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Investigating asthma after coccidioidomycosis among patients with commercial health insurance, United States, 2017–2022

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Abstract

Background: The relationship between asthma and coccidioidomycosis has not been fully described. We have hypothesized that *Coccidioides* could trigger inflammatory airway responses, similar to other fungi. Objectives: To estimate the frequency of new-onset asthma-related symptoms after coccidioidomycosis and identify potentially associated factors.

Patients/Methods: We used a large health insurance claims database to identify patients with coccidiomycosis with and without an asthma diagnosis code or a short-acting β_2 agonist prescription in the year after diagnosis.

Results: 13% of 1,657 patients with had an asthma diagnosis code or a short-acting β_2 agonist prescription (median 2.5 months later).

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This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

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Conclusions: Increased healthcare provider awareness of asthma as a potential coccidioidomycosis complication could benefit patients, especially female patients and patients with severe pulmonary infection.

Keywords

Coccidioidomycosis; asthma; insurance; health; United States

INTRODUCTION

Some respiratory tract infections are associated with asthma development due to inflammatory damage to the airway mucosal and submucosal tissues.¹ Chronic airway inflammation development has mainly been investigated in the context of respiratory viral infections.¹ Fungal exposure is associated with exacerbation of asthma symptoms.² Exposure to airborne bioparticulate matter containing fungal spores (particularly *Aspergillus*) is a well-established predisposing factor for the development of asthma and other allergic diseases.³ The relationship between asthma and fungal infections like coccidioidomycosis has not been fully described, although one small study linked coccidioidomycosis to worsened asthma outcomes.⁴

Immunocompetent patients with coccidioidomycosis typically present with subacute systemic and pulmonary symptoms. We have hypothesized that *Coccidioides* could trigger inflammatory airway responses, similar to other fungi, resulting in patient concerns regarding their infection returning, and frequently requiring increased healthcare utilization. To estimate the frequency of new-onset asthma-related symptoms after coccidioidomycosis and identify potentially associated factors, we analyzed data from a large U.S. health insurance claims database.

METHODS

We used the Merative™ MarketScan® Commercial/Medicare Database (<https://www.merative.com/documents/brief/marketscan-explainer-general>), which contains health insurance claims data for >48 million patients with employer-sponsored plans including Medicare Supplemental and Medicare Advantage plans throughout the United States during the January 1, 2017 to June 30, 2022 study window. We identified patients diagnosed with coccidioidomycosis using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code B38 who had continuous insurance enrollment in the year before and after the date the coccidioidomycosis diagnosis code was first used (index date) during the study window (Figure 1).

To identify incident diagnoses, we excluded patients with a coccidioidomycosis or asthma diagnosis code or an outpatient prescription for a short-acting β_2 agonist prescription (SABA; a standard treatment for asthma) (albuterol, albuterol sulfate, or levalbuterol) in the year before the index date. Patients for whom coccidioidomycosis or asthma was listed on a laboratory or imaging claim alone were not included, to remove instances in which the diagnosis was most likely being ruled out by a healthcare provider.

To compare patients with coccidioidomycosis with vs. without an asthma diagnosis code or a SABA prescription in the year after the index date, we performed bivariable case-case analyses using χ^2 , Fisher exact, and t-tests at $p < 0.05$. We examined patient demographic characteristics; healthcare provider types visited on the index date; signs, symptoms, and other selected conditions in the 90 days before or on the index date using ICD-10-CM codes (Supplemental Table 1); and outpatient prescriptions. Bivariate comparisons that were significant at $p < 0.2$ were included in a stepwise multivariable logistic regression to estimate adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) for demographic characteristics and clinical features independently associated with asthma diagnosis or SABA prescription.

Last, we identified the proportion of patients who had a new (i.e., not listed in the previous year) asthma diagnosis code or SABA prescription in four separate comparison cohorts meeting the 2-year continuous enrollment criteria. The cohorts were: 1) 12.4 million patients with a healthcare visit for any reason, 2) 1.3 million patients with influenza, 3) 1,412 patients with aspergillosis, 4) 1,320 patients with candidal sepsis during the study window.

MarketScan data are fully de-identified, so this analysis was not subject to review by the Centers for Disease Control and Prevention institutional review board.

RESULTS

Among 6,074 patients with coccidioidomycosis during the study window, 2,748 (45%) met continuous enrollment criteria. In the year before the index date, 296 (11%) were excluded for having a previous coccidioidomycosis diagnosis, 381 (14%) were excluded for having an asthma diagnosis code, and 755 (27%) were excluded for having an outpatient prescription for a SABA, leaving 1,657 patients for analysis. Among those, 208 (13%) had an asthma diagnosis code ($n=81$) or SABA prescription ($n=165$) in the year after the index date. The median time from the index date to first asthma diagnosis code or first SABA prescription was 77 days (interquartile range [IQR] 22–242).

