses. There was a dramatic increase in multiple-cause mortality due to all mycoses, from 1557 deaths in 1980 to 6534 deaths in 1997 (i.e., a 3.4-fold rate increase, from 0.7 to 2.4 deaths per 100,000 population), with a peak in 1989 (10,341 deaths, or 4.2 deaths per 100,000 population). Deaths from HIV-associated opportunistic mycoses accounted for the ma-

Table 2. Demographic trends in mortality due to invasive mycoses in the United States, 1980-1997.

Patient variable	Deaths per 100,000 population, by year				
	1980	1985	1990	1995	1997
Age, years					
0–4	0.13	0.22	0.30	0.31	0.21
5–24	0.13	0.38	0.51	0.45	0.31
25–44	0.32	2.79	6.05	5.45	2.53
45–64	1.21	3.06	4.90	4.74	3.39
⩾65	2.70	5.64	7.33	6.71	6.53
Sex[a]					
Male	0.88	3.18	5.58	4.53	2.62
Female	0.55	1.11	1.75	1.70	1.45
Race[a]					
White	0.83	2.16	3.40	2.84	2.11
Black	1.04	3.89	8.52	7.09	5.05
Other	2.31	6.58	5.68	5.52	5.13
Region[a]					
Northeast	1.35	6.62	11.52	8.18	4.73
Midwest	0.79	1.71	2.89	3.00	1.99
South	1.02	2.92	5.41	5.68	4.00
West	0.67	2.34	4.12	3.92	1.62

[a] Age-standardized mortality rates.

jority of the increase. The trend in fungal mortality from all mycoses associated with malignancy showed a very gradual increase during the study period.

Mortality by age group. The trend in the mortality rate for invasive mycoses has shown an increase in all age groups (table 2). The highest death rates occur among persons aged ⩾65 years (an increase from 2.7 to 6.5 deaths per 100,000 population). In particular, the death rate in the group aged 25–44 years, after a sustained increase through 1990, recently decreased.

Mortality by sex. Mortality rates for invasive mycoses were consistently higher among males: the rate ratio (male:female) ranged from 1.6 to 3.2 (table 2). On the basis of data unadjusted by age, after adjustment by year, the rate ratio (male:female) was 2.82 (95% CI, 2.78–2.85). Thus, males had a marked rate increase and were almost three times more likely to die from fungal diseases. After deleting all records with an HIV code, the rate ratio (male:female) found by Poisson regression analysis of the mortality data was 1.51 (95% CI, 1.49–1.54).

Mortality by race. Although there has been a marked increase in mortality rates for invasive mycoses across all racial categories, the rate increase has been consistently higher among blacks: the rate ratio (black:white) ranged from 1.3–2.5 (table 2). Using data unadjusted by age, after adjusting by year, we found that the rate ratio (black:white) was 2.31 (95% CI, 2.29–2.35). Thus, blacks were more than twice as likely to die from fungal diseases. After deletion of all records with an HIV code, the rate ratio (black:white) found by Poisson regression analysis of the mortality data was 1.46 (95% CI, 1.43–1.49).

Region. The mortality rate associated with invasive mycosis rose dramatically in all 4 regions of the United States, particularly in the Northeast (table 2).

Specific Mycoses

Opportunistic mycoses associated with HIV infection. Figure 1 illustrates the trends in mortality due to pneumocystosis and cryptococcosis. The trend in multiple-cause mortality associated with pneumocystosis has shown a marked upward trend, with a peak in 1989 at 2.11 deaths per 100,000 population. Subsequently, the mortality due to this mycosis has decreased markedly (a 71% decline). The trend in mortality for pneumocystis associated with HIV infection has closely paralleled the overall disease trend, with a peak in 1989 at 1.71 deaths per 100,000 population, which subsequently decreased by 73%, to 0.46 deaths per 100,000 population, in 1997. In comparison, the trend in multiple-cause mortality associated with cryptococcosis has shown a much more gradual upward trend, peaking in 1989 at 0.67 deaths per 100,000 population. Subsequently, there has been a gradual decline in the curve. The largest percentage increase (46%) in cryptococcosis-related mortality occurred from 1985 to 1986; from 1989 through 1990, the rate showed only minor changes. Since 1989, the mortality rate for this mycosis has decreased by 31%; the largest percentage decrease (35.2%) occurred in 1996–1997, from 0.46 to 0.30 deaths per 100,000 population. As demonstrated for pneumocystosis, the trend in overall cryptococcosis mortality and the mortality for this mycosis associated with HIV infection were quite similar.

