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Epidemiological Characterization of Opportunistic Mycoses between the Years 2006 and 2010 in Korea

Je-Seop Park[1], Seung-Hak Cho[2], Seung-Ki Youn[3], Young-Seok Bak[4], Young-Bin Yu[1], and Young Kwon Kim[1]*

[1]*Department of Biomedical Laboratory Science, College of Medical Science, Konyang University, Daejeon 35365, Republic of Korea*
[2]*Division of Enteric Diseases, Center for Infectious Diseases, Korea National Institute of Health, Cheongju 28159, Republic of Korea*
[3]*Division of Quarantine Support, Korea Centers for Disease Control and Prevention, Cheongju 28159, Republic of Korea*
[4]*Department of Emergency Medical Service, College of Medical Science, Konyang University, Daejeon 35365, Republic of Korea*

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**Corresponding author*
Phone: +82-42-600-6371;
Fax: +82-42-600-6378;
E-mail: ykkim3245@konyang.ac.kr

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In order to perform an epidemiological characterization of opportunistic mycosis infections, we collected health insurance data between the years 2006 and 2010 from the Health Insurance Corporation and analyzed the data to determine the prevalence of opportunistic mycoses and treatment management of opportunistic mycoses. The prevalence within the study increased consecutively by 0.02% to 0.12% every year. The annual prevalence of opportunistic mycoses increased from 2.437% in 2006 to 2.709% in 2010. The average annual prevalence was 2.605%. Candidiasis occurred the most frequently, followed by aspergillosis, zygomycosis, and cryptococcosis. The regions with the highest incidences were the capital areas, Gyeonggi and Seoul. By sex, the prevalence in females (4.851%) was 14 times higher than that in males (0.352%). Interestingly, the adults from the 20- to 49-year-old age group showed higher prevalence than children and the elderly. The average duration of hospitalized treatment was 17.31 days and of outpatient treatment was 2.21 days; 3,577 hundred million won was used in total for medical expenses. This study provides useful data to study trends of opportunistic mycoses.

Keywords: Opportunistic mycoses, incidence rate, candidiasis, aspergillosis, cryptococcosis, zygomycosis

Introduction

Opportunistic fungal infections are emerging as an important public health concern and cost burden [11]. The frequency of infections has increased significantly over the past 3 decades [25, 35]. This increase in the frequency of infections is due to the increasing number of critically ill patients [11, 23, 25, 31].

The incidence of fungal infections in South Korea is increasing consistently; however, epidemiological national survey data and other related information for mycoses are lacking.

Opportunistic mycosis is a disease caused by pathogenic fungi when changes in the total number of normal flora occur in people with an abnormal immune system, such as loss of health due to a fungi with limited toxicity, use of immunosuppressive agents due to organ transplant, invasive central venous catheter, invasive surgery to place a medical device, or long-term administration of broad-spectrum antibiotics [11, 12, 24].

The most well-known opportunistic fungal pathogens are *Candida* species. Although >100 species of *Candida* have been described, only 10% of them have been implicated in opportunistic mycosis [25]. Candidiasis is a serious disease with a mortality rate of 10% to 49% for bloodstream infections [8, 18, 25, 26, 32, 34]. The majority of cases (50% to 70%) are caused by *Candida albicans*, followed by *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* for newborns [3, 5, 7, 9, 19, 20, 25, 31].

Aspergillus species that induce aspergillosis have many spores in the air and account for most of the fungi that infect people through the air. *A. fumigatus* is the most frequent cause of aspergillosis, responsible for about 90% of all cases [30]. The mortality rate with invasive aspergillosis

is high, ranging from 50% to 100% in almost all groups of immunocompromised patients [4, 21]. Other important aspergillus species are *A. niger*, *A. flavus*, *A. nidulans*, and *A. terreus* [6, 22, 24].

Cryptococcosis represents a major life-threatening fungal infection in patients with defective cell-mediated immunity and may also complicate organ transplantation. The mass outbreak of serotype B *Cryptococcus neoformans*, which generally occurs in the subtropics, infected and killed healthy people with normal immune systems in Vancouver, Canada, and in the Northwest region of the USA; this proved that fungal infections do not occur only in people with compromised immune systems [10].

