The Direct Cost and Incidence of Systemic Fungal Infections

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ABSTRACT

Objectives: In this study we determined the incidence and direct inpatient and outpatient costs of systemic fungal infections (candidiasis, aspergillosis, cryptococcosis, histoplasmosis) in 1998.
Methods: Using primarily the National Hospital Discharge Survey (NHDS) for incidence and the Maryland Hospital Discharge Data Set (MDHDDS) for costs, we surveyed four systemic fungal infections in patients who also had HIV/AIDS, neoplasia, transplant, and all other concomitant diagnoses. Using a case-control method, we compared the cases with controls (those without fungal infections with the same underlying comorbidity) to obtain the incremental hospitalization costs. We used the Student's *t*-test to determine significance of incremental hospital costs. We modeled outpatient costs on the basis of discharge status to calculate the total annual cost for systemic fungal infections in 1998.
Results: For 1998, the projected average incidence was 306 per million US population, with candidiasis accounting for 75% of cases. The estimated total direct cost was $2.6 billion and the average per-patient attributable cost was $31,200. The most commonly reported comorbid diagnoses with fungal infections (HIV/AIDS, neoplasms, transplants) accounted for only 45% of all infections.
Conclusion: The cost burden is high for systemic fungal infections. Additional attention should be given to the 55% with fungal disease and other comorbid diagnoses.
Keywords: aspergillosis, candidiasis, cryptococcosis, histoplasmosis.

Introduction

The impact of fungal infections on health care and economic expenditures is large and of growing concern. Data in the 1980s showed a dramatic increase in nosocomial fungal infections in the United States [1,2]. Despite this, there are few estimates in the literature for the overall costs of fungal infections. Costs attributable to systemic fungal infections are difficult to estimate because they often occur in conjunction with other diagnoses. Apart from various cost-effectiveness studies of drugs to treat fungal infections [3,4] and cost studies of fungal infections in specific disease populations [5,6], there has not been a general cost study of systemic fungal infections over all diseases. We determined the first-year direct costs of four systemic fungal infections: candidiasis, aspergillosis, cryptococcosis and histoplasmosis.

We also determined the annual incidence of these four fungal infections in the United States. Currently reported incidence rates are highly variable [7,8] and apart from one regional population study [9], consist mostly of nosocomial rates reported voluntarily by hospitals [10,11]. Existing studies focus primarily on one type of fungal infection with a single comorbid diagnosis [12–14]. The study presented here uses relatively large, broad patient populations from the National Hospital Discharge Survey (NHDS) [15] and the Maryland Hospital Discharge Data Survey (MDHDDS) [16]. We address both incidence and costs, particularly the incremental cost of candidiasis, aspergillosis, cryptococcosis and histoplasmosis.

Methods

Our study examined the incidence and first-year costs of systemic fungal infections incurred from the time of hospitalization. We used standard methods for disease-cost estimation described elsewhere [17–20]. Specifically, we computed the pro-

jected 1998 incidence and attributable costs by type of fungal infection and major diagnosis. We applied an aggregate incidence-based approach using large national and state data sets to estimate incidence rates and both hospital and post-hospital, first-year costs.

Incidence

We computed the US incidence of four types of systemic fungal infections—candidiasis, histoplasmosis, aspergillosis, and cryptococcosis fungal infections—using the 1994 and 1996 National Hospital Discharge Survey (NHDS) [15] database. The NHDS data set includes over 275,000 discharges from a national sample of hospitals [21]. These four fungal infections account for almost all cases of systemic fungal infection, and candidiasis alone accounts for up to 85% to 87% of these [9].

Systemic fungal infections were identified in the NHDS database according to the International Classification of Disease, Ninth Revision (ICD-9) codes: candidiasis of the lung (112.4), disseminated candidiasis (112.5), candidiasis of other specified sites, including candidal endocarditis, candidal otitis externa, candidal meningitis, candidal esophagitis, candidal enteritis (112.8) and candidiasis of unspecified site (112.9), infections by *Histoplasma capsulatum* (115.0), infection by *Histoplasma duboisii* (115.1), aspergillosis (117.3) and cryptococcosis (117.5). We searched for these ICD-9 codes in any of the 15 positions for the diagnosis listed at patient discharge.

Given that the NHDS is a nationally representative survey of hospital admissions, the total number of hospitalized fungal infection cases from the NHDS was used as the incidence or rate of infection in the US population. The relative standard errors (RSE) for the NHDS fungal infection estimates were also computed [21,22]. The 1996 NHDS systemic fungal incidence rate was projected and applied to the 1998 US population using the national census data [23].

