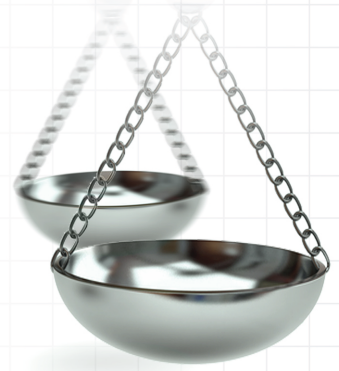




US database study: burden and healthcare resource utilization in adults with systemic endemic mycoses and aspergillosis

Journal of **Comparative Effectiveness Research**

Anna Forsythe^{*1}, Gareth Lewis², Robyn Jordan² & George R Thompson III³

¹Purple Squirrel Economics, New York, NY 10010, USA

²Mayne Pharma, Raleigh, NC 27609, USA

³Department of Medical Microbiology & Immunology & the Department of Internal Medicine, Division of Infectious Diseases, University of California-Davis Medical Center; 4150 Y Street; Sacramento, CA 95817, USA

*Author for correspondence: Tel.: +1 646 478 8213; annaforsythe@pshta.com

Aim: This study evaluated burden of illness in immunocompromised patients with systemic mycoses (SM) eligible for itraconazole treatment, specifically, histoplasmosis, blastomycosis and aspergillosis. **Methods:** A cross-sectional study used an electronic medical record network integrating information from 30 US hospitals, including >34 million patients, to evaluate burden and healthcare resource utilization over 6 months following initiation of antifungal therapy. **Results:** Symptomatic burden experienced by each of the otherwise healthy or age >65 or immunosuppressed cohorts receiving antifungal therapy for SM was comparable but significantly greater in cancer or HIV patients and transplant recipients. Across groups, there was substantially higher healthcare resource utilization in patients with SM versus matched controls without SM. **Conclusion:** The total impact of SM is particularly severe in high-risk or vulnerable populations.

First draft submitted: 4 February 2020; Accepted for publication: 6 April 2020; Published online: 22 April 2020

Keywords: burden • fungal • immunocompromised • infection • systemic mycoses

Systemic mycoses (SM) are a result of fungi entering the body via the lungs, gastrointestinal tract, paranasal sinuses or skin, leading to considerable morbidity and mortality [1]. Despite advances in antifungal therapy, mortality rates for invasive fungal diseases remain high [2]. Immunocompromised patients are at risk for SM, but these infections also can develop in otherwise healthy patients [2]. SM can be categorized between two main types: endemic mycoses and opportunistic infections.

Endemic mycoses are systemic infections caused by fungi including *Histoplasma* spp (causing histoplasmosis), *Coccidioides* spp (causing coccidioidomycosis), *Blastomyces* spp (causing blastomycosis), *Sporothrix* spp (causing sporotrichosis), *Paracoccidioides* spp (causing paracoccidioidomycosis) and *Talaromyces marneffei* (formerly *Penicillium*) (causing talaromycosis) [3]. These fungi are found in soil, wood debris, bat guano and other environmental niches. *Histoplasma* is prevalent in southern USA, central America, South America, Africa and Asia; *Coccidioides* is prevalent throughout western USA and central and South America; *Sporothrix* is prevalent worldwide in tropical and sub-tropical regions and *Blastomyces* is most often found in north America [3].

Opportunistic fungal infections primarily occur in immunocompromised patients [1,3]. The specific fungi are ubiquitous and include *Candida* species (causing candidiasis, the most frequent invasive mycosis in the healthcare setting), *Aspergillus* species (causing aspergillosis), *Cryptococcus* (causing cryptococcosis), the Mucorales (causing mucormycosis) and the agents responsible for chromoblastomycosis and phaeohyphomycosis [1,3]. People at highest risk for SM include those with uncontrolled HIV, systemic malignancy, or neutropenia (low white blood cell count), organ transplant recipients, postoperative patients (major surgery), those with poorly controlled diabetes mellitus and those at the extremes of age [2].

The incidence of systemic fungal infections is rising [3–5] and changes in the epidemiology and burden of infection have been recognized in oncology patients and transplant recipients [6]. This trend has been evident for close to 40 years in the USA; between 1980 and 1997, the annual number of deaths in which an invasive mycosis was

listed on the death certificate increased from 1557 to 6534 — a 320% increase over 17 years attributable in large part at that time to HIV infection [7]. More recent increased incidence has been attributed to various changes leading to an increase in the pool of immunocompromised patients, including an increased number of solid organ and hematopoietic stem cell transplants. Together with acute leukemia, transplants now represent the most common risk factors for opportunistic fungal infections [6,8]. In 2008, over 23,000 organs were transplanted in the USA — twice the amount transplanted 10 years previously [9]. The use of newer and more potent chemotherapeutic agents and regimens, along with continued advances in the treatment of neurologic and rheumatologic diseases, has placed upward pressure on numbers of immunocompromised patients [10,11]. Despite the increasing prevalence of SM, there have been no new classes of antifungal therapy introduced since the azoles in the early 1980s and the echinocandins in 2000 [12]. There have, however, been some advances with new formulations of antifungals to improve bioavailability and tissue distribution.

To better understand the clinical burden of systemic mycoses in the USA, we queried an electronic medical records (EMRs) system from hospital institutions to evaluate the burden of illness, healthcare resource utilization and real-world outcomes in these patients treated with antifungal medications. Our focus was patients with histoplasmosis, blastomycosis and aspergillosis, as we were particularly interested in patients eligible for itraconazole treatment according to its approved usage in the USA.

Methods

Study setting & data

This study used a federated EMR network (TriNetX) containing information on more than 34 million patients from 30 US hospital institutions at the time the network was accessed. The healthcare organizations (HCOs) contributing to the TriNetX data consisted at that time mostly of large academic health centers comprised of main and satellite hospitals and outpatient clinics. Aggregated results from de-identified EMRs can be queried in real-time with an average of 5–6 years of data available from the time of query. The de-identified, health insurance portability and accountability act (HIPAA)-compliant EMR network provides information on patient demographics, ICD-10 codes, Clinical Modification (ICD-10-CM), procedure codes (ICD-10-Procedure Coding systems, Current Procedural Terminology), medications, labs, oncology data, genomics and vital signs. Various and disparate data from numerous healthcare organizations are mapped to control terminologies within the network to simplify the data extraction process. Strong coverage is available for diagnoses, procedures, medications and lab results, while genomics and oncology data are less supported.

