

RESEARCH NOTE

Acute invasive fungal sinusitis: Epidemiology and outcomes in the United States

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INTRODUCTION

Acute invasive fungal sinusitis (AIFS) is a rare and often fatal disease caused by aggressive fungal invasion in the nose and paranasal sinuses, with subsequent thrombosis and progressive tissue necrosis capable of spreading to the orbits and brain over hours. AIFS is most frequently seen in immunocompromised hosts, though cases have been reported among immunocompetent individuals. Despite modern medical and surgical management, mortality has not changed over the last 20 years and remains high%.^{1,2}

Invasive fungal diseases (IFDs), including AIFS, are an emerging major public health problem worldwide, thought to be driven by widespread adoption of aggressive immunosuppressive therapy (e.g., chemotherapy, transplants), increasing use of invasive devices such as central venous catheters, and increase in diabetes.³ Recently, increasing cases of AIFS in COVID-19 patients has been

reported, although the link between the two disorders is not clear.^{4,5}

While AIFS is known to be rare, to our knowledge, the incidence, demography, and mortality of AIFS in the U.S. has not been substantially described. The goal of this study is to evaluate the epidemiology and outcomes of AIFS in the U.S.

METHODS

We conducted a secondary analyses of the 2018 National Inpatient Sample (NIS, HCUP Central Distributor, Rockville, MD). NIS is the largest all-payer database of national hospital discharges. The large sample size (> 35 million hospitalizations) enables national estimates and analyses of rare conditions. NIS is maintained by Agency for Healthcare Research and Quality.⁶

We defined AIFS diagnosis by a rhinosinusitis diagnosis (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] J01.x or J32.x) plus a mycoses diagnosis (ICD-10-CM B44.89 [other forms of aspergillosis], B44.9 [aspergillosis, unspecified], B46.1 [rhinocerebral mucormycosis], B46.5 [mucormycosis, unspecified], B46.8 [other zygomycoses], B46.9 [zygomycosis, unspecified], or B49 [unspecified mycosis]) and a sinonasal procedure (ICD-10-PCS 09xxxZZ) occurring in a single hospitalization with length-of-stay (LOS) > 1 day. We did not include ICD-10-CM diagnoses of dermatophytosis, other superficial mycoses, candidiasis, coccidiomycosis, histoplasmosis, paracoccidiomycosis, sporotrichosis, chromomycosis, and pheomycotic abscess, cryptococcosis, or mycetoma in the AIFS case definition. We also did not include the following subtypes of aspergillosis in AIFS case definition: pulmonary, tonsillar, disseminated, or allergic bronchopulmonary aspergillosis. Patients were excluded if sinonasal procedures were limited to diagnostic procedures or to the nasal septum, or if they had a diagnosis of nasal polyps (ICD-10-CM J33.x). Transfer to hospice was defined by an encounter for palliative care (ICD-10-CM Z51.5), plus transfer to home health care or a facility other than a short term hospital. Mortality was defined by all-cause mortality during the hospitalization, or by transfer to hospice. Relevant concomitant diagnoses were tabulated, including immunocompromised state that we defined by ICD-10-CM diagnoses of neoplasm, liver failure, aplastic anemia, neutropenia, immunodeficiency (ICD-10-CM D80.x [Immunodeficiency with predominantly antibody defects], D81.x [Combined immunodeficiencies], D82.x [Immunodeficiency associated with other major defects], D83.x [Common variable immunodeficiency], D84.x [Other immunodeficiencies], D86.x [Sarcoidosis], D89.x [Other disorders involving the immune mechanism, not elsewhere classified], and D71.x [Functional disorders of polymorphonuclear neutrophils]), transplant status, diabetic ketoacidosis, chronic steroid use, disorders, or iron metabolism, and/or HIV. Diabetes and/or long term insulin use were also analyzed.

Patient and hospital characteristics and outcomes were tabulated. Recommended sample statistical methods account for the weighted sampling design of the data for all models.⁷ Results are presented as weighted national estimates.

RESULTS

In total, there was a weighted estimate of 340 cases of AIFS in the U.S. in 2018. AIFS patient and hospital characteristics were as follows (Table 1). Mean age was 58.0 ± 2.2 years, 55.9% were male, and the majority were Caucasian (50.8%),

followed by Hispanic (23.9%), Black (17.9%), and other races (7.5%). The distribution across income quartiles was 23.9% in the first, 31.3% in the second, 26.9% in the third, and 17.9% in the fourth (highest) income quartile. During hospitalization for AIFS, diagnoses included immunocompromised state in 67.7% and diabetes/long term insulin use in 55.8%. (92.7% received diagnoses of immunocompromised state and/or diabetes/long term insulin use.)

All cases were diagnosed in urban hospitals, and the majority were teaching hospitals (> 95%). 23.5% of cases were transferred in, and 22.1% were transferred out of hospitals. Cases were more common in the South (55.9%) and West (25.0%), than in the Northeast (10.3%) and Midwest (8.8%).