Hospitalization Costs

Hospitalization costs were computed from the 1997 Maryland Hospital Discharge Data Set (MDHDDS) [16]. The MDHDDS, compiled by the Maryland Health Services and Cost Review Commission, contains over 610,000 discharges from all nonfederal, short-stay hospitals in Maryland. The MDHDDS also contains information on patient demographics, itemized and total hospital charges, and primary payer source. MDHDDS hospitalization charges were converted to costs using hospital-specific cost/charge ratios calculated within the data set. MDHDDS has been used to estimate cost sources in previous studies [24].

It is challenging to determine the cost of fungal infections because of the difficulty of separating these costs from those attributable to underlying or associated diseases. For example, it is impossible to assign certain hospital days as fungal infection costs and others to costs of underlying diseases such as HIV or cancer. Therefore, using a case-control method, we estimated the incremental hospitalization costs due to systemic fungal infection by comparing patients with fungal infections (cases) to patients with the same primary diagnoses but without fungal infections (controls).

Four disease categories of primary diagnoses commonly associated with fungal infections were selected: HIV/AIDS, cancer/neoplasia, transplantation, and "other." Since the "other" group was so large, we categorized the diagnoses for this group into the 17 broad groups specified by the ICD-9 diagnoses.

First, we selected a population of hospitalized patients from the 1997 MDHDDS with systemic fungal infections (cases) according to the ICD-9 codes listed above in any of the 15 possible variable listings for diagnosis. Thereafter, we searched the remaining 14 listings of possible diagnoses for an associated diagnosis of HIV/AIDS, neoplasm, transplant, or "any other" diagnosis. The controls were defined as all other patients without fungal infections and matched to the cases by their primary or first-listed diagnosis. Fourth, we determined the average cost per hospital stay for the cases and controls in each fungal (candidiasis, histoplasmosis, aspergillosis, and cryptococcosis) and diagnostic (HIV/AIDS, neoplasm, transplant, or "any other") group. We also computed the average hospital stays for both cases and controls. Finally, we subtracted the mean costs of the controls from the mean costs of the cases to obtain the incremental costs of the four fungal infections in each diagnostic group.

Student's *t*-test was used to determine the statistical significance of the differences in mean hospitalization costs between cases and controls for each type of fungal infection and principal diagnosis. SAS statistical software (Cary, NC, version 6.12, 2000) and Microsoft Excel (Troy, New York, version 9.0, 2000) were used for data analyses [25,26].

Hospitalization costs included room charges, radiology, operating room, drugs, lab tests, supplies, therapy, and all other charges. Physician

costs based on the Medicare fee schedule and dependent on the average length of hospital stay ($109 + $70 (LOS-1)) were also included. To estimate the annual hospitalization cost of systemic fungal infection for 1998, we projected the MDH-DDS 1997 hospitalization cost by adjusting for medical inflation [27] and applied it to the projected 1998 national incidence rates.

Post-Hospitalization Costs

Post-hospitalization costs were modeled from the proportions of patients discharged in the 1996 NHDS discharge destination categories, i.e., death, home, and short- or long-term care facilities. Those discharged home accrued costs for home health care (1.39 visits monthly), physician visits (1.73 visits monthly), lab tests, medications and general follow-up care [28–31]. Physician costs were obtained from the Medicare fee schedule and based on CPT codes 99211–99215 [31]. The average annual total home-care cost is $4512. Those discharged to a long-term care facility were given nursing home costs for the rest of the year, while those discharged to short-term care were assumed to have nursing home costs for half of the year. Nursing home costs were determined from average annual costs of nursing home stays ($54,787/ year) in the Medicare/Medicaid population [32]. Patients who died in hospital only had hospital costs attributed to the overall cost of their fungal infection. All post-hospitalization costs were projected to 1998 values using the Consumer Price Index [27].

Post-hospital drug costs were assumed to be included in nursing home costs during both short- and long-term care, but were included separately for patients discharged to home and for the 6 months spent at home by patients discharged to short-term care facilities. The outpatient drug therapy was modeled using drug treatment guidelines and expert clinicians [33–36]. Drug costs were determined from the 1998 Red Book average wholesale price (AWP) [37].

Mortality rates were also considered in computing post-hospitalization costs. Literature-reported mortality rates associated with fungal infections are highly variable, ranging from 2.8% to 70%, depending in part on the underlying comorbidities and whether total or in-hospital rates are reported [6,38–41]. Since approximately 7% of patients admitted with fungal infections subsequently died in the hospital, we attributed additional deaths to those discharged alive to account for deaths over the remaining year. We included an additional

15% post-hospitalization mortality for patients going to home care and an additional 21% mortality for patients discharged to either short- or long-term nursing home care and varied these values in the sensitivity analysis.