Design & study population

This study was a cross-sectional observational study which queried the EMR network during November 2017; hence, the average data available span the period 2012–2017. Patients aged ≥ 18 years old with SM were included in an initial data capture using different pathogenic fungal organisms using ICD-10-CM diagnosis codes of B38–B44: coccidioidomycosis (B38), histoplasmosis (B39), blastomycosis (B40), paracoccidioidomycosis (B41), sporotrichosis (B42), chromoblastomycosis and phaeohyphomycosis (B43) and aspergillosis (B44). This study focused on symptoms, clinical burden, resource use and treatment in patients diagnosed with histoplasmosis, blastomycosis and aspergillosis. These three organisms were selected as we were seeking to understand the clinical burden specifically in patients who would be eligible for itraconazole treatment according to its approved uses in the USA. To further refine the adult systemic mycoses patient population, medication data was used to identify antifungal medications (fluconazole, itraconazole, voriconazole, posaconazole, amphotericin B, liposomal amphotericin B, terbinafine, micafungin and caspofungin) from patients with fungal infection diagnoses. It should be noted that, although different lipid formulations of amphotericin B are available, distinguishing between them was not possible using the data extraction tools from this EMR network; however, this data extraction tool was able to distinguish between liposomal amphotericin B and amphotericin (i.e., nonliposomal amphotericin B).

Patients, who included those treated in the inpatient or outpatient setting were further categorized into six nonmutually exclusive cohorts using diagnosis codes and medication data: otherwise healthy controls; elderly aged ≥ 65 years old; those receiving immunosuppressant medication (including biologicals, e.g., infliximab and adrenal corticosteroids, e.g., prednisone); cancer patients; transplant recipients (solid organ transplant or hematopoietic stem cell transplant recipients); and HIV-positive patients. Patients could be included in more than one cohort as the cohorts were not mutually exclusive. The inclusion and exclusion criteria were built into the data extraction parameters. For example, group 1 excluded all criteria defining groups 2–5 and so on for the other groups.

Inclusion criteria were: mycoses diagnosis (histoplasmosis, blastomycosis or aspergillosis); and treatment with systemic antifungal therapy. Further inclusion criteria were based on defining characteristic as described for groups 2–5.

All patients in the six cohorts were initially identified by their EMR denoting a systemic mycosis (as defined above with a diagnosis code for a pathogenic fungal organism) and having been prescribed at least one antifungal agent. The otherwise healthy cohort (group 1) EMRs showed a fungal diagnosis and also included treatment with one or more of the antifungal medications only. The otherwise healthy (group 1) and elderly patient (group 2) cohorts did not include patients whose records described the use of immunosuppressant or antineoplastic therapies, receipt of transplants or diagnosis of HIV/AIDS. Similarly, immunosuppressed patients (group 3) were defined as those being treated with an immunosuppressant therapy, but excluded if also treated with an antineoplastic agent, were a receipt of a transplant (solid organ transplant or hematopoietic stem cell transplant recipients) or had a diagnosis of HIV/AIDS. The same inclusion logic was applied for fungal patients in the cancer cohort (group 4) as showing treatment with antineoplastic therapy; the transplant cohort (group 5) had received a transplant; lastly, HIV/AIDS patients (group 6) were defined as those a diagnosis of HIV infection and could be at any stage of their disease.

Patients were not mutually exclusive because some fell into multiple cohorts, for example, the elderly cohort was a sub-population of the healthy cohort; patients in the cancer, transplant or HIV/AIDS cohorts could be overlapping as well. To facilitate comparisons between outcomes in this study, control cohorts were created of patients without a history of systemic mycoses and antifungal treatment but were comprised of the analogous disease profile of immunosuppressed or cancer patients, transplant recipients and HIV/AIDS patients.

Outcomes

Study outcomes to assess the burden of illness in patients with systemic mycoses were identified within 6 months after initiation of a patient's first antifungal agent. The study outcomes for the control cohorts were assessed 6 months from the start of immunosuppression therapy for the immunosuppressed patients without SM; the start of antineoplastic therapy for cancer patients without SM; the time of a transplant procedure for transplant recipients without SM; and time of diagnosis for the HIV/AIDS patients without SM. Therefore, all patient cohorts had a common denominator as a follow-up of 6 months so that outcomes could be compared.

Symptom burden

The prevalence of symptoms arising from the systemic mycoses infections (whether constitutional, respiratory, metabolic, gastrointestinal or other signs of infection) were identified within 6 months of starting an antifungal medication. Initially, SM cohorts (groups 2–5) were compared with the otherwise healthy cohort (group 1) as a reference. Systemic mycoses cohorts were further compared with the analogous control cohorts of similar categories (i.e., immunosuppressed, with cancer/transplants/HIV-positive). The rate of symptoms for each cohort was defined from the start of therapy for the primary disease (whether immunosuppressant medication [group 3], antineoplastic therapy [group 4]), completion of a transplant procedure (group 5) or the time of HIV/AIDS diagnosis (group 6).

Treatment utilization

The proportion of patients prescribed each antifungal treatment of interest (itraconazole, fluconazole, liposomal amphotericin B, voriconazole, terbinafine, micafungin, posaconazole, caspofungin, amphotericin B, flucytosine) was summarized among the six SM patient cohorts.

Healthcare resource utilization

Healthcare resource utilization was defined as the number of visits to a healthcare provider (clinic or emergency room) and/or the number of hospitalizations. Healthcare resource use was assessed in the 6 months following treatment with antifungals for the SM patient cohorts or study control cohorts without SM: immunosuppressed (treatment with immunosuppressants), cancer (time of antineoplastic therapy), transplant (time of transplant) or HIV/AIDS (time of diagnosis).