Opportunistic mycoses not associated with HIV infection. Figure 2 illustrates the trends in mortality due to candidiasis, aspergillosis, and other mycoses. The trend in multiple-cause

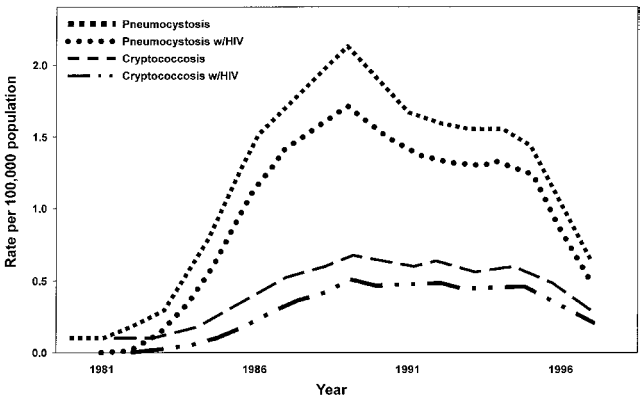

Figure 1. Mortality in the United States, 1980–1997, due to pneumocystosis and cryptococcosis in persons infected and persons not infected with HIV.

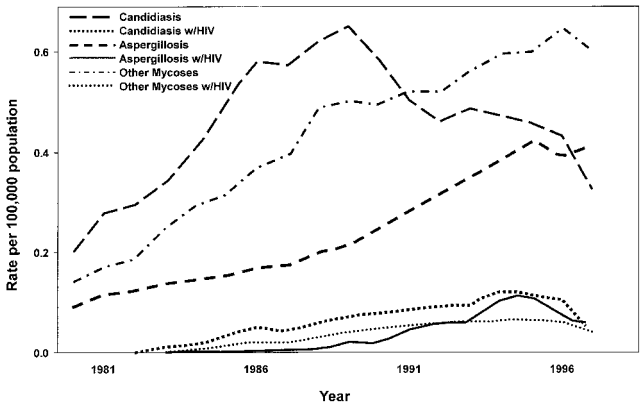

Figure 2. Mortality in the United States, 1980–1997, due to candidiasis, aspergillosis, and other mycoses in persons infected and persons not infected with HIV.

mortality rates associated with candidiasis showed a markedly steady increase during the study period to a peak in 1989, and this was followed by a gradual decline. Since 1989, the mortality rate for this mycosis has decreased by 50%. The same trend was evident among patients with malignancy-associated disease (data not shown). The rate of deaths from systemic candidiasis associated with HIV infection continued a definite but gradual increase through 1994; however, subsequently, the rate has decreased by 69%, from 0.12 to 0.04 deaths per 100,000 population. The trend in mortality associated with aspergillosis has demonstrated an almost exponential increase, peaking in 1995 at 0.42 deaths per 100,000 population. Since 1980, there has been a 357% increase in the mortality from this invasive mycosis. Despite a continued increase in the mortality due to aspergillosis associated with malignancy during the study period, from 0.04 deaths per 100,000 population in 1980 to 0.15 deaths per 100,000 population in 1997 (data not shown), since 1995 there has been a steady decline in mortality due to this mycosis associated with HIV infection.

The trend in multiple-cause mortality rates associated with category "other mycoses" has shown a markedly steady increase (329%) during the study period, from 0.14 deaths to 0.60 deaths per 100,000 population. In 1997, the mortality rate for this disease category ranked second only to that of pneumocystosis. The mortality rate for the other mycoses associated with malignancy has shown a less marked increase (240%) during the study period, from 0.05 to 0.17 deaths per 100,000 population (data not shown). There was a slight decrease in 1997 in the trend in mortality rates for the other mycoses associated with HIV infection.

Endemic Mycoses

The trends in mortality rates associated with histoplasmosis and coccidioidomycosis are given in figure 3. Despite smaller numbers compared with the opportunistic mycosis categories, the trend in histoplasmosis mortality rate has markedly increased, together with a more gradual and less marked increase in mortality due to coccidioidomycosis. The mortality rates for each of these mycoses were similar prior to 1984, when an upsurge in histoplasmosis mortality caused them to diverge. Recently, the gap in mortality rates associated with these mycoses has narrowed considerably, to 0.064 per 100,000 population deaths from histoplasmosis and 0.055 deaths per 100,000 population deaths from coccidioidomycosis in 1997, which is the smallest difference between these rates since 1980. Since 1980, there has been no change in histoplasmosis or coccidioidomycosis mortality rates associated with malignancy (<0.01 deaths per 100,000 population; data not shown); however, both the histoplasmosis and coccidioidomycosis mortality rates associated with HIV infection have decreased since 1994. Mortality associated with blastomycosis was the lowest of all the mycoses studied (the highest rate for this mycosis was 0.03 per 100,000 population), and no discernible trend could be determined (data not shown).