The class zygomycetes contains the genera *Rhizopus*, *Mucor*, *Rhizomucor*, and *Lichtheimia* (formerly *Absidia*); fungal infections are most commonly linked to *Rhizopus* species [27]. Zygomycosis is a rare emerging opportunistic infection frequently associated with immunosuppressed patients, including hematopoietic stem-cell transplantation recipients, those with poorly controlled diabetes mellitus, and patients with hematologic malignancies (especially with neutropenia) [1, 13–15]. The prevalence and overall mortality of zygomycosis were 36% and 44%, respectively [28].

In Korea, however, the epidemiology of opportunistic fungal infections is not well described and data regarding incidence are scant. Therefore, the purpose of this study was to build a basic database for effective fungal infection control by performing the epidemiological characterization of these infections from 2006 to 2010, using the database of Health Insurance Corporation.

Materials and Methods

Study Design

Health insurance data between the years 2006 and 2010 were collected from the Health Insurance Corporation and analyzed. The diseases of opportunistic fungal infections were divided into four groups, including candidiasis (KoICD, *Korea International Classification of Diseases*: B37), aspergillosis (B44), cryptococcosis (B45), and zygomycosis (B46).

The number of incidence was analyzed by considering medical records for one case if the case was duplicated within 2 months for candidiasis and 6 months in the case of aspergillosis, cryptococcosis, and zygomycosis (Fig. 1).

Epidemiological Analysis

In order to determine the significance of opportunistic mycosis that causes diseases, we performed an epidemiological analysis of annual and regional prevalence and age- and sex-specific patterns of the prevalence for each opportunistic mycosis. The annual prevalence of opportunistic infections was calculated, where patients with the disease who had been treated multiple times were counted as one case per year in the data analysis. The regional prevalence was calculated according to the locations of the medical institutions where the treatments had been provided.

Duration of Hospitalization and Cost Analysis of Therapy

The number of convalescence days of inpatients and outpatients for opportunistic mycosis was calculated for the last 5 years, and medical care cost was calculated and classified as personal charges and insurance charges from insurance items from the Health Insurance Corporation database. No insurance charge item was excluded from the medical care cost.

Results

Gyeonggi (1,560,554 cases) and Seoul (1,393,553 cases) had the highest rates of occurrence of infection, and Jeju (64,231 cases) had the lowest rate of occurrence (Table 1). The prevalence in females (93.17%) was 14 times higher than that in males. The highest rates of infection occurred in patients in their 20s to 40s (Table 2). The average

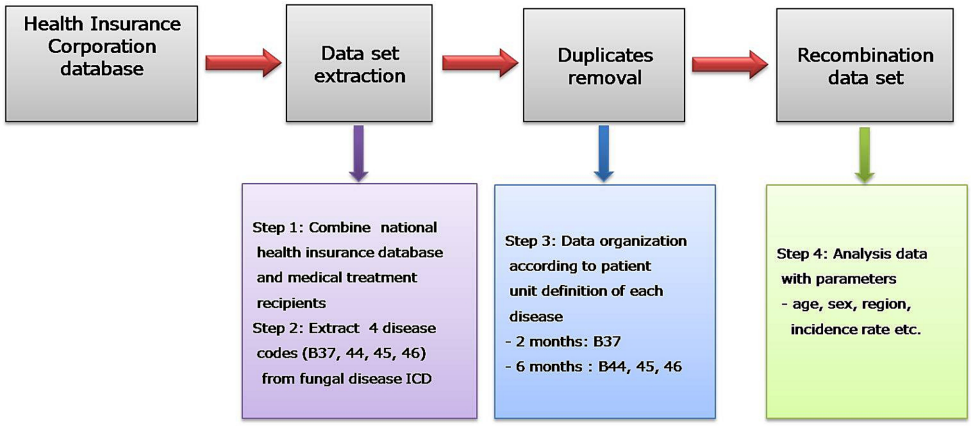

Fig. 1. Analysis algorithm chart of the National Health Insurance database.

Table 1. Prevalence rate of opportunistic mycoses by year and regions.