Statistical analysis

Unadjusted descriptive statistics were conducted to summarize characteristics of patients within each of the six study cohorts. Percentages and means, with standard deviations, were calculated. The percentage of patients in each

Table 1. Summary of systemic mycoses disease in electronic medical record sample.

Disease	n	%	ICD-10 code
Aspergillosis	12,530	37.7	B44
Blastomycosis	1080	3.2	B40
Chromomycosis and phaeomycotic abscess	190	0.6	B43
Coccidioidomycosis	4650	14.0	B38
Histoplasmosis	14,560	43.8	B39
Paracoccidioidomycosis	80	0.2	B41
Sporotrichosis	310	0.9	B42
Systemic mycoses (total)	33,230	100.4[†]	

EMR sampled 26 October 2017.

[†]Total >100% due to a small number of patients with more than one infection.

EMR: Electronic medical record.

Table 2. Characteristics of antifungal treated patients with systemic mycoses.

Patient cohorts	Otherwise healthy	Age ≥ 65	Immunosuppressant medication	Cancer	Transplant recipient	HIV
n, (%)	2321 (17.2)	769 (5.7)	5513 (40.7)	3284 (24.3)	1099 (8.1)	532 (3.9)
Age, mean (SD), years	52 (21)	74 (7)	55 (20)	57 (19)	55 (16)	50 (12)
Male, %	51	54	50	53	62	79
White, %	65	71	77	78	76	44
African-American, %	16	11	13	12	13	39

No specific data were available on age ranges or on racial breakdown of remaining patients.

SD: Standard deviation.

cohort affected by each symptom burden was calculated. The percent difference in symptom prevalence was also determined for comparisons of interest. Two-tailed t-tests were calculated for p-values to indicate the significance of each difference. Differences in healthcare resource utilization were similarly calculated. Treatment utilization was assessed by considering the proportion of systemic mycoses patients on each treatment, within each cohort. A p-value of <0.05 was defined to be statistically significant.

Results

A total of 34,751,020 patients were queried across the 30 US sites. The annual prevalence of SM was relatively constant: 2012 (n = 6120), 2013 (n = 6080), 2014 (n = 5430), 2015 (n = 5550), 2016 (n = 5600) and the projected data for 2017 (n = 5265). The most prominent fungal infections were histoplasmosis (43.8%), aspergillosis (37.7%) and coccidioidomycosis (14.0%) (Table 1). In total, data from 33,230 patients with SM were available for initial analysis (Table 1); 39% showed treatment with antifungal medications in their EMRs (n = 13,181). Geographically, patients received care in 30 sites, with three sites accounting for over half of all cases: University of Texas Southwestern Medical Center (23%), University of Iowa Hospitals and Clinics (15%) and University of Arizona (11%) (Figure 1.)

Patients with specified SM (histoplasmosis, aspergillosis and blastomycosis) with at least one prescription for one of 11 specific antifungal agents were further categorized: otherwise healthy cohort (n = 2321; 17.2%), aged ≥65 years (n = 769; 5.7%), immunosuppressant medication (n = 5513; 40.7%), cancer (n = 3284; 24.3%), transplant recipients (n = 1099; 8.1%) and HIV/AIDS (n = 532; 3.9%) (Table 2). Patient characteristics for the SM study cohorts are provided in Table 2. The mean ages across the study cohorts were consistent, (50–57 years), excluding the elderly cohort. The HIV/AIDS cohort was notable for three characteristics, youngest mean age (50 years), mainly male (highest proportion, 79%) and lowest proportion of white race (44%). Patients with SM were far more likely to be immunocompromised (77.0%) (cancer [24.3%], transplant recipients [8.1%], HIV/AIDS [3.9%] or receiving systemic immunosuppressant therapy [40.7%]) than not immunocompromised (22.9%) (otherwise healthy [17.2%] or age >65 [5.7%]).

Table 3 compares symptom burden in SM patients who were aged over 65 years (elderly) or immunocompromised versus the otherwise healthy patients (reference cohort) with systemic mycoses. The symptom burden experienced