Mortality occurred in 23.5%, 95% confidence interval (CI) $\pm 5.5\%$, comprised of all-cause in-hospital mortality in 14.7%, CI $\pm 4.0\%$, plus transfer to hospice in 8.8%, CI $\pm 3.8\%$ of AIFS patients (Table 2). There was no association between mortality and fungal organism, diabetes/long term insulin use, or the immunocompromising illnesses studied (all $p > 0.05$). The average LOS for hospitalization was 21.9 days with corresponding average total charges per hospitalization of \$455,000.

DISCUSSION

Epidemiology data from the U.S. for IFD is scarce,⁸ and to our knowledge, this is the first report on the national epidemiology of AIFS. Limited reviews constitute most of the existing AIFS literature; the largest meta-analysis included 807 patients, with an average of only 16 patients per article (range 4–46).¹ This study identified and characterized 340 inpatients with an AIFS diagnosis in the U.S. within a 1-year period.

Other studies of fungal diseases demonstrate variations according to geographic, racial, and socioeconomic characteristics.^{9,10} When compared with the US Census population data, Black and Hispanic populations appear disproportionately affected by AIFS in this study, for reasons that are speculative. Clinical, biologic, and genetic factors, along with age, gender, and race, do have central roles in influencing health outcomes. Furthermore, evidence continuously emerges that the social determinants of health impact a variety of outcomes. Research into these domains with AIFS has yet to be investigated.

In a large systematic review, Turner et al. identified a 49.7% survival rate, though survival rates reported in the literature have generally varied from 20%–80%.¹ In this study, mortality was on the lower end of this range. We suspect this reflects selection bias in previous case series, and miscoding and misclassification bias in the present study, as we identified AIFS by a combination of

TABLE 1 Acute Invasive Fungal Sinusitis Patient and Hospital Characteristics

	% (N = 490)	Standard error
Age, in years (mean, SE)	58.0	2.2
Sex, male	55.9%	6.3%
Population		
White	50.8%	6.3%
Black	17.9%	4.6%
Hispanic	23.9%	5.2%
Other	7.5%	4.4%
Median household income quartile		
1	23.9%	5.0%
2	31.3%	5.7%
3	26.9%	5.4%
4	17.9%	4.8%
Other selected hospital diagnoses	92.7%	3.0%
Immunocompromised state(s)	67.7%	6.2%
Aplastic anemia/Neutropenia/Bone marrow deficiency	42.6%	9.5%
Neoplasm	38.2%	6.3%
Transplanted status	16.2%	4.6%
Diabetic ketoacidosis	13.2%	4.1%
Immunodeficiency (other than HIV)	8.8%	3.5%
Chronic steroid use	4.4%	2.4%
HIV	a	a
Liver failure	a	a
Connective tissue disorder/Rheumatoid arthritis	a	a
Iron metabolism disorder	a	a
Diabetes or long term insulin use	55.8%	5.7%
Fungal organism		
Mucor	45.6%	6.5%
Aspergillus	32.4%	5.6%
Unspecified mycosis	22.1%	6.1%
Transferred in	23.5%	6.7%
Transferred out	22.1%	7.7%
Hospital region		
Northeast	10.3%	3.7%
Midwest	8.8%	3.5%
South	55.9%	6.6%
West	25.0%	5.6%

^aOmitted due to small cell size, in accordance with the Healthcare Cost and Utilization Project (HCUP) Data User Agreement.

TABLE 2 Outcomes of Acute Invasive Fungal Sinusitis

	% (N = 490)	Standard error
Mortality	23.5%	5.5%
All cause in-hospital mortality	14.7%	4.0%
Transferred to hospice	8.8%	3.8%
LOS, in days (mean, SE)	21.9	2.1
Total charges (mean, SE)	\$455,000	\$68,000

ICD-10 codes. We could not definitively exclude patients who had pulmonary or other fungal infections whose diagnoses were coded as unspecified or other mycoses, and who during the same hospitalization also had sinus surgery for indications other than AIFS, including chronic invasive fungal sinusitis (CIFS). CIFS is believed to be rare and is mainly described in cases from Sudan, India, and Pakistan¹¹; hence the authors feel CIFS is unlikely to heavily bias the study. Data regarding severity of illness, medications including steroids, pathology, and long term outcomes are not available in the NIS and are considered limitations. Our results likely underestimate the rate of immunocompromised states, as only diagnoses for the individual hospitalization (and not past medical history) are captured in the NIS.

To conclude, IFD are an emerging major global public health problem. This study advances the understanding of the epidemiology and outcomes of AIFS in the U.S. Given the recent alarming surge of post-COVID AIFS in India, our findings have generated benchmark data for future surveillance in the U.S.

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CONFLICTS OF INTEREST

Amber U. Luong serves as a consultant for Aerin Medical (Austin, TX, USA), Glaxo-SmithKline (Brentford, UK), Lyra Therapeutics (Watertown, MA, USA), Sanofi (Paris, France), Stryker (Kalamazoo, MI, USA), and Third Wave Therapeutics (San Francisco, CA, USA); she also serves on the advisory board for ENTvantage Dx (Austin, TX, USA).

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