The median age of all patients with coccidioidomycosis was 51 years (IQR 39–60). Patients with coccidioidomycosis who had an asthma diagnosis code or SABA were more frequently female than patients who did not (63% vs. 44%, $p < 0.001$) (Table 1). In total, 78% of patients with coccidioidomycosis were from the West, and 95% were from non-rural areas. Patients who had an asthma diagnosis code or SABA were less likely to have visited a family practice or internal medicine provider (30% vs. 38%, $p=0.024$) and more likely to have visited a pulmonologist (21% vs. 15%, $p=0.013$) or be hospitalized (22% vs. 12%, $p < 0.001$) on the index date. Overall, disseminated (5%) and cutaneous (3%) coccidioidomycosis were infrequent.

Symptoms and clinical findings that were more common among patients who had an asthma diagnosis code or SABA included: cough (40% vs. 31%, $p=0.005$), dyspnea (34% vs. 19%, $p < 0.001$), pleural effusion (16% vs. 7%, $p < 0.001$), sepsis (15% vs. 6%, $p < 0.001$), hypoxemia (9% vs. 3%, $p < 0.001$), myalgia (9% vs. 2%, $p=0.005$), and acute respiratory failure (4% vs. 1%, $p=0.002$). Other diagnoses more common among patients who had

an asthma diagnosis code or SABA included: unspecified pneumonia (34% vs. 25%, $p=0.034$), smoking (15% vs. 9%, $p=0.004$), chronic obstructive pulmonary disease or other chronic lower respiratory disease (13% vs. 7%, $p=0.006$), bacterial pneumonia (10% vs. 4%, $p<0.001$), and bronchitis or unspecified lower acute respiratory infection (8% vs. 4%, $p=0.007$). Forty-eight percent of patients with coccidioidomycosis received outpatient antifungal medication, primarily fluconazole (46%), which was more frequently received by patients who had an asthma diagnosis code or SABA compared with patients who did not (55% vs. 45%, $p=0.005$).

On multivariable analysis, the odds of having an asthma diagnosis code or SABA were highest for women (aOR 2.5, 95% CI 1.8–3.5) and patients with sepsis (aOR 2.3, 95% CI 1.3–3.8), hypoxemia (aOR 2.0, 95% CI 1.0–4.0), or bronchitis (aOR 2.0, 95% CI 1.1–3.7) (Supplemental Table 2).

The proportion of patients with a new asthma diagnosis or SABA prescription in the comparison cohorts was: 6% among those with any healthcare visit, 9% among those with influenza, 11% among those with candidal sepsis, and 20% among those with aspergillosis.

DISCUSSION

The associations identified in this large study concerning coccidioidomycosis and new indicators of asthma-related symptoms advance understanding of relationships between fungi and asthma. Our results suggest that this phenomenon may be more common in patients with more severe pulmonary coccidioidomycosis (as approximated by the need for hospitalization, antifungal treatment, and the presence of clinical complications such as hypoxemia and sepsis). Although our study was not designed to estimate the excess risk for developing asthma-related symptoms attributable to coccidioidomycosis, the proportion of patients with a new asthma diagnosis code or SABA prescription (13%) among those with coccidioidomycosis was higher than that among each of the comparison cohorts except for the aspergillosis cohort. The finding that female patients with coccidioidomycosis were more frequently affected is consistent with the higher national asthma prevalence among women (10%) than men (6%).⁵ We recognize that patients with coccidioidomycosis may have had underlying and previously unrecognized airway hyperresponsiveness or asthma that was quiescent and then unmasked following coccidioidomycosis; however, these data support the hypothesis that *Coccidioides* may predispose patients to developing inflammation-mediated airway obstruction as observed with other airborne fungi.^{2,3}

Fungi and other pathogens within the pulmonary bronchioles allow for persistence of antigens that cause direct injury to the airways. For example, *Aspergillus* proteases drive mucus abnormalities via MUC5AC,⁶ and impaired antigen clearance promotes an allergic response through prolonged stimulation of Th2-type immune cells. *Aspergillus* proteases and allergens have also been found to cause airway inflammation and remodeling in animal models, and recent work has found an alkaline protease that damages bronchiolar cell junctions triggering inflammation and airway hyperresponsiveness.⁷ Since orthologues to these antigens are present in *Coccidioides* spp (heat shock protein hsp1, 60S ribosomal protein L3, heat shock protein SSB, fructose 1,6-bisphosphate aldolase among others),

a similar pathophysiologic mechanism in humans might explain development of airway hyperresponsiveness following infection.