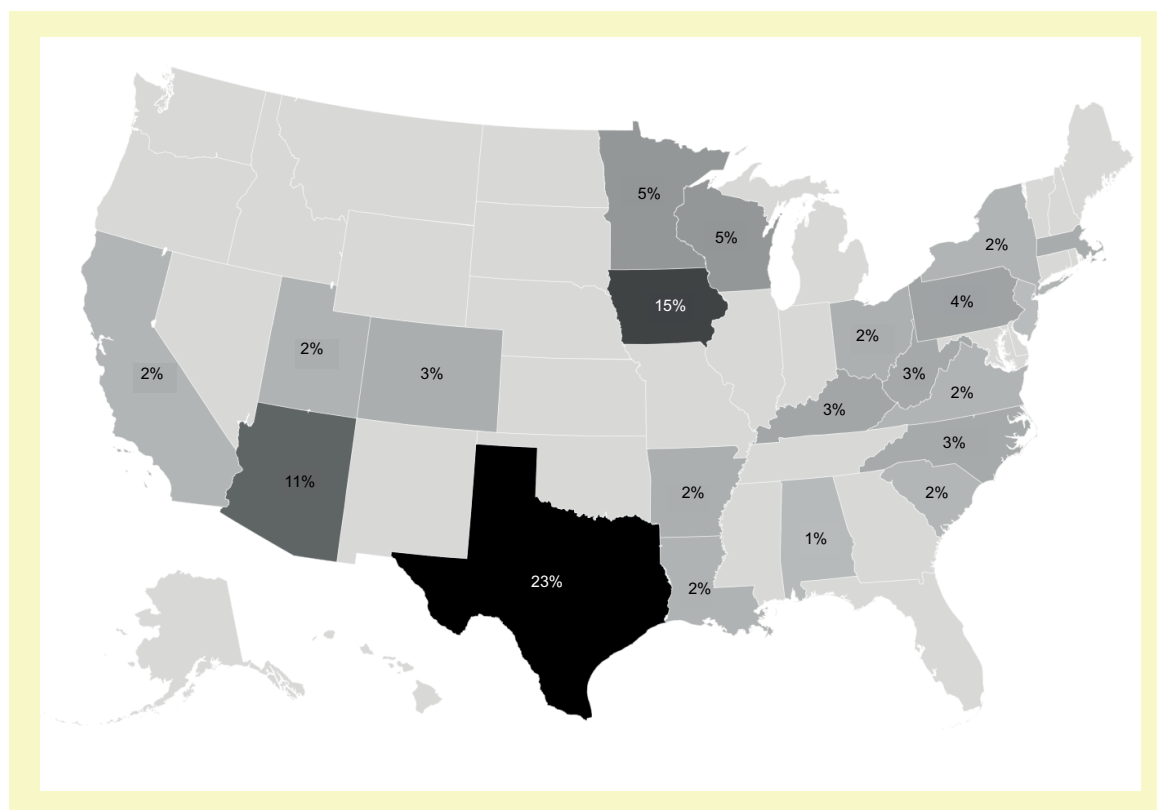


Figure 1. Geographic distribution of cases.

by elderly SM patients for almost all symptoms and symptom classes was broadly similar to the reference cohort, exceptions were the higher prevalence of malaise and fatigue, edema and metabolic symptoms (hypertension, hyperlipidemia and diabetes mellitus) in elderly patients.

All metabolic symptoms, including hypokalemia, were significantly more prevalent in patients on immunosuppressants. Among patients on immunosuppressants, symptom burden was significantly higher among those with SM compared with the control cohort, but the difference in symptom burden for the SM versus control cohort was even more pronounced in the cohorts with cancer, transplant recipients and patients with a history of HIV infection. In those three cohorts, virtually all symptoms were significantly more prevalent in the SM cohort than in the reference cohort, with the exceptions of diabetes mellitus in the HIV/AIDS cohort and abdominal/pelvic pain and acute upper respiratory tract infection in the immunosuppressant cohort (Table 3).

Symptom burden in immunocompromised patients with SM (on immunosuppressants, with cancer, transplant recipients or HIV/AIDS) was also compared with patients with the same immunocompromising feature or condition, but without systemic mycoses (control cohorts). The control cohorts (matched non-systemic mycoses) had substantially larger sample sizes: immunosuppressants ($n = 4,166,383$), cancer ($n = 774,313$), transplant recipients ($n = 37,913$) and HIV/AIDS patients ($n = 91,275$). Patient cohorts with SM and cancer or HIV/AIDS show a uniformly consistent higher prevalence for all symptoms listed (Table 4). Furthermore, when compared with control cohorts of comparable patients without SM (measured as $\Delta\%$), SM patients with cancer or HIV/AIDS had much higher rates of constitutional symptoms (cancer 999%; HIV/AIDS 760%), respiratory symptoms (1190%; 624%), metabolic symptoms (630%; 450%), gastrointestinal symptoms (844%; 576%) and infections (i.e., influenza and pneumonia, acute upper respiratory infection and severe sepsis) (2265%; 955%) (Table 4).

Patients with SM and on immunosuppressants also bore a significantly higher symptom burden compared with their control cohort, albeit with numerically lower percentage differences compared with the cancer or HIV/AIDS patients. Transplant recipients appeared to show the lowest percentage differences in symptom prevalence compared with their respective control cohort, notably, in pain and gastroesophageal reflux disease, the differences were not

Table 3. Symptom burden for antifungal treated patients with systemic mycoses.

Study cohorts	Healthy (reference) n = 2321 (%)	Age >65 years n = 769		Immunosuppressant medication n = 5513		Cancer n = 3284		Transplant recipient n = 1099		HIV-positive n = 532	
List of symptoms		%	Δ % [†]	%	Δ % [†]	%	Δ % [†]	%	Δ % [†]	%	Δ % [†]
Constitutional symptoms											
Malaise and fatigue	11.10	15.70	41	12.86	16	56.97	413	34.68	213	46.80	322
Depression, other mood disorders	10.34	11.65	13	13.79	33	35.72	246	22.12	114	44.17	327
Headache	5.15	4.43	-14	6.55	27	36.51	609	18.70	263	36.28	605
Vision disturbances	3.04	3.42	13	3.25	7	20.86	587	7.02	131	25.75	748
Sleep disorder	7.59	10.25	35	13.21	74	41.08	441	21.16	179	27.82	266
Fever	8.86	7.85	-11	10.24	16	65.41	638	46.97	430	52.26	490
Pain	6.37	5.32	-17	9.39	47	36.57	474	15.19	138	29.51	363
Dizziness	2.78	3.92	41	3.42	23	21.59	675	9.66	247	21.99	690
Edema	5.82	9.37	61	9.77	68	39.25	574	21.95	277	24.44	320
Rash	3.80	3.42	-10	4.62	22	38.92	925	21.77	473	33.27	776
Abnormal weight loss	4.22	4.94	17	5.12	21	22.14	425	6.85	62	28.01	564
Respiratory symptoms											
Dyspnea	19.58	23.16	18	24.20	24	63.61	225	38.81	98	56.58	189
Pain in throat & chest	12.36	12.91	4	12.75	3	48.87	295	22.39	81	51.13	314
Cough	13.76	14.18	3	16.40	19	55.05	300	23.79	73	55.45	303
Metabolic symptoms											
Hypertension	26.37	41.01	56	34.87	32	68.54	160	54.96	108	53.38	102
Hyperlipidemia	12.11	21.77	80	16.92	40	37.52	210	21.33	76	32.14	165
Diabetes mellitus	18.57	23.04	24	24.65	33	37.52	102	29.32	58	19.36	4
Hypokalemia	6.84	7.47	9	9.12	33	52.07	662	34.50	405	35.71	422
Gastrointestinal symptoms											
Abdominal/pelvic pain	10.46	9.87	-6	12.46	19	53.7	414	30.47	191	52.82	405
Gastroesophageal reflux disease	13.88	15.32	10	26.60	92	54.93	296	28.80	107	30.26	118
Nausea and vomiting	7.93	7.34	-7	11.34	43	61.48	675	43.28	446	45.86	478
Diarrhea	6.50	7.34	13	10.16	56	57.64	787	43.55	570	49.44	661
Infections											
Influenza/pneumonia	20.08	21.39	7	24.69	23	72.53	261	41.62	107	61.09	204
Acute upper respiratory	5.91	4.94	-16	7.40	25	42.63	622	16.24	175	32.89	457
Severe sepsis	3.21	5.06	58	5.64	76	30.05	837	11.50	259	18.98	492

As the queries were performed in real-time, the number of patients in each population may vary slightly.