Sensitivity Analyses

One-way sensitivity analyses were calculated for incidence, mortality, and drug costs. For our analysis, we chose the best estimates for the base case. High and low values for incidence, mortality, and drug costs were used to calculate a range of cost estimates. Incidence was varied by excluding ICD-9112.8 and 112.9 (for candidiasis of other sites and unspecified site, respectively) for the low-incidence case (37,555) and by applying the higher systemic fungal incidence from the MDHDDS (144, 462) for the high-incidence case. We also varied mortality rates for the sensitivity analysis according to the wide range of values quoted in the literature [7–9,38,41]. We assumed no post-hospital deaths in the home-care group and 15% in nursing homes for the high-cost range and 35% and 48% mortality in the home-care and nursing home groups, respectively, for the low-cost case. Outpatient drug costs were also varied from the base case using the range of doses and lengths of drug treatment recommended in the treatment guidelines [33–36].

Results

Incidence

Table 1 shows the rates for fungal infections from the NHDS data, reported per million US population and per 10,000 hospital patients in 1994 and in 1996. Candidiasis is the most frequent systemic fungal infection, accounting for as much as 80% of reported cases. Histoplasmosis has the lowest rate, most likely because of the endemic nature of the disease. The incidence of hospitalization for systemic fungal infections was 306 per million in 1996.

Much of the clinical, epidemiological, and cost literature on fungal infections focuses on the occurrence in patients with three comorbid diagnoses: HIV/AIDS, neoplasia, or transplantation. However, our analyses show that these diagnoses are associated with only 44% of all hospitalizations for systemic fungal infection. HIV/AIDS and neoplasia are the diagnoses associated with the highest proportions (22% and 21%, respectively) of systemic fungal diseases. Patients with HIV/ AIDS account for 79% of the hospitalizations for

Table 1 Incidence rates of hospitalized fungal infection cases by year and type of infection. Relative standard error (RSE) of N expressed as percent of the estimate, computed as described in [21,22]

	NHDS* 1996				NHDS 1994			
	N	RSE*	Rate per million US population	Rate per 10,000 hospital patients	N	RSE†	Rate per million US population	Rate per 10,000 hospital patients
Total	82,608	7.52	305.62	27.05	78,928	10.89	303.23	25.59
Candidiasis	61,680	8.43	228.19	20.19	62,815	12.04	241.33	20.37
Histoplasmosis	3,681	31.28	13.62	1.21	4,950	40.58	19.02	1.60
Aspergillosis	9,261	19.93	34.26	3.02	5,195	39.62	19.96	1.68
Cryptococcosis	7,987	21.41	29.55	2.61	5,968	36.99	22.93	1.93

*Computed as described in [22].
†Computed as described in [21].
NHDS, National Hospital Discharge Survey.

cryptococcosis, and those with neoplasms account for as much as 42% of the hospitalizations for systemic aspergillosis. Transplant patients, another patient group prone to systemic fungal infections, account for only 1% of the total patients diagnosed with fungal infections.

The remaining 56% of patients hospitalized for fungal infections, exclusive of HIV/AIDS, neoplasms, or transplants belong to the "other diagnosis" group. In the "other" category, patients diagnosed with diseases of the respiratory system comprise the highest proportion (15%) of all fungal infections. Patients with comorbid diagnoses involving the respiratory tract account for 17% of cases of systemic candidiasis, 15% of histoplasmosis, 18% of all aspergillosis and only 0.7% of cryptococcosis. Another 14% of patients with systemic fungal infections have concomitant "other diagnoses" of infectious and parasitic diseases (not including fungal disease), followed by diseases of the digestive system (7%), disease of the circulatory system (5%), injuries and poisonings (5%), and miscellaneous diagnoses (10%).

Inpatient Hospital Costs by Type of Infection and Associated Diagnoses

The mean cost comparison between cases and controls is enumerated in Table 2. Projected to 1998, the incremental, weighted, average hospitalization cost per person attributable to systemic

Table 2 Hospitalization mean and incremental cost per person between patients with and without fungal infection by underlying morbidity from the analysis of the 1997 MDHDDS

Fungal infection	Underlying morbidity	Mean cost without infection US$ (SEM)	Mean cost with infection US$ (SEM)	Prob>T	Incremental costs US$	Incremental cost projected to 1998	Weighted average* US$
Candidiasis							14,804
	HIV	9036 (155)	12288 (745)	0.0001	3256	3356	
	Neoplasm	8975 (53)	26188 (1757)	0.0001	17212	17763	
	Transplant	72706 (2344)	119926 (12721)	0.0001	47221	48732	
	Other	7024 (16)	22752 (934)	0.0001	15728	16231	
Histoplasmosis							329
	HIV	9247 (153)	10312 (2948)	0.8072	7621	1673	
	Neoplasm	9104 (54)	11971 (2689)	0.5283	2868	2960	
	Transplant	—	—	—	—	—	
	Other	7070 (16)	6354 (971)	0.4665	−739	−739	
Aspergillosis							36,867
	HIV	9160 (150)	40469 (8041)	0.0014	31309	32311	
	Neoplasm	9045 (53)	55474 (8056)	0.0001	46429	47915	
	Transplant	73980 (2309)	157929 (65129)	0.0096	83949	86635	
	Other	7066 (16)	31916 (4629)	0.0001	24850	25645	
Cryptococcosis							6,328
	HIV	9122 (156)	12462 (717)	0.0000	3340	3447	
	Neoplasm	9097 (54)	27010 (9558)	0.0737	14684	15154	
	Transplant	—	—	—	—	—	
	Other	7069 (16)	25542 (6135)	0.0051	18473	19064	
Total							15,813

