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 MDHDDS 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
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
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 histoplasmosis (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 cryptococcosis 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
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-healthcare 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,
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

<table>
<thead>
<tr>
<th>Variations in:</th>
<th>Low case‖</th>
<th>Base case‖</th>
<th>High case‖</th>
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<tr>
<td>Incidence:</td>
<td>37,555</td>
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<td>144,462</td>
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<td>6,000</td>
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<td>26,000</td>
<td>31,200</td>
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<td>Home-care mortality (%):</td>
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<td>15</td>
<td>0</td>
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<tr>
<td>Total home-care costs (millions $)</td>
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<td>1,555</td>
<td>1,578</td>
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<tr>
<td>Cost/person ($)</td>
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<td>15</td>
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<tr>
<td>Total nursing-home costs (millions $)</td>
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<td>676</td>
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<tr>
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<td>Cost/person ($)</td>
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‖ICD-9s included 112.4, 112.5 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.

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