[†]Δ % = percent difference compared with healthy controls; unbolded values correspond to p-values >0.01; bold values correspond to p-values <0.01.

significant. For three metabolic symptoms, rates were significantly lower in systemic mycoses patients compared with control cohort [hypertension (-16%), hyperlipidemia (-27%) and diabetes mellitus (-16%).

Antifungal treatment utilization among the patients with SM is summarized for the six study cohorts in Table 5. Drug utilization adds up to over 100% because some patients received more than one antifungal agent, either in combination or sequentially, during the data collection period. Fluconazole was the most commonly

Table 4. Comparison of symptom burden between patients with systemic mycoses versus no systemic mycoses (control cohort).

Study cohorts List of symptoms	Immunosuppressant medication			Cancer			Transplant recipient			HIV-positive		
	Control cohort n = 4,166,383	SM cohort n = 5513	Percent difference	Control cohort n = 774,313	SM cohort n = 3284	Percent difference	Control cohort n = 37,913	SM cohort n = 1099	Percent difference	Control cohort n = 91,275	SM cohort n = 532	Percent difference
	%	%	Δ %	%	%	Δ %	%	%	Δ %	%	%	Δ %
Constitutional symptoms												
Malaise and fatigue	3.72	12.86	246	6.63	56.97	759	20.68	34.68	68	5.47	46.80	756
Depression, other mood disorders	5.83	13.79	137	6.47	35.72	452	15.53	22.12	42	15.32	44.17	188
Headache	3.48	6.55	88	3.17	36.51	1050	9.59	18.70	95	5.11	36.28	610
Vision disturbances	1.62	3.25	100	1.57	20.86	1230	3.29	7.02	114	3.21	25.75	703
Sleep disorder	5.31	13.21	149	5.54	41.08	642	17.71	21.16	19	4.64	27.82	500
Fever	3.08	10.24	233	4.32	65.41	1415	27.38	46.97	72	4.60	52.26	1035
Pain	3.8	9.39	141	4.88	36.57	650	12.76	15.19	19	3.34	29.51	783
Dizziness	1.76	3.42	94	1.92	21.59	1024	5.71	9.66	69	1.95	21.99	1028
Edema	1.86	9.77	425	2.97	39.25	1220	18.54	21.95	18	1.90	24.44	1189
Rash	3.94	4.62	17	2.61	38.92	1388	12.52	21.77	74	4.27	33.27	680
Abnormal weight loss	0.79	5.12	550	1.75	22.14	1161	4.72	6.85	45	2.83	28.01	890
Average			198			999			57			760
Respiratory symptoms												
Dyspnea	5.85	24.20	314	5.33	63.61	1094	21.28	38.81	82	7.87	56.58	619
Pain in throat and chest	4.29	12.75	197	4.31	48.87	1033	14.37	22.39	56	7.03	51.13	627
Cough	6.34	16.40	159	3.57	55.05	1444	12.35	23.79	93	7.64	55.45	626
Average			223			1190			77			624
Metabolic symptoms												
Hypertension	17.19	34.87	103	17.90	68.54	283	65.36	54.96	-16	19.41	53.38	175
Hyperlipidemia	8.70	16.92	94	8.63	37.52	335	29.24	21.33	-27	8.05	32.14	299
Diabetes mellitus	7.08	24.65	248	7.66	37.52	390	34.88	29.32	-16	7.48	19.36	159
Hypokalemia	1.43	9.12	538	3.23	52.07	1511	26.35	34.50	31	2.82	35.71%	1168
Average			246			630			-7			450
Gastrointestinal symptoms												
Abdominal/pelvic pain	5.51	12.46	126	6.7	53.7	700	22.30	30.47	37	8.74	52.82	504
Gastroesophageal reflux disease	7.76	26.60	243	7.97	54.93	589	28.06	28.80	3	6.15	30.26	392
Nausea and vomiting	3.66	11.34	210	7.04	61.48	773	33.3	43.28	30	5.61	45.86	717
Diarrhea	2.09	10.16	385	4.07	57.64	1315	33.60	43.55	30	6.26	49.44	690
Average			241			844			25			576
Infections												
Influenza and pneumonia	3.07	24.69	705	3.09	72.53	2250	16.92	41.62	146	7.75	61.09	689
Acute upper respiratory	11.59	7.40	-36	3.76	42.63	1035	9.02	16.24	80	4.58	32.89	619
Severe sepsis	0.46	5.64	1114	0.83	30.05	3512	5.30	11.50	117	1.14	18.98	1558
Average			594			2266			114			955

As the queries were performed in real-time, the number of patients in each population may vary slightly, Δ % = percent difference, unbolded values correspond to p-values >0.01; bold values correspond to p-values <0.01.

SM: Systemic mycoses.

Table 5. Treatment utilization of selected antifungal therapies among patients with systemic mycoses.