*Weighted averages per incident case of the incremental cost projected to 1998.
MDHDDS, Maryland Hospital Discharge Data Survey.

candidiasis, histoplasmosis, aspergillosis and cryptococcosis is $15,813 (range from $15,646 to $16,758). Aspergillosis accounts for the largest incremental per-person hospitalization costs of all fungal infections ($36,867). Candidiasis also accounts for a high incremental cost of $14,804. The incremental hospitalization cost for cryptococcosis is $6328, while the incremental hospitalization cost for histoplasmosis is only $329 per case.

Transplant patients have the highest mean additional hospitalization costs per person attributable to any type of fungal infection, $53,470. Patients with neoplasms incur an additional cost per person of $21,571, while those with a diagnosis of HIV/AIDS incur much lower per-person costs for fungal infections ($4128). These three diagnoses, however, represent only 44% of patients hospitalized with systemic fungal infections. The remaining patients, with fungal infections from all "other diagnoses" incur an additional $16,506 per person for hospitalization costs on average.

Statistical analyses reveal that the average differences in hospital costs between patients with and without fungal infections matched by diagnosis (cases and controls) are statistically significant ($p < .01$) (Table 2) for all systemic fungal infections and all comorbid diagnoses except for cryptococcosis in patients with neoplasms and patients with histoplasmosis in any diagnostic category, where the differences were not significant. The incremental hospitalization cost due to histoplasmosis is not statistically significant, most likely because of the small number of cases of histo-plasmosis ($n = 47$) in the 1997 MDHDDS used to estimate costs.

Over all diagnoses and types of fungal infections, the room rate contributes the most to total hospitalization costs (47%). Drug costs account for 17% of total hospitalization costs across all fungal types and laboratory costs contribute significantly (11%) to the total costs. Other factors contribute between 3% and 6% to total hospitalization costs. Patients with aspergillosis have the lengthiest additional hospital stay (19 days), and those with candidiasis stay an average of 14 additional days in the hospital.

We also investigated who was paying the largest burden of the hospitalization costs for these fungal infections based on the NHDS 1996 data. Government insurance is primarily responsible, covering 67% of hospitalization costs, with Medicare paying 44% and Medicaid, 20%. Private insurance covers 24% and the recipient of services

pays only 3%; the remainder is not specified. Medicare pays for almost half of the total hospitalization costs for candidiasis and aspergillosis. The cost burden of histoplasmosis is borne primarily by "other private insurance" (32%) and Medicaid (29%) and to a lesser extent, Medicare (20%) and self-pay (13%). Fifty-four percent of the costs associated with cryptococcosis are paid by Medicaid and to a lesser extent by Medicare (19%), other government payers (19%), and other private insurance (17%).

Post-Discharge Status and Hospital Mortality

Discharge status obtained from the 1996 NHDS data reveals that 75% of patients are discharged to home, 18% go to nursing home care (6% short-term and 12% long-term), and 6.8% of patients die in the hospital. Our hospital mortality rates are comparable to one previously reported in the literature (9%) for nosocomial fungal infections [42].

Discharge status varies by type of fungal infection. Patients with cyptococcosis infections have the highest in-hospital death rate per admission (16%), followed by candidiasis (6.3%). Aspergillosis and histoplasmosis are associated with similar inpatient mortality rates of 3.9% and 3.4% of hospital deaths, respectively. Patients with systemic aspergillosis are most frequently discharged to home (86.6%). The majority of patients diagnosed with systemic histoplasmosis, candidiasis, or cryptococcosis were also discharged home (80.6%, 73.4%, and 71.8%, respectively). The largest proportion (14.6%) of patients discharged to long-term nursing homes are those diagnosed with systemic candidiasis. Only 1% to 6% of patients with other fungal types are discharged to nursing homes.

Outpatient Costs

The cost of post-hospitalization outpatient care in the first year is $1192 million for all patients, which accounts for 47% of total costs (Table 3). Outpatient costs and costs per prevalent case are highest for candidiasis patients. Nursing home care accounts for the largest proportion (57%) of all outpatient costs ($676 million) following discharge from hospital for systemic fungal infections, despite being the final destination for only 18% of the discharges.

