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BRIEF REPORT

Histoplasmosis-Associated Hospitalizations in the United States, 2001–2012

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We examined trends in histoplasmosis-associated hospitalizations in the United States using the 2001–2012 National (Nationwide) Inpatient Sample. An estimated 50 778 hospitalizations occurred, with significant increases in hospitalizations overall and in the proportion of hospitalizations associated with transplant, diabetes, and autoimmune conditions often treated with biologic therapies; therefore, histoplasmosis remains an important opportunistic infection.

Keywords. histoplasmosis; *Histoplasma*; hospitalization; United States.

Histoplasmosis is caused by inhalation of the environmental fungus *Histoplasma*. In the United States, the traditionally defined histoplasmosis-endemic areas include those surrounding the Ohio and Mississippi River valleys, but *Histoplasma* likely exists in microfoci both within and outside these regions. Histoplasmosis is often described as the most common endemic mycosis in the United States; however, the true burden is unknown because national surveillance does not exist for this infection, and the likelihood of severe infections requiring hospitalizations varies by host factors. Although highly active antiretroviral therapy (HAART) has helped mitigate the risk for histoplasmosis among persons living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), other high-risk patient populations may be emerging, such as those being treated with immune-modulating biologic agents.

To examine trends in histoplasmosis-associated hospitalizations by specific patient populations, we analyzed data from the Healthcare Cost and Utilization Project (HCUP), a family of databases sponsored by the Agency for Healthcare Research and Quality that comprise the largest collection of publicly available all-payer healthcare data in the United States.

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METHODS

The HCUP's National (referred to as Nationwide before 2012) Inpatient Sample (NIS) is a database of hospital inpatient stays derived from billing data from approximately 1000 community hospitals [1]. The 2012 NIS is a 20% stratified sample of discharges from all participating hospitals; before 2012, the NIS contained all discharges from a sample of hospitals. To produce national estimates, discharges are assigned specific sampling weights based on hospital census region, rural/urban location, teaching status, bed size, and ownership. Each year of the NIS contains more than 7 million unweighted discharges; weighted, it estimates more than 36 million discharges yearly.

We identified histoplasmosis-associated hospitalizations in the 2001–2012 NIS using any *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) diagnosis codes 115.00–115.99. Dichotomous variables were created to identify discharges with selected comorbid conditions using the following ICD-9 codes: HIV/AIDS (042), solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) (V42 [excluding V42.3–V42.5], 996.8), diabetes mellitus (249.xx, 250.xx), chronic obstructive pulmonary disease ([COPD] 490, 491, 492, 494, 496). We also identified the following conditions commonly treated with biologic agents: rheumatoid arthritis (714.0, 714.2), inflammatory bowel disease (555.xx, 556.xx), and psoriasis (696.0, 696.1, 696.8).

National estimates of histoplasmosis-associated hospitalizations and 95% confidence intervals (CIs) were obtained using HCUP-supplied discharge weights [2] and were examined by age group, sex, admission month, presence of comorbid conditions, length of stay, hospital charges, and in-hospital mortality. We calculated annual rates per 100 000 persons using population statistics from the US Census Bureau. A weighted least-squares technique (WLS) [3] that accounted for the NIS sample design and for uncertainty around estimated rates was used to test for linear trends in annual overall and comorbidity-specific histoplasmosis-associated hospitalization rates and to calculate average annual percent change (APC). To estimate APC, we performed the WLS on the log-transformed rates, and the delta method was used to approximate the variances used as weights. In addition, logistic regression with survey data analysis software was used to assess changes over time in the proportion of hospitalizations associated with the comorbidities of interest.

RESULTS

An estimated 50 778 (CI, 46 241–55 313) histoplasmosis-associated hospitalizations occurred during 2001–2012. Histoplasmosis was listed as the primary diagnosis in 20.2% (n = 10 277; CI, 9251–11 303) of all histoplasmosis-associated hospitalizations. Yearly rates were consistently highest among persons ≥65

years old (2012 rate, 3.8 per 100 000 persons; CI, 3.3–4.2), followed by persons 45–64 years old (2012 rate: 2.5; CI, 2.2–2.8) and 18–44 years old (2012 rate, 1.1; CI, .9–1.4); rates were lowest among persons <18 years old (2012 rate, 0.2; CI, .1–.4). Overall, 58.1% of histoplasmosis-associated hospitalizations were for males, and yearly rates were consistently higher among males (2012 rate, 1.9 per 100 000; CI, 1.7–2.1) than females (2012 rate, 1.4; CI, 1.2–1.6). Most histoplasmosis-associated hospitalizations were in the Midwest (43.2%; 2012 rate, 3.3 per 100 000 persons; CI, 2.9–3.7) and the South (44.0%; 2012 rate, 2.0; CI, 1.7–2.4). Rates in 2012 were similar in the Northeast (rate, 0.5; CI, .3–.6) and the West (rate, 0.4; CI, .3–.5). No major differences were observed between primary and all-listed histoplasmosis-associated hospitalizations in the age-, sex-, and region-specific analyses. No seasonal variation was observed.