Other aspects may confound the relationship between coccidioidomycosis and asthma. For example, in some geographic areas, particulate matter levels have been positively associated with coccidioidomycosis cases.⁸ Dust particle inhalation may induce asthma exacerbations by molecular mechanisms involving Toll-like receptors on naïve CD4+ T cells leading to both Th2 and Th17 activation.⁹ Th2 activation leads to airway eosinophilia and mucus hypersecretion, while Th17 activation facilitates neutrophil migration; all this can contribute to asthma-like symptoms and may serve as cofactors enhancing airway hyperreactivity following coccidioidomycosis.

The main limitation of this analysis is potential misclassification inherent in health insurance claims data, which do not necessarily reflect definitive asthma diagnoses using spirometry. The validity of medical coding data for identifying asthma has been studied extensively. A systematic review showed that use of ≥ 1 asthma diagnosis code over a 1-year period is a commonly used method to identify patients with asthma in administrative data and can be valid.¹⁰ Including asthma medications in the case classification algorithm may improve case detection¹⁰; in one study, nearly half of adults prescribed asthma medication lacked an asthma diagnosis code.¹¹ SABA prescriptions in our study may reflect off-label use to reduce coccidioidomycosis-related symptoms such as wheezing or chest tightness. Our analysis cannot ascertain causality and might also overestimate new-onset asthma in adult patients with a history of childhood asthma or a more distant history of adult asthma >1 year before coccidioidomycosis. Lastly, the dataset lacks information on race/ethnicity; medications administered during hospitalization; and laboratory, imaging, and pulmonary function testing results, all of which may have provided additional insight.

In summary, healthcare providers seeing patients who have recently had coccidioidomycosis should be aware of the possibility for subsequent airway hyperreactivity, particularly among women and patients who have had more severe pulmonary infection. Future investigations using other clinical data sources would advance understanding of this phenomenon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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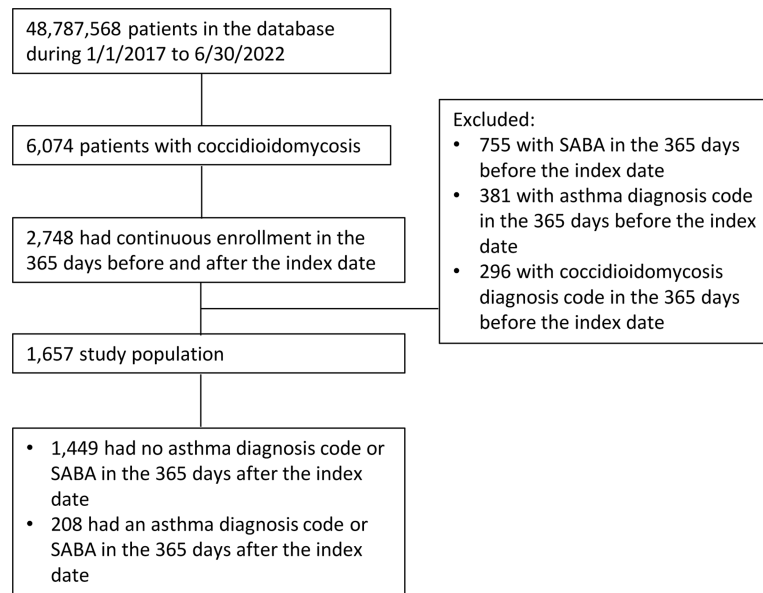


Figure 1. Patient flow diagram

Table 1.

Characteristics of patients with coccidioidomycosis with and without a new asthma diagnosis code or outpatient short-acting β_2 agonist (SABA) prescription after coccidioidomycosis