Study cohort	Weighted average	Otherwise healthy (n = 2321)		Age >65 (n = 769)		Immunosuppressant medication (n = 5513)		Cancer (n = 3284)		Transplant recipient (n = 1099)		HIV (n = 532)	
Antifungal	%	n	%	n	%	n	%	n	%	n	%	n	%
Fluconazole	56.05	1067	45.02	306	38.73	2212	41.09	2259	66.68	902	82.07	367	68.98
Itraconazole	19.50	594	25.06	156	19.75	1386	25.75	440	12.99	88	8.01	200	37.59
Voriconazole	53.51	600	25.32	257	32.53	2460	45.70	2367	69.86	844	76.80	119	22.37
Posaconazole	13.94	135	5.70	54	6.84	394	7.32	714	21.07	299	27.21	20	3.76
Ketoconazole	6.90	135	5.70	59	7.47	359	6.67	256	7.56	53	4.82	68	12.78
Amphoterecin B	3.60	58	2.45	16	2.08	170	3.08	145	4.72	47	4.28	10	1.88
Amphotericin B liposomal	11.57	143	6.03	46	5.82	468	8.69	518	15.29	166	15.10	94	17.67
Caspofungin	7.26	19	0.80	12	1.52	174	3.23	463	13.67	123	11.19	13	2.44
Micafungin	15.10	116	4.89	53	6.71	424	7.88	751	22.17	356	32.39	32	6.02
Flucytosine	0.23	10	0.42	0	0	13	0	10	0	10	0.9	10	1.88
Terbinafine	2.81	99	4.18	30	3.80	162	3.01	86	2.54	12	1.09	18	3.38

Table 6. Healthcare resource utilization over a 6-month period for patients with systemic mycoses and without systemic mycoses.

Cohorts	Otherwise healthy	Age >65	Immunosuppressant medication			Cancer			Transplant recipients			HIV/AIDS		
Number of patients	n = 2321	n = 769	Control 4,166,383	SM 5513	% difference	Control 775,313	SM 3284	% difference	Control 37,913	SM 1099	% difference	Control 91,275	SM 532	% difference
	%	%	%	%	Δ %	%	%	Δ %	%	%	Δ %	%	%	Δ %
Outpatient	62.0	62.6	46.6	56.5	21.2	51.5	67.0	30.1	73.0	82.3	12.7	48.2	60.2	24.9
ER	15.9	13.9	32.4	20.2	-37.7	7.61	22.5	196	20.3	26.0	28.1	16.9	30.3	79.3
Hospitalization	26.6	32.5	17.5	36.9	110.9	8.88	50.2	465	65.1	74.5	14.4	13.3	39.1	194

Bold values are statistically significant $p < 0.01$.

ER: Emergency room; SM: Systemic mycoses.

prescribed treatment when measured across all cohorts, with 56.0% (weighted average) of all patients using this medication, followed by voriconazole (53.5%) and itraconazole (19.5%). Liposomal amphotericin B was prescribed at an intermediate rate (11.6%) (Table 5). Treatment utilization was consistent for the top three antifungals across cohorts; however, more itraconazole was prescribed on a percentage basis than voriconazole for HIV/AIDS patients. Slightly more voriconazole than fluconazole was prescribed for patients on immunosuppressant medication (45.70 vs 41.09%) and patients with cancer (69.86 vs 66.86%). Notably, although itraconazole use was third-most frequent antifungal across all cohorts, its use in transplant recipient patients was lower and it was ranked 7th as antifungal treatment in these patients (Table 5).

Healthcare resource utilization (HCRU) over a 6-month period was assessed and patients with SM consistently utilized all three HCRU modes (ER [emergency room], hospitalisation or outpatient visits) more frequently than their corresponding control cohorts, with the exception of ER visits for patients on immunosuppressant medications, 20.2% of patients with SM compared with 32.4% of control patients on immunosuppressants presenting to ER (Table 6). Highest hospitalization rates were observed in SM transplant recipients (74.5%), followed by non-SM transplant recipients (65.1%). SM patients who underwent transplant and SM with cancer showed the highest rates of outpatient visits, 82.3 and 67.0%, respectively (Table 6). Generally (with one exception noted above), across all patient cohorts with SM, there was higher HCRU compared with the control study cohorts without systemic mycoses, these differences were statistically significant ($p < 0.01$) (Table 6).

Discussion

This study evaluated outcomes associated with the burden of illness for patients with SM, focusing on those eligible for itraconazole treatment according to its approved uses in the USA. In this study, a majority of patients were immunocompromised in some manner (77.0%), with the data showing that these patients (whether cancer or HIV

patients, those on immunosuppressant therapy or transplant recipients) have a significantly higher overall burden of illness than SM patients that are otherwise healthy or elderly (≥ 65 years old). Given the magnitude in the frequency of reported symptoms for the immunocompromised cohorts, these patients have a substantially greater burden of illness arising from systemic mycoses. Because the database captures symptoms regardless of cause, it is also possible that these patients had a greater symptom burden due to comorbid conditions and/or adverse effects of treatment, in addition to the effects of SM infection.

The relative percentage of constitutional symptoms which were experienced in both otherwise healthy and elderly SM cohorts may be secondary to comorbidities and age-related physiological changes leading to increased patient symptomatology (Flevari *et al.*) [13]. This is consistent with our study findings where a higher incidence of constitutional symptoms was observed in the elderly healthy cohort compared with otherwise healthy younger (i.e., < 65 years old) patients. It would be useful to have additional detail beyond what was available in this database in order to better understand the relationship between age and burden of systemic mycoses. It was also noted that SM patients in the immunosuppressed cohort experienced higher rates of constitutional symptoms when compared with both the otherwise healthy SM cohort and the immunosuppressed control groups that did not have SM, findings that suggest the immunosuppressed population may have had a greater burden of disease.

The largest differences in symptom burden in SM immunocompromised patients (i.e., immunosuppressant medication, cancer, transplant or HIV) compared with otherwise healthy SM patients were observed in cancer patients as shown in Table 3. Additionally, in cancer patients with SM compared with cancer without SM, there was commonly 10–20 $\times$ greater incidence of many reported symptoms, across all symptom classes. As these patients are frequently neutropenic secondary to recent chemotherapy it is not surprising that more severe symptoms were observed in this cohort. This high symptom burden is also likely exacerbated by the documented concomitant mental, physical and emotional distress that accompanies an active cancer diagnosis along with symptom burden for patients with systemic mycoses [14].