DISCUSSION

Our analysis of mortality data confirms a recent, marked upward trend in overall mortality due to the invasive mycoses and highlights important differences between specific mycoses according to both patient demographics and underlying immunocompromising conditions (in particular, HIV infection). The exact burden of mycotic infections has been difficult to estimate. There is evidence from a few recently published reports on hospital discharge data that the incidence of mycotic diseases (in particular, invasive candidiasis) has been increasing during the past 2 decades [1, 2, 5]. In addition, reports have suggested that mortality due to invasive mycoses has increased recently [3, 5, 7, 10]. The 2 major factors responsible for the

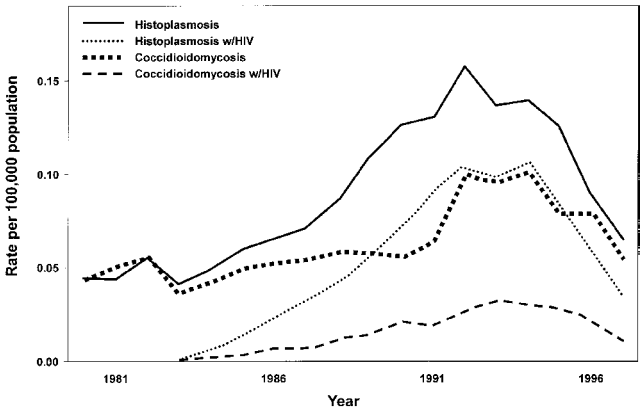

Figure 3. Mortality in the United States, 1980–1997, due to endemic mycoses in persons infected and persons not infected with HIV.

emergence of fungal infections have been the HIV disease epidemic and the many advances of modern medicine (including solid organ and bone marrow transplantation) that enable or prolong the survival of critically ill and susceptible patients. In addition, the aging of the population has increased the number of susceptible persons.

A limitation of the death-certificate data included in this analysis is the relatively small number of deaths found to be associated with mycotic infection, overall. These data almost certainly severely underestimate the true mortality due to these infections because of failures to clinically diagnose mycotic infection. A second limitation of our study is that only the information contained on the death certificate was available, and we have no data on the validity of the diagnosis of mycotic disease in these patients, which usually requires microbiological and/or histopathologic evidence of infection. Despite these limitations, the trends seen in our analysis should be generalizable, and to our knowledge this is only the second study to analyze trends in national mortality data for specific mycoses, thus extending the initial observations of Selik et al. [3] with regard to pneumocystosis, cryptococcosis, and histoplasmosis among HIV-infected persons.

There is no ongoing national surveillance system for mycotic infections. A major drawback to the establishment of routine surveillance useful for guiding specific prevention efforts for these infections is the insensitivity of the current diagnostic methods and the requirement for culture and/or histopathologic evidence of invasive infection. While newer diagnostic fungal blood culture methods with superior performance characteristics have recently become available, false-negative results continue to occur for patients with invasive candidiasis and are particularly problematic for patients with aspergillosis. Moreover, since the majority of these are opportunistic infections affecting critically ill patients often at the extremes of age, clinicians may be reluctant to perform invasive biopsy procedures and instead elect to institute presumptive antifungal treatment for these patients. The diagnosis of invasive mycotic diseases is also certainly affected by the recent dramatic decline in the national autopsy rate [11].

The major trends we found in mortality rates for all mycoses, by age, sex, race, and region, reflect predominantly the demographics of the HIV epidemic during the study period. Specifically, multiple-cause mortality associated with mycoses increased markedly among males. Deaths associated with mycoses also occurred more often among blacks. In addition, the Northeast was the region with the highest mortality associated with mycoses, which may be a reflection of both a concentration of the US population and a higher distribution of HIV-infected persons in this area. Of the 2 age groups with the highest mortality rates associated with mycotic infection, persons aged 25–44 years probably accounted for most of the HIV-infected persons. The other age group with very high (the highest) mortality associated with mycoses was persons aged $\geqslant$65 years, which is the age category most likely to have an increased incidence of underlying diseases, including malignancy.

Our study found that during the period 1980 through 1997, the trend in mortality due to HIV-associated opportunistic mycoses increased to a peak in 1989 and has since undergone a marked and steady decline. This trend is most dramatic for pneumocystosis and to a lesser extent for cryptococcosis. Coincident with the onset of these declining trends was the introduction of antiretroviral therapy and recommendation of the use of trimethoprim-sulfamethoxazole as routine prophylaxis for HIV-associated pneumocystosis [12]. Factors that may have influenced the decrease in mortality associated with cryptococcosis during this period include improved antifungal therapy and the reduced incidence of this opportunistic infection among HIV-infected patients that has been reported for 1992–1994 [6]. A further marked decline in these mortality rates was observed after 1995 and may be related to the introduction, in 1996, of highly active antiretroviral therapy, which has proven to be very effective in prolonging the survival of AIDS patients and decreasing the incidence of many of the infectious complications (including mycotic infections) and noninfectious complications of this disease [13–21].