		No. (%) patients				
		Opportunistic	Candidiasis	Aspergillosis	Cryptococcosis	Zygomycosis
Year	Population	*N* = 6,255,789	*N* = 6,238,869	*N* = 10,878	*N* = 2,091	*N* = 3,951
2006	48,039,415	1,170,670 (2.437)	1,167,176 (2.430)	2,411 (0.0050)	421 (0.0009)	552 (0.0014)
2007	48,138,077	1,218,149 (2.536)	1,215,049 (2.529)	1,982 (0.0041)	349 (0.0007)	769 (0.0016)
2008	48,297,184	1,276,862 (2.658)	1,273,294 (2.651)	2,128 (0.0044)	500 (0.0010)	940 (0.0019)
2009	48,456,369	1,288,948 (2.683)	1,285,206 (2.675)	2,316 (0.0048)	582 (0.0012)	844 (0.0017)
2010	48,606,787	1,301,160 (2.709)	1,298,144 (2.702)	2,041 (0.0042)	239 (0.0005)	736 (0.0015)
Region						
Gyeonggi	56,551,740	1,560,554 (2.760)	1,557,233 (2.754)	2,192 (0.0039)	376 (0.0007)	753 (0.0013)
Seoul	51,095,550	1,393,553 (2.727)	1,389,758 (2.720)	2,090 (0.0041)	543 (0.0011)	1,162 (0.0023)
Busan	17,874,948	395,876 (2.215)	394,976 (2.210)	572 (0.0032)	107 (0.0006)	221 (0.0012)
Gyeongnam	16,135,777	362,936 (2.249)	361,675 (2.241)	953 (0.0059)	81 (0.0005)	227 (0.0014)
Incheon	13,450,538	339,512 (2.524)	338,724 (2.518)	585 (0.0043)	98 (0.0007)	105 (0.0008)
Gyeongbuk	13,403,668	255,731 (1.908)	254,903 (1.908)	513 (0.0038)	111 (0.0008)	204 (0.0015)
Daegu	12,483,557	288,345 (2.310)	287,715 (2.305)	453 (0.0036)	74 (0.0006)	103 (0.0008)
Chungnam	10,101,597	246,136 (2.437)	245,401 (2.429)	426 (0.0042)	160 (0.0016)	149 (0.0015)
Jeonnam	9,623,250	226,407 (2.353)	225,470 (2.343)	585 (0.0061)	94 (0.0010)	258 (0.0027)
Jeonbuk	9,309,885	204,829 (2.200)	203,535 (2.186)	844 (0.0091)	193 (0.0021)	257 (0.0028)
Chungbuk	7,597,760	178,127 (2.345)	177,739 (2.339)	289 (0.0038)	50 (0.0007)	49 (0.0006)
Gangwon	7,560,489	154,729 (2.047)	154,252 (2.040)	281 (0.0067)	90 (0.0012)	106 (0.0014)
Daejeon	7,410,556	190,538 (2.571)	190,215 (2.567)	229 (0.0031)	47 (0.0006)	47 (0.0006)
Gwangju	7,132,220	216,886 (3.041)	216,229 (3.032)	409 (0.0057)	26 (0.0004)	222 (0.0031)
Ulsan	5,546,060	177,399 (3.199)	176,939 (3.190)	383 (0.0069)	25 (0.0005)	52 (0.0009)
Jeju	2,812,290	64,231 (2.284)	64,105 (2.280)	74 (0.0026)	16 (0.0006)	36 (0.0013)

Table 2. Prevalence rate of opportunistic mycoses by age and sex.