Respiratory symptoms were common in patients with SM in this study, reflecting that the predominant site of infection in these patients is the lung [15,16]. The rates of pulmonary symptoms in all immunosuppressed patients with systemic mycoses were higher than the otherwise healthy counterparts that have systemic mycoses. Constitutional symptoms such as fever, malaise, pain, abnormal weight loss, were increasingly prevalent across the spectrum with SM from otherwise healthy patients (4–11%); elderly patients (5–16%) to cancer patients (22–57%) (Table 3). Other sites of infection for the target organisms include the bloodstream, splenic and liver abscess, urinary tract and central nervous system sites [17].

The observed increases in prevalence of metabolic symptoms in SM patients compared with control cohorts may be due to direct effects of infection on metabolism or exacerbation of comorbidities during active and ongoing infection. Alternatively, infection of endocrine organs, thus adversely affecting regulatory controls on metabolism may contribute to observed rates of metabolic symptoms [18,19]. In addition, current antifungal agents (polyenes, azoles) used for prophylaxis and/or treatment of mycoses also have adverse endocrine and metabolic effects, including hypoadrenalism, hypogonadism, hypoglycemia, dyslipidemia and hyperkalemia or hypokalemia [18,20,21].

Gastrointestinal infection by SM pathogens is uncommon [22]. Gastrointestinal symptoms tend to be nonspecific (e.g., nausea) unless distinct organs such as the liver, bowel, or pancreas are directly invaded. The results reported in this study for the rates of gastrointestinal symptoms arising from SM are consistent with similar findings from prior research, with the highest incidences in the cancer cohort, relatively less of an increase compared with control in the HIV cohort and the transplant cohort mostly resembling the otherwise healthy cohort.

With rising incidence of invasive fungal infections, the burden of symptoms in patients at high-risk of fungal infections is a high priority for healthcare professional and decision-makers. In one large epidemiological study of invasive fungal infections utilizing data from an integrated US health network (Intermountain Healthcare), invasive fungal infections were associated with a high rate of hospital admissions (76.2%) and high 1-year all-cause mortality rate of 28.8% [2]. The conditions or diseases that place patients at higher risk for invasive fungal infections are themselves associated with high symptom burden. This study documented the very high rates of constitutional, respiratory, metabolic, gastrointestinal and infection-related symptoms that are attributable to SM or the accompanying treatment. This study also documented substantially increased HCRU rates attributable to SM.

Given the high burden of SM in terms of symptoms and HCRU, there is a clear impetus for timely diagnosis of SM with identification of the pathogen, which can improve outcomes through prompt initiation of the appropriate antifungal therapy. Currently, many hospitals must send testing off-site for aspergillus and histoplasmosis, which

can delay diagnosis and initiation of targeted treatment [23,24]. Of note, 56% of prescriptions in this study were for fluconazole, which is inactive against aspergillosis (38% of diagnoses) and less effective than itraconazole against histoplasmosis and blastomycosis, which together accounted for 47% of diagnoses [8,24,25]. Thus, a substantial number of patients were receiving fluconazole for a disease not optimally treated with this agent. It is possible that fluconazole is sometimes prescribed empirically until fungal testing results are available or fluconazole may be chosen due to limited drug–drug interactions and predictable bioavailability [26].

Future research in larger populations, including among patients with other forms of SM beyond the three pathogens studied here, would be valuable in establishing the burden of SM more broadly. This study was intentionally narrowly focused on pathogens of interest based on our objective of understanding the patient population eligible for itraconazole treatment in the USA, but there would be value in conducting similar analyses on other systemic fungal infections, including candidiasis, cryptococcosis, mucormycosis and pneumocystis infection. It would also be useful to study treatment patterns and outcomes of treatment using real-world evidence, to better understand whether patients are being adequately treated or if there is unmet clinical need in SM.

Limitations

The main limitation in utilizing ‘live’ cross-sectional EMR data relates to the lack of longitudinal data, patients diagnosed with systemic mycoses based on ICD-10 codes were the starting point for data capturing. Capturing EMR data at a fixed point in time precludes re-running the analysis to include or exclude features not accounted for at the time of querying. It is important to note that the EMR database interrogated gives insight into the rate of symptoms experienced per cohort, but not the severity, nor the duration of impact at the patient level or clinical significance of these symptoms (potentially responsible for delays in next chemotherapy cycle etc). In addition, it is acknowledged that there are limitations to the estimates of healthcare resource utilization, as the total HCRU cannot be fully determined from the EMR data available (e.g., supplemental nursing support, at-home care, rehabilitation support, etc.). HCRU was measured as the percentage of total number of patients in the specified group that sought care. This would not account for repeat visits; hence, HCRU would likely be underestimated if there were repeat visits by patients in those groups (i.e., SM patients) shown to use more healthcare resources. HCRU was also not captured at a high level of granularity; for example, hospitalization is not further divided into intensive care unit versus standard unit care. Finally, although different lipid formulations of amphotericin B are available, this level of granularity was not available using the data extraction tools from this EMR network.

Conclusion

To the authors’ knowledge, this is the first study which evaluates the real-world symptom burden and HCRU attributable to systemic mycoses in patients with additional select comorbid conditions. Of note, the observation that the majority of patients who contract a systemic fungal infection are immunocompromised is significant. Given the rising age profile of the US population, associated increases in the rates of serious illnesses including cancers, conditions requiring organ transplants and other chronic conditions that result in long-term compromised immune responses, it is expected that there will be a corresponding increase in high-risk patients vulnerable to invasive fungal infections. The nature of the comorbidities affecting these patients causes substantial symptomatic burden of illness.

This study provides a basis and reference point for further investigation of quality of life in patients with SM, as well as corresponding healthcare resource utilization and economic burden.

Acknowledgments

Parts of this study were previously published at the International Society for Human and Animal Mycology, Congress of the European Hematology Association and International Immunocompromised Host Society Symposium in 2018.

Financial & competing interests disclosure

G Lewis and R Jordan are employees of Mayne Pharma, which sponsored the research. A Forsythe is an employee of Purple Squirrel Economics, which acted as a consultant to Mayne Pharma. GR Thompson III acted as a consultant to Mayne Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

K Sandman of Purple Squirrel Economics provided editorial support. This work was sponsored by Mayne Pharma.