Additional outpatient medication costs amount to $236 million or $2859 annually per person. The highest average annual drug cost per person ($23,295) is associated with aspergillosis. The use of liposomal amphotericin B in this group accounts for some of the elevated drug cost, since

Table 3 Projected 1998 total costs and average per-incident case (PIC) by fungal infection

	Total (N = 82608)		Candidiasis (N = 61680)		Histoplasmosis (N = 3681)		Aspergillosis (N = 9261)		Cryptococcosis (N = 7987)	
	Total cost (millions $)	PIC ($)	Total cost (millions $)	PIC ($)	Total cost (millions $)	PIC ($)	Total cost (millions $)	PIC (*$)	Total cost (millions $)	PIC (*$)
Total costs	2,576.75	31,193	1,698.85	27,543	52.54	14,275	674.12	72,792	151.23	18,934
Total inpatient	1,384.35	16,758	971.04	15,743	3.96	1,076	351.19	37,921	58.15	7,281
Hospital	1,306.29	15,813	913.11	14,804	1.21	329	341.42	36,867	50.54	6,328
Physician	78.06	945	57.93	939	2.75	747	9.77	1,054	7.61	953
Total outpatient	1,192.39	14,434	727.81	11,800	48.58	13,199	322.92	34,871	93.07	11,653
Home care	279.78	3,387	208.90	3,387	12.47	3,387	31.36	3,387	27.05	3,387
Drugs	236.14	2,859	13.81	224	5.97	1,622	215.73	23,295	0.62	78
Short-term care	141.95	1,718	105.99	1,718	6.32	1,718	15.91	1,718	13.72	1,718
Long-term care	534.52	6,470	399.11	6,470	23.82	6,470	59.92	6,470	51.68	6,470

our model estimates that 40% of patients discharged from the hospital take liposomal amphotericin B for an average of 70 days. Drug costs are much lower for cryptococcosis, but higher for histoplasmosis ($6 million) despite its low incidence. When 17% of the inpatient costs attributed to inpatient medication ($225 million) is added to the outpatient drug costs ($236 million), the total drug cost constitutes 18% of total direct costs associated with all systemic infections in the first year.

Total Costs

The total direct incremental cost of the first year of treatment of systemic fungal infections in the United States is $2.6 billion. Figure 1 divides the total cost into hospitalization and post-hospitalization costs, including nursing home, home health care, and outpatient medications. Hospitalization (including physician fees) contributes the highest proportion to total cost, or 54% ($1.4 billion). For the almost 15,000 patients (18% of the hospitalized sample) discharged to either short-term or long-term nursing home care, the additional nursing home costs account for 26% of total costs ($676 million), $535 million for long-term nursing home care, and $142 million for short-term nursing home care. Among the 75% of patients discharged to home, the additional home-health-care cost (including physician visits, lab tests, and home-care workers) is $280 million. Outpatient medications contribute significantly ($236 million or 11%) to the total cost, but total inpatient and outpatient drug costs account for 18% of the total costs.

As shown in Table 3, total costs are highest for candidiasis ($1.7 billion), primarily because of its high incidence. Candidiasis accounts for 75% of all

systemic fungal infections and 66% of the total cost of these. Aspergillosis accounts for 26% ($674 million) of costs, and cryptococcosis and histoplasmosis costs are $151 million and $53 million, respectively, representing only 6% and 2% of all costs for systemic fungal infections. Per-person weighted average annual costs were $31,193. This per-person cost is highest for aspergillosis at $72,792, which is more than twice the overall average. The average incremental per-person hospitalization costs account for most of this difference, because the high inpatient mortality associated with aspergillosis reduces outpatient cost.

Sensitivity Analysis

Because of the large variation in reported incidence and mortality rates [7–9,42,43], we calculate total costs using ranges of incidence and mortality around the base case as shown in Table 4. Varying the fungal incidence from 161 per million to 534 per million resulted in a total cost range between $978 million and $6 billion. Changing the mortality rates for patients discharged to home from 0% to 35% has very little effect (3%) on total direct costs ($1525–$1578 million). However,
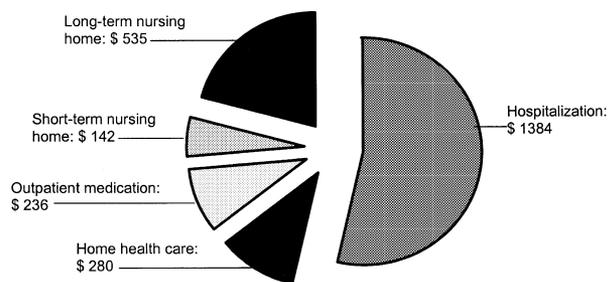

Long-term nursing home: $ 535
Short-term nursing home: $ 142
Outpatient medication: $ 236
Home health care: $ 280
Hospitalization: $ 1384

Figure 1 Total costs by type of cost.

changes in mortality estimates in the nursing home from 15% to 48% have a greater (22%) effect on total costs ($574–$699 million). Changes in the estimated duration of drug treatment changed total costs by only 5%. Overall, the lowest total estimate is $853,000 or $22,700 per prevalent case while the highest total estimate is $6.1 billion or $42,500 per prevalent case.