		No. (%) patients				
		Opportunistic	Candidiasis	Aspergillosis	Cryptococcosis	Zygomycosis
Sex	Population	*N* = 6,255,789	*N* = 6,238,869	*N* = 10,878	*N* = 2,091	*N* = 3,951
Male	121,384,162	427,062 (0.352)	418,037 (0.344)	6,184 (0.0051)	928 (0.0008)	1,913 (0.0016)
Female	120,153,670	5,828,727 (4.851)	5,820,832 (4.845)	4,694 (0.0039)	1,163 (0.0010)	2,038 (0.0017)
Age						
0-9	27,724,299	489,991 (1.767)	488,717 (1.767)	157 (0.0006)	351 (0.0013)	766 (0.0026)
10-19	33,060,697	142,038 (0.430)	141,436 (0.430)	265 (0.0008)	136 (0.0004)	201 (0.0006)
20-29	37,329,397	1,329,195 (3.561)	1,328,346 (3.561)	443 (0.0012)	81 (0.0002)	325 (0.0009)
30-39	42,264,128	1,839,110 (4.352)	1,837,532 (4.352)	924 (0.0022)	133 (0.0003)	521 (0.0012)
40-49	41,286,367	1,461,955 (3.641)	1,459,201 (3.541)	1,966 (0.0048)	251 (0.0006)	537 (0.0013)
50-59	27,180,185	621,667 (2.287)	618,090 (2.287)	2,841 (0.0105)	267 (0.0010)	469 (0.0017)
60-69	18,404,769	231,075 (1.256)	227,625 (1.256)	2,531 (0.0138)	368 (0.0020)	551 (0.0030)
70-79	10,654,688	113,090 (1.061)	110,815 (1.061)	1,446 (0.0136)	381 (0.0036)	448 (0.0042)
80-89	3,260,919	25,184 (0.772)	24,655 (0.772)	288 (0.0088)	115 (0.0035)	126 (0.0039)
90-	435,853	2,484 (0.570)	2,452 (0.570)	17 (0.0039)	8 (0.0018)	7 (0.0016)

Table 3. Convalescence days and medical costs for opportunistic mycoses.

Origin	Patient	Frequency (*N*)	Average convalescence (days)	Persons cost of care (won)	Total cost (100 million)	Self cost (100 million)	Insurance cost (100 million)
Opportunistic	Inpatient	30,880	17.31	4,730,406	1,461	203	1,258
	Outpatient	6,123,242	2.21	34,555	2,116	593	1,523
Candidiasis	Inpatient	26,563	15.13	3,573,693	949	130	819
	Outpatient	6,111,380	2.21	32,893	2,010	579	1,431
Aspergillosis	Inpatient	2,822	34.11	14,286,411	403	57	346
	Outpatient	7,602	8.20	1,064,113	81	11	70
Cryptococcosis	Inpatient	805	25.56	7,400,280	60	9	51
	Outpatient	1,192	8.78	1,141,597	13	1	12
Zygomycosis	Inpatient	690	22.93	7,062,986	49	7	42
	Outpatient	3,068	3.86	365,627	11	1	10

duration of hospitalized treatment was 17.31 days and of outpatient treatment was 2.21 days. Total medical expenses cost 3,577 hundred million won. Among the total expenses, hospitalizations cost 1,461 hundred million won and outpatient treatments cost 2,116 hundred million won (Table 3).

Prevalence of Opportunistic Mycosis Infections Between the Year 2006 and 2010 in Korea

A total of 6,255,789 infections by opportunistic mycosis were analyzed during the 5-year study period. Approximately 1.25 million cases occurred each year (Table 1). The prevalence rate according to resident population increased consecutively. The annual prevalence of opportunistic mycoses increased from 2.437% in 2006 to 2.709% in 2010. The average annual prevalence was 2.605%. The rate of infection according to region ranged from 3.199% in Ulsan to 1.908% in Gyeongbuk.

As shown in Table 2, age-specific patterns were observed in the opportunistic mycoses. By age group, there was a high rate of prevalence in people aged 30 to 39 years (4.35%), whereas the prevalence rate was low in people aged 10 to 19 years (0.430%) and aged 80 years and over (0.570% to 0.772%).

Prevalence of Different Opportunistic Mycoses

As shown in Table 1, candidiasis (6,238,869 cases, 99.73%) occurred most frequently, followed by aspergillosis (10,878 cases, 0.17%), zygomycosis (3,951 cases, 0.06%) and cryptococcosis (2,091 cases, 0.03%).

Candidiasis. Candidiasis was the most frequently observed opportunistic mycosis, and the annual prevalence of candidiasis increased from 2.430% in 2006 to 2.702% in 2010. The average annual prevalence of candidiasis was highest at 2.597% among all of the types of opportunistic mycoses. The regional prevalence was highest in Ulsan (3.190%) and lowest in Gyeongbuk (1.908%) (Table 1). As shown Table 2, age-specific patterns of candidiasis prevalence showed that the prevalence in patients in their 30s (4.352%) was highest, especially in fertile women. The prevalence among females (4.845%) was 14 times higher than that among males (0.344%).