	Total		Asthma code/SABA		No asthma/SABA		
	n=1,657	%	n=208	%	n=1,449	%	p-value
Sex							<0.001
Male	892	53.8%	77	37.0%	815	56.2%	
Female	765	46.2%	131	63.0%	634	43.8%	
Median age (interquartile range)	51.0	(39–60)	52.0	(40–59)	51.0	(38–60)	0.288
Age group in years							0.267
<18	78	4.7%	12	5.8%	66	4.6%	
18 to 44	488	29.5%	50	24.0%	438	30.2%	
45 to 64	855	51.6%	117	56.3%	738	50.9%	
≥65	236	14.2%	29	13.9%	207	14.3%	
US census region of primary beneficiary's residence (n=1,635)							0.050
Northeast	50	3.1%	1	0.5%	49	3.4%	
Midwest	132	8.1%	14	6.9%	118	8.2%	
South	175	10.7%	17	8.3%	158	11.0%	
West	1,278	78.2%	172	84.3%	1,106	77.3%	
Urban/rural classification (n=1,506)							0.156
Non-rural	1,424	94.6%	183	92.4%	1,241	94.9%	
Rural	82	5.4%	15	7.6%	67	5.1%	
Season of index date							0.985
Winter	460	27.8%	56	26.9%	404	27.9%	
Spring	431	26.0%	55	26.4%	376	25.9%	
Summer	362	21.8%	47	22.6%	315	21.7%	
Fall	404	24.4%	50	24.0%	354	24.4%	
Provider type(s) on index date [†]							
Acute care hospital	416	25.1%	65	31.3%	351	24.2%	0.029
Allergy/immunology	16	1.0%	1	0.5%	15	1.0%	0.710
Family practice or internal medicine	611	36.9%	62	29.8%	549	37.9%	0.024
Infectious disease	130	7.8%	12	5.8%	118	8.1%	0.234
Laboratory	182	11.0%	15	7.2%	167	11.5%	0.063
Other	639	38.6%	77	37.0%	562	38.8%	0.625
Pulmonary disease	254	15.3%	44	21.2%	210	14.5%	0.013
Radiology	182	11.0%	29	13.9%	153	10.6%	0.145
Unknown	41	2.5%	3	1.4%	38	2.6%	0.306
Coccidioidomycosis form on index date [†]							
Pulmonary	819	49.4%	117	56.3%	702	48.4%	0.035
Cutaneous	48	2.9%	5	2.4%	43	3.0%	0.650

	Total		Asthma code/SABA		No asthma/SABA		
	n=1,657	%	n=208	%	n=1,449	%	p-value
Disseminated	76	4.6%	7	3.4%	69	4.8%	0.368
Other or unspecified	825	49.8%	103	49.5%	722	49.8%	0.934
Hospitalized on the index date	216	13.0%	46	22.1%	170	11.7%	<0.001
Symptoms and clinical findings ^{†‡}							
<i>Systemic</i>							
Fever	320	19.3%	50	24.0%	270	18.6%	0.065
Chills, without fever	13	0.8%	4	1.9%	9	0.6%	0.069
Generalized hyperhidrosis	44	2.7%	7	3.4%	13	0.9%	0.496
Sepsis	113	6.8%	31	14.9%	82	5.7%	<0.001
Fatigue or malaise	301	18.2%	35	16.8%	266	18.4%	0.592
Myalgia	79	4.8%	18	8.7%	61	4.2%	0.005
Nausea or vomiting	94	5.7%	15	7.2%	79	5.5%	0.305
<i>Pulmonary</i>							
Cough	528	31.9%	84	40.4%	444	30.6%	0.005
Dyspnea	342	20.6%	71	34.1%	271	18.7%	<0.001
Wheezing	14	0.8%	4	1.9%	10	0.7%	0.088
Chest pain	320	19.3%	43	20.7%	277	19.1%	0.595
Hypoxemia	54	3.3%	18	8.7%	36	2.5%	<0.001
Acute respiratory failure	24	1.4%	8	3.8%	16	1.1%	0.002
Solitary pulmonary nodule	323	19.5%	41	19.7%	282	19.5%	0.932
Other nonspecific abnormal finding of lung field	544	32.8%	87	41.8%	457	31.5%	0.003
Pleural effusion	137	8.3%	34	16.3%	103	7.1%	<0.001
Diseases of mediastinum	13	0.8%	3	1.4%	10	0.7%	0.217
Pulmonary fibrosis	65	3.9%	12	5.8%	53	3.7%	0.142
<i>Upper respiratory</i>							
Acute pharyngitis, unspecified	65	3.9%	10	4.8%	55	3.8%	0.482
Nasal congestion and postnasal drip	34	2.1%	5	2.4%	29	2.0%	0.607
<i>Other signs and symptoms</i>							
Erythema nodosum	47	2.8%	5	2.4%	42	2.9%	0.688
Other erythematous conditions	25	1.5%	6	2.9%	19	1.3%	0.117
Enlarged lymph nodes	128	7.7%	21	10.1%	107	7.4%	0.171
Headache	112	6.8%	13	6.3%	99	6.8%	0.754
Low back pain	118	7.1%	19	9.1%	99	6.8%	0.227
Abdominal pain	178	10.7%	32	15.4%	146	10.1%	0.021
Pain in joint	229	13.8%	27	13.0%	202	13.9%	0.708
Rash and other nonspecific skin Eruption	146	8.8%	18	8.7%	128	8.8%	0.932
Other diagnoses ^{†‡}							