Summary points

- Despite advances in antifungal therapy, mortality rates for invasive fungal diseases remain high, with immunocompromised patients especially vulnerable to opportunistic infection.
- This study queried electronic medical records of over 34 million patients from 2012 to 2017 in the USA to evaluate the burden of illness, healthcare resource utilization and real-world outcomes in patients treated with antifungal medications, with a focus on histoplasmosis, blastomycosis and aspergillosis.
- Symptomatic burden experienced by each of the otherwise healthy or age >65 or immunosuppressed cohorts receiving antifungal therapy for systemic mycoses (SM) was comparable but significantly greater in cancer or HIV patients and transplant recipients.
- Among the patient cohorts with SM, those in which patients also had cancer or HIV/AIDS showed a consistently higher prevalence for all symptoms listed.
- The most commonly prescribe treatments were fluconazole (56.0%), voriconazole (53.5%) and itraconazole (19.5%).
- The highest hospitalization rates were observed in transplant recipients with SM (74.5%), who also had the highest rates of outpatient visits (82.3%).
- Healthcare resource utilization was higher across all patient cohorts with SM relative to control cohorts without SM infection.

References

Papers of special note have been highlighted as: • of interest

- De Pauw BE. What are fungal infections? *Mediterr. J. Hematol. Infect. Dis.* 3(1), e2011001 (2011).
- Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and clinical features of invasive fungal infection in a US health care network. *Open Forum Infect. Dis.* 5(8), ofy187 (2018).
- **Real-world evidence from a US database on invasive fungal infections.**
- Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. *Crit. Rev. Microbiol.* 36(1), 1–53 (2010).
- Pegorie M, Denning DW, Welfare W. Estimating the burden of invasive and serious fungal disease in the United Kingdom. *J. Infection* 74(1), 60–71 (2017).
- Benedict K, Derado G, Mody RK. Histoplasmosis-associated hospitalizations in the United States, 2001–2012. *Open Forum Infect. Dis.* 3(1), ofv219 (2016).
- Low C-Y, Rotstein C. Emerging fungal infections in immunocompromised patients. *F1000 Med. Rep.* 3, 14 (2011).
- McNeil MM, Nash SL, Hajjeh RA *et al.* Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin. Infect. Dis.* 33(5), 641–647 (2001).
- Enoch DA, Yang H, Aliyu SH, Micallef C. The changing epidemiology of invasive fungal infections. In: *Human Fungal Pathogen Identification. Methods in Molecular Biology, Vol. 1508*. Lion T (Ed.). Humana Press, NY, USA, (2017).
- US Department of Health and Human Services. Organ Procurement and Transplantation Network (OPTN). (2020). <https://optn.transplant.hrsa.gov/>
- Garbee DD, Pierce SS, Manning J. Opportunistic fungal infections in critical care units. *Crit. Care Nurs. Clin. N. Am.* 29(1), 67–79 (2017).
- Lockhart SR, Guarner J. Emerging and reemerging fungal infections. *Semin. Diag. Pathol.* 36(3), 177–181 (2019).
- **Comprehensive review of fungal infections with a focus on the Americas.**
- Miller RA. A case for antifungal stewardship. *Curr. Fungal Infect. Rep.* 12(1), 33–43 (2018).
- Flevvari A, Theodorakopoulou M, Velegraki A, Armaganidis A, Dimopoulos G. Treatment of invasive candidiasis in the elderly: a review. *Clin. Interv. Aging* 8, 1199–1208 (2013).
- Meijer A, Roseman M, Delisle VC *et al.* Effects of screening for psychological distress on patient outcomes in cancer: a systematic review. *J. Psychosomat. Res.* 75(1), 1–17 (2013).
- Razzuk MA, Urschel HC, Paulson DL. Systemic mycoses – primary pathogenic fungi. *Ann. Thorac. Surg.* 15(6), 644–660 (1973).
- Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. *Curr. Opin. Pulm. Med.* 16(3), 242–250 (2010).
- Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: diagnosis & clinical management. *Indian J. Med. Res.* 139(2), 195–204 (2014).
- Lionakis MS, Samonis G, Kontoyiannis DP. Endocrine and metabolic manifestations of invasive fungal infections and systemic antifungal treatment. *Mayo Clin. Proc.* 83(9), 1046–1060 (2008).

19. Ruhnke M, Schwartz S. Recent developments in the management of invasive fungal infections in patients with oncohematological diseases. *Ther. Adv. Hematol.* 7(6), 345–359 (2016).
- **Review on the diagnosis and treatment of fungal infections in hematologic oncology.**
20. Chang Y-L, Yu S-J, Heitman J, Wellington M, Chen Y-L. New facets of antifungal therapy. *Virulence* 8(2), 222–236 (2017).
21. Thompson GR, Chang D, Wittenberg RR, McHardy I, Semrad A. *In vivo* 11 β -hydroxysteroid dehydrogenase inhibition in posaconazole-induced hypertension and hypokalemia. *Antimicrob. Agents Chemother.* 61(8), DOI: 10.1128/AAC.00760-17 (2017).
22. Avcu G, Karapinar DY, Yazici P *et al.* Difficult diagnosis of invasive fungal infection predominantly involving the lower gastrointestinal tract in acute lymphoblastic leukaemia. *Med. Mycol. Case Rep.* 11, 1–4 (2016).
23. Denning DW, Perlin DS, Muldoon EG *et al.* Delivering on antimicrobial resistance agenda not possible without improving fungal diagnostic capabilities. *Emerg. Infect. Dis.* 23(2), 177–183 (2017).
24. Limper AH, Adenis A, Le T, Harrison TS. Fungal infections in HIV/AIDS. *Lancet Infect. Dis.* 17(11), e334–e343 (2017).
25. Salzer HJF, Burchard G, Cornely OA *et al.* Diagnosis and management of systemic endemic mycoses causing pulmonary disease. *Respiration* 96(3), 283–301 (2018).
26. Kriengkauyiat J, Ito JI, Dadwal SS. Epidemiology and treatment approaches in management of invasive fungal infections. *Clin. Epidemiol.* 3, 175–191 (2011).