Aspergillosis. The prevalence of aspergillosis decreased slightly from 0.0050% in 2006 to 0.0042% in 2010. The regional prevalence was highest in Jeonbuk (0.0091%) and lowest in Jeju (0.0026%) (Table 1). The age-specific prevalence rate was highest in patients in their 60s (0.0138%) to 70s (0.0136%), and the gender-specific rates were similar between females (0.0039%) and males (0.0051%) (Table 2).

Cryptococcosis. The prevalence rate of cryptococcosis was highest in 2009 (0.0010%), but decreased in 2010 (0.0005%). The prevalence was highest in Jeonbuk (0.0021%) (Table 1). The age-specific prevalence rate was highest in patients in their 70s (0.0036%) to 80s (0.0035%), and the gender-specific rates were similar between females (0.0010%) and males (0.0008%) (Table 2).

Zygomycosis. The prevalence of zygomycosis gradually rose from 0.0014% in 2006 to 0.0019% in 2008, but decreased thereafter (Table 1). By region, the prevalence was highest in Gwangju (0.0031%). The age-specific prevalence was highest in patients in their 70s (0.0042%) and gender-specific rates were similar between females (0.0017%) and males (0.0016%) (Table 2).

Convalescence Days and Medical Care Charges According to Different Opportunistic Mycoses

The number of convalescence days for inpatients was 15.13 days for candidiasis, 34.11 days for aspergillosis, 25.56 days for cryptococcosis, and 22.93 days for zygomycosis (Table 3). The number of convalescence days for outpatients was 2.2 days for candidiasis, 8.20 days for aspergillosis, 8.78 days for cryptococcosis, and 3.86 days for zygomycosis.

The treatment cost for opportunistic mycosis from 2006 to 2010 was 3,577 hundred million won, with personal charges of 796 hundred million won and insurance charges of 2,781 hundred million won. Among the total cost, about 83% (2,959 hundred million won of the cost) was used for the treatment of candidiasis.

Discussion

Opportunistic mycoses are fungal infections of the human body that occur in immunocompromised patient and the virulence of these fungi are naturally low. Several surveys indicate a rising incidence of fungal infections. National autopsy data from Japan between 1969 and 1994 showed increased prevalence of visceral mycoses [33], and national hospital admission data in Australia between 1995 and 1999 showed increasing hospitalizations for candidiasis and aspergillosis [29]. According to US death certificate data from 1980 to 1997, the number of deaths due to fungal infections increased 3.4 times [16]. Single-center data from India also show an increase in mucormycosis over time [17]. The impact of human immunodeficiency virus infection and the improvement of medical technology in the region have resulted in an increased population of immunocompromised patients and, consequently, more hospitals are reporting invasive fungal infections [2]. The incidence of fungal infections increased as the number of diabetes mellitus, organ transplant, AIDS, and chemotherapy for malignant neoplasm also increased.

Rapid industrialization and urbanization have concentrated the population and instigated global warming. Economic development has changed cultural life and the westernized diet has changed ecosystems. Owing to all these factors, new and various pathogens such as opportunistic infection-causing fungi have increased.

Opportunistic mycoses mainly occurred in individuals of under 9 years and elders over the age of 60 with weak immune systems. Aspergillosis had a high prevalence among those in their 60s to 70s, cryptococcosis had a high prevalence among those in their 70s to 80s, and zygomycosis had a high prevalence among those in their 70s. Interestingly, candidiasis had a higher prevalence rate for childbearing women in their 20s to 40s.

Since the disease threatens healthy life and is predicted to increase health care cost, effective management and epidemiological studies are needed to reduce the high medical costs, facilitate healthy lifestyles, and establish a variety of preventive measures such as dietary improvement for the recovery of the immune system and environmental improvements for preventing the spread of infection from unclean surroundings. Patients with opportunistic mycoses experience a reduced quality of life and increased medical costs. If we adequately analyze and observe the progress of opportunistic mycoses with effective management and systematic study, these patients will be able to lead a better life.

This study attempted to determine the roadmap for diagnosis and treatment as well as steps to curb the rising prevalence of opportunistic fungal infections by using the data obtained from the National Health Insurance Corporation database. If the trends of prevalence according to year, region, gender, and age can be continuously analyzed and observed, these data can be a useful resource for determining the changes in the trend of opportunistic fungal pathogens.

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