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Serious fungal infections in Korea

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Abstract Information on the incidence and prevalence of fungal infections is of critical value in public health policy. However, nationwide epidemiological data on fungal infections are scarce, due to a lack of surveillance and funding. The objective of this study was to estimate the disease burden of fungal infections in the Republic of Korea. An actuarial approach using a deterministic model was used for the estimation. Data on the number of populations at risk and the frequencies of fungal infections in those populations were obtained from national statistics reports and epidemiology papers. Approximately 1 million people were estimated to be affected by fungal infections every year. The burdens of candidemia (4.12 per 100,000), cryptococcal meningitis (0.09 per 100,000), and *Pneumocystis* pneumonia (0.51 per 100,000) in South Korea were estimated to be comparable to those in other countries. The prevalence of chronic pulmonary aspergillosis (22.4 per 100,000) was markedly high, probably due to the high burden of tuberculosis in Korea. The low burdens of allergic bronchopulmonary aspergillosis (56.9 per 100,000) and severe asthma with fungal sensitization (75.1 per 100,000) warrant further study. Oral candidiasis (539 per 100,000) was estimated to affect a much larger population than noted in previous studies. Our work provides valuable insight on the epidemiology of fungal infections; however, additional studies are needed.

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In association with the LIFE program at http://www.LIFE-worldwide.org.

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Introduction

The importance of fungal disease in public health has been constantly increasing. While their incidence is much lower than that of bacterial infections, fungal infections result in significant clinical and economic burdens. In most counties, surveillance for fungal diseases does not exist, which makes the determination of population-based incidence and prevalence difficult [1]. The lack of reliable data on the epidemiology of fungal disease eventually leads to insufficient funding and research. The situation in Korea is not very different, with only a few reports mostly from individual centers. Such studies are often inept for estimating incidence at the national level, as they are usually retrospective studies focused on patients with specific risk factors.

Korea has unique characteristics with respect to the epidemiology of the risk factors of fungal infections. While the incidence of human immunodeficiency virus (HIV) infection is relatively low and "endemic fungi" are virtually nonexistent, the burden of tuberculosis (TB) and the number of immunocompromised hosts are high.

Actuarial approaches using a deterministic model to estimate the national burden of fungal infections have been recently employed by multiple researchers [2]. The

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methodology of the LIFE program (http://www.LIFE-worldwide.org) used the prevalence of predisposing conditions at the national level and the incidence of certain mycoses among people at risk to calculate the estimated incidence of fungal infections. We aimed to estimate the burden of serious fungal infections in Korea using this method.

Methods

Basic information on population structure was identified using 2010 national census data [3]. We searched for previous studies on the national epidemiology of fungal diseases in PubMed. We also searched for data on the national epidemiology of risk factors for fungal infections. When national data were not available, we searched for regional or international reports for use as surrogates. As HIV/acquired immune deficiency syndrome (AIDS) and TB are reportable diseases in Korea, data on the incidence of these conditions were acquired from the annual reports of the Korea Centers for Disease Control and Prevention (KCDC) [4, 5]. An estimate of the antiretroviral coverage rate was obtained from the World Health Organization (WHO) Global Health Observatory (GHO) data repository [6]. Reports based on the Korea Central Cancer Registry (KCCR) [7] and the Korean Study Group of Hematopathology [8] were used to determine the annual incidence and composition of hematologic malignancies. The numbers of allogeneic hematopoietic stem cell transplants (HSCTs) and solid organ transplants (SOTs) were obtained from the annual reports of the Korean Society of Bone Marrow Transplantation and the Korean Network for Organ Sharing [9]. The prevalence of chronic obstructive pulmonary disease (COPD) was derived from the 2008 Korean National Health and Nutrition Examination Survey [10]. The number of adult asthma patients was calculated with an age-specific prevalence from National Health Insurance reimbursement data [11]. Information on the utilization of intensive care unit (ICU) beds was obtained from the Health Insurance Review and Assessment Service (http://opendata.hira.or.kr).