Discussion

The cost burden of fungal infections nationally is high, with an annual cost of $2.6 billion. Total US health expenditures in 1998 were $1.1 trillion [44]. Thus, approximately 0.24% of total US health expenditures are spent on systemic fungal infections. This is high considering that only 0.03% of the total US population contracts fungal infections. The average annual health expenditure per person in the United States is $4,094, while the average added expenditures for patients with fungal infections is $31,200 per person, almost eight times greater.

The cost estimates used in this paper are based on the best available resources for developing national estimates, such as the NHDS, the Medicare fee schedule, and the Medicare national nursing home survey. The large sample sizes are a strength of these data sets because of the low incidence

rates of fungal infections. However, several qualifications should be noted:

1. All fungal infections as tallied in the NHDS by the corresponding ICD-9 codes were assumed to include both nosocomial and community-acquired cases.
2. Although hospital rates were used to estimate incidence, some community-acquired cases might not have been admitted to the hospital and therefore our estimates may be low. We accounted for this in the sensitivity analyses by increasing the total number of systemic infections from 82,608 to 144,462 cases.
3. Attributable cost is estimated by comparing the average costs of hospitalization by matching patients with the same diagnosis with and without fungal infections. However, we were only able to match patients based on admitting diagnoses, and the patients might differ on factors other than fungal infections. While most differences in severity of disease diagnosis may be attributable to the fungal infection itself, other disease factors might contribute to and bias the results. Therefore, the cost attributable to systemic fungal infections should be considered a maximum estimate and further study on better-matched cases should be considered.

Our incidence figures are comparable to those in the literature when we take into consideration both the location of the studies and the diagnoses included. One such study by Rees et al. [9] based in the San Francisco Bay Area reported a rate for candidiasis of 72.8 per million, which is much lower than the rate we observed for candidiasis of 305.6 per million. However, when we recalculated our incidence rates using the same ICD-9s as those in the Rees study, the candidiasis incidence was 59.3 per million, which is more comparable. Rees et al. [9] also reported rates somewhat lower than those reported here for aspergillosis (12.4 vs. 19.2 per million) which may be a result of stricter diagnostic criteria requiring two positive bronchoalveolar lavages. When determining cost, we chose a more inclusive definition or diagnostic criteria.

Most reports on fungal infections focus on rates, costs, and treatments for fungal infections associated with three main diagnoses—HIV/AIDS, neoplasia, and transplantation—because of the high prevalence of fungal infections in these diagnoses [4,12–14,45–48]. However, we found that fungal infections associated with all other diagnoses make up 55% of all cases requiring hospitalization for such infections, higher than in the

Table 4 Sensitivity analysis: Effects of variations in incidence, mortality and outpatient drug treatment duration on total costs of fungal infections

Variations in:	Low case*	Base case†	High case‡
Incidence:	37,555	82,608	144,462
Total costs (millions $)	978	2,577	6,000
Cost/person ($)	26,000	31,200	41,500
Home-care mortality (%):	35	15	0
Total home-care costs (millions $)	1,525	1,555	1,578
Cost/person ($)	24,600	25,100	25,400
Nursing-home mortality (%):	48	21	15
Total nursing-home costs (millions $)	574	676	699
Cost/person ($)	38,500	45,300	46,800
Outpatient drug duration:			
Total drug cost (millions $)	171.1	236.1	301.2
Total costs (millions $)	2,512	2,577	2,642
Cost/person ($)	30,409	31196	31982
All factors:	37,555	82,608	144,462
Total costs (millions $)	853	2,577	6,144
Cost/person ($)	22,700	31,200	42,500

*ICD-9s restricted to 112.4 and 112.5 only.
†ICD-9s included 112.4, 112.5, 112.8, and 112.9 and projected 1998 cases from NHDS 1996.
‡Projected 1998 cases from Maryland 1997 data.

other three diagnoses combined. There have been several studies on the additional risk factors for susceptibility to nosocomial fungal infections from causes such as central lines, urinary catheters, mechanical ventilation and nosocomial transmission [10,49–51], antifungal drug resistance [52], neutropenia [53] and immunosupression [54,55]. The National Nosocomial Infections Surveillance (NNIS) tracks rates of nosocomial infections in postsurgical intensive-care units and among patients using catheters and central lines [56]

Subsequent studies are needed to further explore the incidence of and preventive treatments for fungal infections among patients in the "other" diagnostic categories (respiratory and circulatory diseases), who may also be neutropenic or immunocompromised. NNIS surveys do include all high-risk patients, but more attention should be given to prevention of these risk factors in "other" diagnostic groups as well.