When we examined the trends in mortality associated with the mycoses not associated with HIV infection, invasive candidiasis demonstrated a marked and steady increase through 1989, followed by a steady decrease through the remainder of the study period. The overall mortality trend for this mycosis resembled that seen for the HIV-associated mycoses; however, the factors responsible for this trend are unclear. Since we eliminated superficial mycotic infections from our analysis, the trend we observed in candidiasis is likely to reflect only the trends in candidemia and invasive candidiasis, rather than more characteristic HIV-associated disease manifestations (oropharyngeal candidiasis and esophagitis). Opportunistic invasive candidiasis is an uncommon complication in HIV-infected persons, although a recent report on active, population-based surveillance for candidemia in Atlanta and San Francisco, conducted by the Centers for Disease Control and Prevention during 1992–1993, identified HIV infection as an underlying medical condition in 10% of patients [5]. Recent reports have indicated that invasive infection with non-*albicans* species of *Candida* may be emerging among a growing group of high-risk patients, which may be directly related to the more widespread use of antifungal prophylaxis in this population [5, 22–24]; however, these infections are generally considered to be associated with reduced lethality.

As seen in figure 2, overall mortality associated with invasive candidiasis was predominantly a reflection of mortality among persons not infected with HIV. The trend in mortality asso-

ciated with aspergillosis continued to increase markedly during the study period. This trend is likely to be related to increased numbers of persons at risk for the infection, due to advances in modern medicine, such as bone marrow and solid organ transplantation. A similar, even more dramatic, upward trend was observed for the mortality associated with the less specific category "other mycoses." While the causative factor(s) for this upward trend is uncertain, it is likely to be similar to that hypothesized to explain the trend in aspergillosis-related mortality.

Among the endemic mycoses, the trend in overall mortality associated with histoplasmosis is closely similar to those for the HIV-associated mycoses, except that the peak mortality occurred somewhat later than was seen for either pneumocystosis or cryptococcosis. As shown in figure 3, a major determinant of the trend in overall mortality from histoplasmosis was the mortality from histoplasmosis in HIV-infected persons. While the peak mortality associated with coccidioidomycosis corresponded with that of histoplasmosis, the relative contribution of HIV-associated disease was much less, perhaps suggesting that the increase in mortality associated with this mycosis reflects recent increases in disease incidence, particularly in California and Arizona [25–27].

During the study period, approaches to the prevention of opportunistic fungal infections have changed markedly, particularly for HIV-infected persons. Antifungal prophylaxis with oral azoles has been shown in controlled trials to reduce the risk for mucosal (oropharyngeal, esophageal, and vaginal) candidiasis, cryptococcosis, and histoplasmosis in patients with advanced HIV disease [28–32]. However, the routine primary administration of fluconazole to HIV-infected patients is not recommended because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant *Candida* species to develop, the possibility of drug interactions, the cost of prophylaxis, and the relatively low incidence of these opportunistic infections in HIV-infected patients currently [33].

Formulating effective strategies to improve the outcome for patients with opportunistic mycoses not associated with HIV infection, in particular invasive aspergillosis, has continued to be a challenge to both clinicians and public health practitioners. Making the diagnosis early enough to allow for initiation of effective antifungal therapy has been difficult, and better diagnostic tools are needed to identify infected patients and allow for institution of timely and effective antifungal therapy. Clinical series have demonstrated a case fatality rate of >80% among these patients, findings which have led to the use of presumptive therapeutic approaches for high-risk patients [34]. Attempts to limit patients' exposure to these ubiquitous fungal microorganisms have included establishment of protected environments in hospitals, which are supplied with air from high-efficiency particulate air filters. Such measures are extremely costly, may be discomforting to the patient, and may be ineffective if the patient leaves the protective environment. To date, the efficacy of azole chemoprophylaxis for invasive aspergillosis has not been clearly established, but it may be reasonable to offer itraconazole to individual patients at particularly high risk of developing this infection, such as allogeneic bone marrow transplant recipients receiving corticosteroids for graft-versus-host disease.

In conclusion, our data have shown a marked increase in mortality associated with mycotic diseases—in particular, AIDS-associated and other opportunistic mycoses—and highlight the need for continuing surveillance for these infections. Further prospective studies are needed to evaluate the morbidity and better define the factors associated with poor outcome in high-risk populations.

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