Results and discussion

The Republic of Korea is an Organisation for Economic Co-operation and Development (OECD) high-income country by World Bank classification. The gross domestic product per capita in 2013 was $25,870. According to the 2010 Population Census, the last year of the national census, the total population was approximately 47.99 million (adults 40 million; 23.84 million male, 24.15 million female), 16.2% of whom were younger than 15 years old and 11.3% of whom were 65 years or older. The mean and median age was 38.1 years. The estimated burden of fungal infections is shown in Table 1.

Pneumocystis jirovecii pneumonia

As the prevalence of HIV/AIDS is relatively low in Korea, the majority of *Pneumocystis jirovecii* pneumonia (PCP) and cryptococcal meningitis cases are not associated with HIV. Among the 1114 patients newly diagnosed with HIV, 246 had a CD4+ T-cell count less than 200. Based on local reports [12], we estimated that 20% of the newly diagnosed HIV patients with a low CD4+ T-cell count would present with PCP. Among non-HIV/AIDS risk factors, the incidence among patients who underwent HSCT ($n = 1898$) was estimated to be 1.3% [13]. Also, we estimated an incidence of 4.5% in patients with B-cell lymphoma ($n = 3551$), which accounts for 78% of 4553 patients with non-Hodgkin lymphoma [14] and 0.9% in liver transplant recipients ($n = 1209$) [15]. It was found that PCP affected 49 patients with HIV/AIDS and 195 patients with other immunocompromising conditions. The total annual incidence of PCP was estimated to be 245 cases.

Cryptococcal meningitis

Previous reports on the incidence of non-AIDS-associated cryptococcal meningitis in Korea could not be found. Instead, the distribution of non-AIDS predisposing factors for cryptococcal meningitis was reported in a single-center study between 1995 and 2008, in which the use of immunosuppressants (45.4%), SOT recipient (21.2%), malignancy (15.1%), and diabetes (15.1%) were identified as non-HIV underlying diseases in patients with cryptococcal meningitis [16]. Consequently, we estimated the number of total cases of cryptococcal meningitis from the number of HIV-associated cases. The proportion of patients with AIDS presenting with cryptococcal meningitis was estimated to be 2.5% [12] and the HIV-associated cases were estimated to comprise 14% of the total cases [16]. Based on our calculation, cryptococcal meningitis was estimated to affect 44 patients annually.

The burdens of cryptococcal meningitis and PCP were largely similar to previous estimates from other countries (Table 2) [2]. The low prevalence of HIV and easier access to treatment might have resulted in a similar burden to countries in Western Europe; however, the results must be interpreted with caution, as non-HIV immunocompromising conditions might contribute more to both cryptococcal meningitis and PCP than HIV/AIDS in this setting.

Aspergillus infections

We divided the infections caused by *Aspergillus* into four categories: invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA) after TB, allergic

Table 1 Burdens of fungal diseases in Korea according to underlying disease

	Rate (per 100,000)[a]	Total burden	Number of infections per underlying disorder per year				
			None	HIV/AIDS	Respiratory	Cancer + immunocompromised	ICU
Pneumocystis pneumonia	0.51	245	N/A[b]	49	N/A	195	N/A
Cryptococcal meningitis	0.09	44	38	6	N/A	N/A	N/A
Invasive aspergillosis	4.48	2150	N/A	N/A	1428	722	N/A
Chronic pulmonary aspergillosis[c]	22.4	10,754	N/A	N/A	10,754	N/A	N/A
Allergic bronchopulmonary aspergillosis[c]	56.9	27,312	N/A	N/A	27,312	N/A	N/A
Severe asthma with fungal sensitization[c]	75.1	36,052	N/A	N/A	36,052	N/A	N/A
Candidemia	4.12	1976	1522	N/A	N/A	N/A	455
Candida peritonitis	0.47	227	N/A	N/A	N/A	N/A	227
Oral candidiasis	539	258,754	N/A	2294	N/A	256,460	N/A
Esophageal candidiasis	290	139,400	128,692	670	N/A	10,038	N/A
Recurrent vulvovaginal candidiasis	3810[d]	460,102	460,102	N/A	N/A	N/A	N/A
Mucormycosis	0.14	68	N/A	N/A	N/A	68	N/A
Fungal keratitis	0.06	29	29	N/A	N/A	N/A	N/A
Tinea capitis[c]	94.0	45,087	45,087	N/A	N/A	N/A	N/A
Total burden		985,079					