In our analysis of incidence in the 1994 and 1996 NHDS, we found no significant change in incidence between those 2 years despite previous reports in the literature that cited large increases in the incidence of systemic fungal infections in the 1980s [1,2]. Further studies are required to determine whether the incidence of systemic fungal diseases has stabilized in recent years, influenced perhaps by better preventive measures and treatments for neutropenia.

References

1 Banerjee S, Emori T, Culver D, et al. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. National Nosocomial Infection Surveillance. Am J Med 1991;91: S86S–9.

2 Pfaller M. Epidemiology and control of fungal infections. Clin Infect Dis 1994;19:S8–13.

3 Dranitsaris G, Phillips P, Rotstein C, et al. Economic analysis of fluconazole versus amphotericin B for the treatment of candidemia in non-neutropenic patients. Pharmacoeconomics 1998;13:509–18.

4 Torfs K. Economic aspects of treatment of fungal infections in cancer patients. European J Clin Microbiol Infectious Dis 1997;16:98–107.

5 Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin Infect Dis 1998;27:781–8.

6 Goff DA, Sierawski SJ, Fass RJ. Cost analysis of candida infection among surgical intensive care unit patients. Clin Drug Invest 1996;12:176–80.

7 Beck-Sague CM, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. J Infect Dis 1993; 167:1247–51.

8 Yamamura DLR, Rotstein C, Nicolle LE, et al. Candidemia at selected Canadian sites: results from the fungal disease registry, 1992–1994. Fungal Disease Registry of the Canadian Infectious Disease Society. CMAJ 1999;160:493–9.

9 Rees JR, Pinner RW, Hajjeh RA, et al. The epidemiological features of invasive mycotic infections in the San Francisco Bay Area. 1992–1993: results of population-based laboratory active surveillance. Clin Infect Dis 1998;27:1138–47.

10 Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on candida species. Clin Infect Dis 1995;20:1526–30.

11 VandenBergh M, Verweij P, Voss A. Epidemiology of nosocomial fungal infections: invasive aspergillosis and the environment. Diagn Microbiol Infect Dis 1999;34:221–7.

12 Viscoli C, Girmenia C, Marinus A, et al. Invasive fungal infection group EORTC. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28:1071–9.

13 Tollemar J, Ericzon BG, Holmberg K, et al. The incidence and diagnosis of invasive fungal infections in liver transplant recipients. Transplant Proc 1990;22:242–4.

14 Hajjeh RA. Disseminated histoplasmosis in persons infected with human immunodeficiency virus. Clin Infect Dis 1995;August 21(Suppl. 1):S108–10.

15 National Hospital Discharge Survey. Hyattsville, MD: National Center for Health Statistics, 1997.

16 Maryland Hospital Discharge Data Survey. Glen Burnie, MD: St. Paul Computer Center, 1997.

17 Hay J. Econometric issues in modeling the cost of AIDS. Health Policy 1989;11:125–45.

18 Cooper BS, Rice DP. The economic cost of illness revisited. Soc Secur Bull 1976;39:21–36.

19 Hartunian NS, Smart CN, Thompson MS. The incidence and economic costs of cancer, motor vehicle injuries, coronary heart disease, and stroke: a comparative analysis. Am J Public Health 1980; 70:1249–60.

20 Hodgson TA, Meiners MR. Cost of illness methodology: a guide to current practices and procedures. Milbank Memorial Fund Q Health Soc 1982;60:429–62.

21 Graves E, Gillum B. 1994. Summary: National Hospital Discharge Survey. Advance data from vital and health statistics, Vol. 278. Hyattsville, MD: National Center for Health Statistics, 1996.

22 Graves E, Owings M. Summary: National Hospital Discharge Survey. Advance Data 1998. Hyattsville, MD: National Center for Health Statistics, 1998, 1–11.

23 US Census Bureau, Population Division, Populations Projections Branch, Washington, DC 20233. Available from: URL: http://wwwcensusgov/population/estimates/. First accessed 1996.

24 Cook P, Lawrence B, Ludwig J, et al. The medical costs of gunshot injuries in the United States. JAMA 1999;282:447–54.

25 Microsoft Excel 97. Troy, New York: Microsoft Corporation, 2000.

26 The SAS, System for Windows. 6.12 ed. Cary, NC. SAS Institute, Inc., 1999–2000.

27 Consumer Price Index. Monthly Labor Review and Handbook of Labor Statistics. Washington, DC: Bureau of Labor Statistics, 1999.