Overall, histoplasmosis-associated hospitalizations increased from 2604 in 2001 (rate, 0.9 per 100 000 persons; CI, .7–1.1) to 5175 in 2012 (rate, 1.7; CI, 1.5–1.8) (APC, 6.8%; $P < .001$) (Figure 1). Likewise, significant increases were observed for all comorbidity-specific histoplasmosis-associated hospitalizations (conditions treated with biologic agents, APC: 14.8%, $P < .001$; transplant, APC: 12.9%, $P < .001$; diabetes, APC: 8.9%, $P < .001$; COPD, APC: 4.5%, $P < .001$; none of these comorbidities, APC: 3.1%, $P = .001$) except for HIV/AIDS ($P = .74$).

The proportion of histoplasmosis-associated hospitalizations that listed a diagnosis of HIV/AIDS decreased from 21.5% in 2001 to 17.3% in 2012 ($P = .008$) (Figure 1). In contrast,

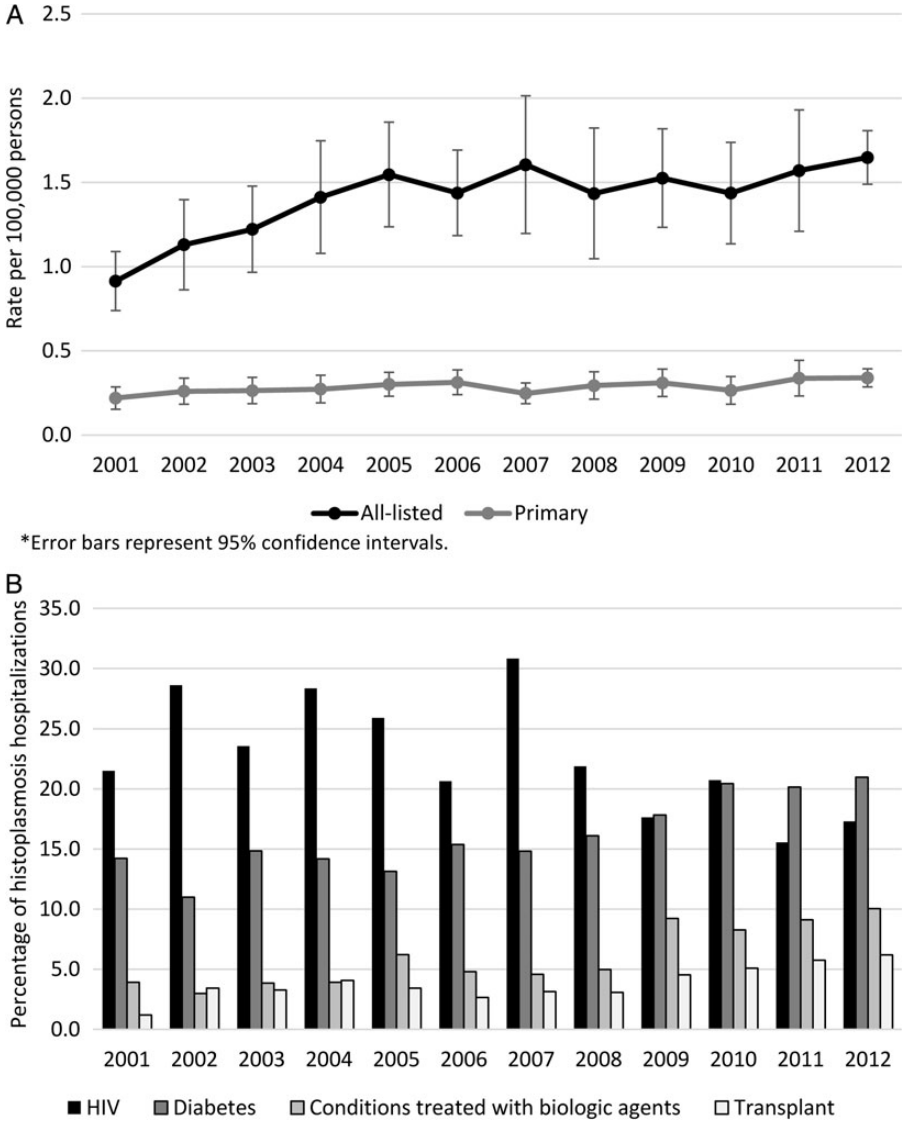

Figure 1. (A) Annual rates of all-listed and primary histoplasmosis-associated hospitalizations per 100 000 persons (*) and (B) percentage of all-listed histoplasmosis-associated hospitalizations with selected comorbidities, United States, 2001–2012. Abbreivation: HIV, human immunodeficiency virus.

significant increases occurred in the proportion of histoplasmosis-associated hospitalizations that listed transplant ($P = .001$), diabetes ($P < .001$), and conditions treated with biologic agents ($P < .001$). No significant trends were observed for COPD or for histoplasmosis-associated hospitalizations that did not list any of the conditions described above.