[a] Rate per 100,000 people in Korea

[b] Not available or not applicable

[c] Prevalences were estimated instead of incidences

[d] Prevalence per 100,000 adult females, not per total population

bronchopulmonary aspergillosis (ABPA), and severe asthma with fungal sensitization (SAFS). To estimate IPA annual incidence in patients with hematologic malignancies and SOTs, we assumed that IPA occurs in 14.7% of patients who undergo allogeneic HSCT, 0.76% of liver transplant recipients, 0.24% of kidney transplant recipients, 8.8% of lung transplant recipients, and 0.8% of heart transplant recipients [13, 17, 18]. We assumed an incidence of 5% for patients with either acute myeloid leukemia (AML) or non-AML hematologic malignancy [19]. Aplastic anemia, which is not included in the national cancer surveillance, was estimated to account for 3.7% of hematologic disease-associated IPA [20]. Also, we estimated the number of IPA cases in patients with COPD by applying the incidence rate of 1.6% of admissions due to COPD [21]. Overall, IPA was estimated to affect 2150 patients annually. The burden of invasive aspergillosis was similar between Korea and European countries, which could be explained by the comparable incidence of immunocompromising conditions, such as hematologic malignancies and SOTs.

For CPA after TB, we assumed a 22% cavitation rate among patients treated for TB [22]. It was assumed that 22% and 2% of the patients with cavitary and non-cavitary TB, respectively, develop CPA. The 5-year prevalence was calculated assuming an annual attrition rate of 15%. These assumptions translate into 2324 new cases of CPA associated with TB every year, which leads to the 5-year period prevalence of 7324 cases. The incidence of pulmonary infection by nontuberculous mycobacteria (NTM) is high in Korea, as in other Asian countries, and NTM lung disease has recently been identified as a risk factor for CPA [23]. Due to the absence of national data on the epidemiology of NTM, we used two recent Japanese studies to estimate the annual incidence of NTM lung disease at 12 per 100,000 [24, 25]. When 10% of patients with NTM lung disease were assumed to develop CPA in 5 years [23], the 5-year prevalence of NTM-associated CPA was estimated at 6 per 100,000, which translates to 2879 patients.

Based on a previous study in Korea, it was assumed that TB was the underlying cause of CPA in 93% of cases, except those associated with NTM [26]. The total number of CPA cases was estimated at 10,754. The high prevalence of CPA, in our opinion, is the most significant finding in our study. The estimated prevalence in Korea exceeded 20 cases per 100,000 population, which was approximately 8-fold higher than that in Germany but similar to that in Russia. The reason for this large difference with countries in Western Europe seems to be the high prevalence of TB and NTM infections in Korea. The burden of pulmonary TB has been on a steady decrease but it still affects nearly 100 patients per 100,000 population (2012) with a low mortality of 4.8%, leaving a substantial number of patients at risk of CPA. Our study clearly shows the secondary impact of TB from CPA, which will likely last long after the TB itself is cured, as

Table 2 Comparison of the national burden of fungal infections in select countries. Estimates for other countries are from the Global Action Fund for Fungal Infections (GAFFI) [2]

Burden of fungal infections (per 100,000)	Korea	Belgium	Denmark	Germany	Vietnam	Russia
Population (millions)[a]	50.2	11.1	5.6	80.6	89.7	143.5
GDP per capita (USD)[a]	25,998	46,625	59,818	46,441	1909	14,487
Estimated HIV prevalence (%)[b]	0.02	0.13	0.1	0.08	0.27	0.70
Estimated TB prevalence (per 100,000)[c]	106	11	8.7	7.5	208	115
Serious fungal infections						
Cryptococcal meningitis	0.09	0.09	0.04	0.07	0.15	0.21
Pneumocystis pneumonia	0.51	1.10	1.50	1.30	0.67	0.99
Invasive aspergillosis	4.48	6.08	5.30	5.10	16.0	2.27
Chronic pulmonary aspergillosis	22.4	6.00	4.80	2.90	61.0	36.6
Allergic bronchopulmonary aspergillosis (ABPA)	56.9	208	131	154	26.0	123
Severe asthma with fungal sensitization (SAFS)	75.1	274	139	203	34.0	162
Candidemia	4.12	5.00	9.40	4.60	5.00	8
Candida peritonitis	0.47	0.75	3.10	4.60		
Oral candidiasis	539		13.80	141		33.92
Esophageal candidiasis	290		6.80	4.7	36	8.01
Recurrent *Candida* vaginitis	3810	3149	2700	3068	3893	3481
Mucormycosis	0.14		0.02	0.02	0.12	0.16
Histoplasmosis	0.00			0.02		
Fungal keratitis	0.06		0.05	0.04	7.0	
Tinea capitis	94.0		3.30		457	42.6