28 Hellinger FJ. The lifetime cost of treating a person with HIV. JAMA 1993;270:474–8.

29 Rietmeijer CA, Davidson AJ, Foster CT, et al. Cost of care for patients with human immunodeficiency virus infection – patterns of utilization and charges in a public health care system. Arch Intern Med 1993;153:219–25.

30 Gable CB, Tierce JC, Simison D, et al. Costs of HIV+/AIDS at Cd4 (+) counts disease stages based on treatment protocols. J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:413–20.

31 Physician Fees: a Comprehensive Guide for Fee Schedule Review and Management. James B. Davis; Los Angeles, CA: Practice Management Information Corporation, 1998.

32 Saunders WD. HCFA: Health Care Financing Administration 1998 Data Compendium. Baltimore, MD: Office of Strategic Planning, 1998.

33 Gallis HA, Drew RH, Pickard WW. Amphotericin B. 30 years of clinical experience. Rev Infectious Diseases 1990;12:308–29.

34 Kauffman CA. Role of azoles in antifungal therapy. Clin Infect Dis 1996;22:S148–53.

35 Klepser ME, Lewis RE, Pfaller MA. Theraphy of candida infections: susceptibility testing, resistance and therapeutic options. Ann Pharmacother 1998; 32:1353–61.

36 Robinson RF, Nahate MC. A comparative review of conventional and lipid formulations of amphotericin B. J Clin Pharm Ther 1999;24:249–57.

37 Drug Topics Red Book. Montvale, NJ: Medical Economics Company, 1998.

38 Karlowsky JA, Zhanel GG, Klym KA, et al. Candidemia in a Canadian tertiary care hospital from 1976 to 1996. Diagn Microbiol Infect Dis 1997; 29:5–9.

39 Lam HH, Althaus BL. Antifungal prophylaxis in bone marrow transplant. Ann Pharmacother 1995; 29:921–4.

40 Noskin G, Pietrelli L, Gurwith M, Bowden R. Treatment of invasive fungal infections with amphotericin B colloidal dispersion in bone marrow transplant recipients. Bone Marrow Transplant 1999;23:697–703.

41 Wenzel RP. Nosocomial canididemia – risk factors and attibutable mortality. Clin Infect Dis 1995;20: 1531–4.

42 Harbarth S, Ruef C, Francioli P, Widmer A, Pittet D. Nosocomial infections in Swiss university hospitals: a multi-centre survey and review of the published experience. Schweiz Med Wochenschr 1999; 129:1521–8.

43 Cornwell E, Belzberg H, Berne T, et al. The pattern of fungal infections in critically ill surgical patients. Am Surg 1995;61:847–50.

44 Levit K, Cowan C, Lazenby H, et al. Health spending in 1998. Health Aff 2000;19:124–32.

45 Hajjeh RA, Conn LA, Stephens DS, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. J Infect Dis 1999;179:449–54.

46 Ribaud P. Fungal infections and the cancer patient. Eur J Cancer 1997;33:S50–4.

47 Krcmery V Jr. Emerging fungal infections in cancer patients. J Hosp Infect 1996;33:109–17.

48 Merhav H, Mieles L. Amphotericin B lipid complex in the treatment of invasive fungal infections in liver transplant patients. Transplant Proc 1997; 29:2670–4.

49 Jarvis WR, Gayres RP, Culver DH, et al. National Nosocomial Infections Surveillance (NNIS) System Report: Data summary from October to April 1998. Altanta, GA: US Department of Health and Human Services, 1998. Available from: URL: http://www.cdc.gov/ncidod/hip/surveill/nnis.htm. First accessed February 2001.

50 Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. Crit Care Med 1999;27:887–92.

51 Taylor GD, Buchananchell M, Kirkland T, et al. Trends and sources of nosocomial fungaemia. Mycoses 1994;37:187–90.

52 Lewis R, Klepser M. The changing face of nosocomial candidemia: epidemiology, resistance, and drug therapy. Am J Health Syst Pharm 1999;56:525–33.

53 Walsh T, Hiemenz J, PAP. Editorial response: risk factors for invasive fungal infections—all neutropenic patients are not the same. Clin Infect Dis 1994;18:793–8.

54 Richardson M, Kokki M. Diagnosis and prevention of fungal infection in the immunocompromised patient. Blood Rev 1998;12:241–54.

55 Vartivarian S, Anaissie E, Bodey G. Emerging fungal pathogens in immunocompromised patients—classification, diagnosis, and management. Clin Infect Dis 1993;17:S487–91.

56 Gaynes R, Culver D, Emori T, et al. The National Nosocomial Infections Surveillance System: plans for the 1990s and beyond. Am J Med 1991;91:S116–20.