	Total		Asthma code/SABA		No asthma/SABA		
	n=1,657	%	n=208	%	n=1,449	%	p-value
Acute nasopharyngitis or acute upper respiratory infections of multiple and unspecified sites	122	7.4%	19	9.1%	103	7.1%	0.295
Acute sinusitis	77	4.6%	13	6.3%	64	4.4%	0.240
Allergic contact dermatitis	10	0.6%	2	1.0%	8	0.6%	0.363
Allergic rhinitis	95	5.7%	16	7.7%	79	5.5%	0.194
Anxiety disorder	153	9.2%	30	14.4%	123	8.5%	0.006
Atopic dermatitis	16	1.0%	1	0.5%	15	1.0%	0.710
Bronchitis or unspecified lower acute respiratory infection	75	4.5%	17	8.2%	58	4.0%	0.007
Cancer	162	9.8%	17	8.2%	147	10.1%	0.405
Chronic obstructive pulmonary disease (COPD) or other chronic lower respiratory disease	128	7.7%	26	12.5%	102	7.0%	0.006
Chronic sinusitis	43	2.6%	6	2.9%	37	2.6%	0.779
Conjunctivitis	12	0.7%	1	0.5%	11	0.8%	1.000
COVID-19 [§]	44	6.4%	7	10.0%	37	6.0%	0.198
Depression	112	6.8%	20	9.6%	92	6.3%	0.079
Diabetes	247	14.9%	36	17.3%	211	14.6%	0.298
Fibromyalgia	22	1.3%	7	3.4%	15	1.0%	0.014
Food allergy	4	0.2%	0	0.0%	4	0.3%	1.000
HIV	22	1.3%	1	0.5%	22	1.5%	0.510
Hypersensitivity pneumonitis	0	0.0%	0	0.0%	0	0.0%	n/a
Hypertension	454	27.4%	53	25.5%	401	27.7%	0.507
Hypothyroidism	154	9.3%	17	8.2%	137	9.5%	0.552
Immune-mediated inflammatory Disease	157	9.5%	18	8.7%	139	9.6%	0.666
Influenza	30	1.8%	4	1.9%	26	1.8%	0.784
Overweight and obesity	162	9.8%	28	13.5%	134	9.2%	0.056
Pneumonia	440	26.6%	73	35.1%	367	25.3%	0.003
Viral pneumonia	21	1.3%	4	1.9%	17	1.2%	0.324
Bacterial pneumonia	78	4.7%	20	9.6%	58	4.0%	<0.001
Organism unspecified	428	25.8%	71	34.1%	357	24.6%	0.034
Smoking (current or past)	157	9.5%	31	14.9%	126	8.7%	0.004
Solid organ or hematopoietic stem cell transplantation	44	2.7%	8	3.8%	36	2.5%	0.253
Vitamin D deficiency	136	8.2%	13	6.3%	123	8.5%	0.271
Eosinophilia on in the year after index date	40	2.4%	5	2.4%	35	2.4%	0.992
Testing on or in the year after index date							
Chest CT	603	36.4%	97	46.6%	506	34.9%	0.001
Spirometry	239	14.4%	70	33.7%	169	11.7%	<0.001
Nitric oxide expired gas determination	10	0.6%	5	2.4%	5	0.3%	0.004
Outpatient prescription medications							

	Total		Asthma code/SABA		No asthma/SABA		
	n=1,657	%	n=208	%	n=1,449	%	p-value
Antifungals [¶]	793	47.9%	117	56.3%	696	48.0%	0.010
Fluconazole	765	46.2%	115	55.3%	650	44.9%	0.005
Itraconazole	33	2.0%	4	1.9%	29	2.0%	1.000
Posaconazole	7	0.4%	1	0.5%	6	0.4%	1.000
Voriconazole	17	1.0%	2	1.0%	15	1.0%	1.000
Biologic drug ^{††}	2	0.1%	0	0.0%	2	0.1%	1.000

[†]Non-mutually exclusive categories

[‡]In the 90 days before or on the index date

[§]For patients with index date on or after January 1, 2020 (n=686)

[¶]In the 7 days before to 6 months after the index date

^{††}Benralizumab, dupilumab, mepolizumab, omalizumab, or reslizumab in the year after index date