[a] World Development Indicators, World Bank

[b] Health at a Glance 2011: OECD Indicators, Organisation for Economic Co-operation and Development

[c] Global Health Observatory, World Health Organization

CPA often requires prolonged treatment and results in long-term morbidity. Also, the pulmonary infection by NTM was estimated to cause almost one-third of CPA in our study. The incidence of NTM in Korea has been known to be higher than in European countries, but accurate data on the national burden do not exist. National surveillance on the epidemiology of NTM and NTM-associated CPA are warranted.

ABPA and SAFS were assumed to affect 2.5% of adults with asthma and 33% of the worst 10% of adult asthmatics, respectively [27]. Cystic fibrosis was not taken into account due to its extreme rarity in Korea. Among the 1,092,475 adult asthmatics estimated from National Health Insurance claim data, 27,312 are likely to be affected by ABPA and 36,052 by SAFS. The burdens of ABPA and SAFS in our study were markedly lower than those in studies from developed countries. Our estimations for both conditions were almost entirely dependent on the estimated prevalence of asthmatic adults. Although the single payer in universal coverage used as the source provided reliable data, misdiagnosis and miscoding could undermine its accuracy [11]. Moreover, there are no data on fungal sensitization in Korea. Thus, further research in this area is needed to establish a more accurate estimation.

Other invasive mold infections

The incidence of mucormycosis among patients with AML has been reported to range from 1 to 8%, so the approximate rate of 4% was used for our estimation. It was also assumed that the incidence of mucormycosis after allogeneic HSCT and SOT was 0.4% [28] and 0.1% [29], respectively. As the reported incidence after SOT was very low, we assumed a combined incidence for all types of SOTs. Diabetes was not included in the calculation because no reliable report on the incidence in this population could be found. Overall, mucormycosis is estimated to affect 68 patients annually. Imported cases of endemic invasive fungal infections (e.g., histoplasmosis, blastomycosis, coccidioidomycosis) have been rarely reported in Korea and were excluded from consideration.

Candida infections

The Korean Nosocomial Infections Surveillance System (KONIS), a multicenter network of hospitals in Korea, reported that the pooled rate of bloodstream infection in ICUs was 1.47 cases/1000 patient-days, and 15.2% of them were caused

by *Candida* species [30]. Based on this information, we assumed the incidence of candidemia at 0.22 cases/1000 patient-days. As the Health Insurance Review and Assessment Service received insurance claims for 2,066,045 patient-days of ICU stay in 2013, it was estimated that the annual incidence of candidemia in the ICU is 455 cases. Based on a prospective study on candidemia in various Asian countries, we estimated that 23% of candidemia occurs in ICUs [31]. Local data on the incidence of *Candida* peritonitis could not be found, so we assumed that the incidence rate of *Candida* peritonitis was 50% of that of candidemia in ICUs, based on a large multicenter study in France [32]. The incidence of candidemia was estimated to be comparable to those in other countries.

There have been a few recent studies on the species distributions of candidemia in Korea. The largest among them was a multicenter study on 636 cases from 15 centers between 2007 and 2008 [33]. *Candida albicans* was the most common species (39.6%), followed by *C. tropicalis* (23.4%), *C. parapsilosis* (20.8%), and *C. glabrata* (11.3%). Another multicenter study (2008–2009) and more recent unpublished data from a nationwide collaborative group (2011) both demonstrated similar results [34].