In-hospital death occurred in 4.9% of hospitalizations overall. Mean length of stay was 8.5 days (standard error [SE] = .0.15), compared with 4.6 days (SE = 0.02) for nonhistoplasmosis-associated hospitalizations. The mean hospital charge for a histoplasmosis-associated hospitalization in 2012 was $72 956 (SE = $3409), compared with $36 699 (SE = $453) for a nonhistoplasmosis-associated hospitalization. Total charges for histoplasmosis-associated hospitalizations in 2012 were an estimated $371 million.

DISCUSSION

We provide an update on US histoplasmosis-associated hospitalizations, demonstrating their substantial and increased burden on the healthcare system in recent years. Prior analyses of histoplasmosis at the national level have been limited to a single year [4] or to a specific patient population [5], and our findings related to demographic and regional features are consistent with those studies' results; however, to our knowledge, national trends have not been recently described. The observed increase in hospitalizations may indicate an increased number of susceptible persons with underlying conditions other than HIV/AIDS. In addition, the increase could partially reflect better provider recognition of histoplasmosis and improved use of diagnostic tests (such as *Histoplasma* antigen detection); however, laboratory testing information is not available in the NIS.

In addition to the limitations of using administrative data to identify histoplasmosis, ICD-9 codes are a crude method for estimating the number of persons potentially receiving biologic therapy, yet we document significant increases in both the rate of histoplasmosis-associated hospitalizations among persons with conditions commonly treated with these therapies and the proportion of all histoplasmosis-hospitalizations that these patents comprise. Starting with the US Food and Drug Administration (FDA) approval of infliximab in 1998, at least 11 additional biologic agents have become available [6]. In 2008, FDA issued a black box warning about the risk for endemic fungal infections associated with tumor necrosis factor (TNF) blockers [6]. A multicenter review of 98 patients who developed histoplasmosis while on TNF-α blocker therapy during 2000–2011 found a high proportion (76%) with disseminated disease, indicating that these infections, although treatable, result in considerable morbidity [7]. We confirm that SOT and HSCT recipients represent another emerging at-risk population; in a previous study, disseminated infection developed in 71% of 52 transplant patients with histoplasmosis, with many cases occurring several years posttransplantation [8].

Before the widespread availability of HAART in 1996, histoplasmosis was estimated to occur in at least 5% of patients with AIDS in histoplasmosis-endemic regions [9]. Since then, fungal opportunistic infections have decreased substantially [10]. For example, in a study of 100 histoplasmosis patients at a tertiary care center in Kentucky, the proportion with HIV infection decreased from 67% in 2000–2001 to 18% in 2008–2009 [11]. Our findings suggest that in the HAART era, the frequency of HIV-associated histoplasmosis hospitalizations has been relatively stable and remains appreciable, highlighting the need for continued prevention measures. The Infectious Diseases Society of America's clinical practice guidelines for histoplasmosis recommend itraconazole prophylaxis for HIV-infected patients with CD4 cell counts under 150 cells/mm^3 in areas where histoplasmosis incidence is >10 cases per 100 patient-years [12]; however, because histoplasmosis is only reportable to public health authorities in 11 states, the nationwide incidence is unknown. Furthermore, in states where histoplasmosis is reportable, passive surveillance almost certainly underestimates the real number of cases. Further work is needed to determine state-specific and national incidence and features of histoplasmosis cases to identify highest-risk populations and possible prevention opportunities.

CONCLUSIONS

Our assessment captures only a portion of the total burden of histoplasmosis in the United States. In addition to the large number of hospitalizations observed in this study, there were several additional cases not severe enough to require hospitalization occur. A review of published US histoplasmosis outbreaks found that approximately one quarter of symptomatic case-patients were hospitalized [13]. Furthermore, the overall percentage of patients with histoplasmosis who are hospitalized may be even lower than this because persons who acquire histoplasmosis during an outbreak may experience more intense exposures and therefore potentially develop more severe disease than those who acquire histoplasmosis sporadically. Improved understanding of the true burden of endemic mycoses such as histoplasmosis, particularly among patients more susceptible to these infections, is needed to further guide risk-based prevention measures.

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