Oral candidiasis (OC) was assumed to occur in 71% of HIV patients with low CD4+ T-cell count and high viral load and in 22% of patients with either higher CD4+ T-cell count or low viral load [35]. Among patients with previously diagnosed HIV, 1580 (18%) are estimated to not be receiving antiviral treatment (ART). If we assume that 50% of those have a CD4 count $<200 \times 10^6$/L, 790 of them are estimated to be at increased risk of OC. Additionally, the reported number of newly diagnosed HIV patients with CD4+ T-cell count <200 was 246. Cancer, especially that being treated with chemotherapy, is a well-known risk factor of OC. A meta-analysis revealed that the prevalence of OC among cancer patients was 7.5% before treatment, 39.1% during treatment, and 32.6% post-treatment [36]. The total incidence of cancer in 2012 was 224,177, and the 5-year cancer prevalence excluding newly diagnosed cases (the number of living cancer patients who had been diagnosed within 5 years) was 517,812. If we assume that all cancer patients underwent at least some kind of treatment during the first year and no further treatment in subsequent years, 256,460 patients with cancer are estimated to be affected by OC annually.

Esophageal candidiasis was reported to occur in 20% of ART-naive HIV patients and in 5% of those on ART [37]. The prevalence of esophageal candidiasis in immunocompetent hosts was reported to be 0.32% in a retrospective study of 88,125 esophagogastroduodenoscopies in Korea [38]. Overall, 398,154 patients are estimated to be affected by oral and esophageal candidiasis annually. The large burden of oral and esophageal candidiasis is a very interesting finding in our study. This was due to two differences in our approach to estimating their prevalence. First, we included patients with cancer in our estimation. As oral candidiasis is a common and disturbing condition in cancer patients, we believe that it is appropriate to evaluate the burden of candidiasis in this population. Second, our estimates on esophageal candidiasis were based on a retrospective survey of esophagogastroduodenoscopy in healthy individuals, in which a prevalence rate of 0.32% was reported [38]. The clinical and socioeconomic implications of this finding might be questionable, as only less than half of those with esophageal candidiasis were reported to be symptomatic.

The prevalence of recurrent vulvovaginal candidiasis was estimated at a "discounted" rate of 6% of women aged 15–50 years, as self-reported vulvovaginal candidiasis probably over-estimates rates [39].

Other mycoses

We estimated the incidence of fungal keratitis as 0.6 per 1,000,000 population, as in Denmark [40], due to the absence of local data. Tinea capitis was reported to account for 20.3% of patients with dermatophytoses visiting a pediatric dermatology clinic in Korea [41]. As the average annual number of dermatophytoses among those under 20 years old in 2006–2010 was 222,107 according to the national healthcare insurance claim data [42], we estimated the annual number of cases of tinea capitis as 45,087 a year.

Our study estimated that a total of 985,079 people in South Korea are affected by fungal infections each year, which is nearly 2.1% of the total population. When only invasive infections were counted, the incidence was estimated at 15,465 cases per year. The only recent study we could find on this subject was based on health insurance claim data from the National Health Insurance Service, a quasigovernmental agency overseeing universal healthcare coverage in Korea [43]. The average annual prevalence of opportunistic mycoses in 2006–2010 was 2.6% according to the study, which was comparable to our results. They identified approximately 1.2 million cases of candidiasis, 2000 cases of aspergillosis, 200–500 cases of cryptococcosis, and 500–900 cases of zygomycosis each year. Incidences from the study, however, were considerably larger than our estimates. The implications of their results are difficult to ascertain, as they did not provide detailed information on the specific types of infections. We believe that the differences were most likely caused by the inclusion of non-invasive infections and presumptive diagnoses in the claims study, perhaps to justify antifungal therapy, as their numbers far exceed those reported from other countries. Patients visiting multiple hospitals, which is not uncommon in Korea, might also have resulted in overestimation.

To our knowledge, this Korean study is the first study performed in East Asia to estimate the burden of serious fungal infections. While the incidence and prevalence of most conditions were comparable to those in other countries, the

burdens of CPA and oropharyngeal candidiasis were markedly higher in our study. More resources and efforts should be concentrated on achieving a better understanding of the burden of fungal infections, considering the significant consequences of invasive mycoses in both personal and social contexts.

Compliance with ethical standards

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Conflict of interest All authors report nothing to declare.

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