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국내 아스페르길루스증에 대한 항진균제 처방 현황

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Real-world Prescribing Patterns of Antifungal drugs in Patients with Aspergillosis

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ABSTRACT

Background: Globally, the number of patients with aspergillosis is increasing, and the mortality rate remains high. This study aimed to investigate prescribing patterns of antifungal drugs for patients with aspergillosis in South Korea using real-world data. **Methods:** This retrospective cross-sectional study was performed using National Patient Sample (NPS) data collected by the Health Insurance Review and Assessment Service (HIRA) during 2011-2020. The use of antifungal drugs in patients with aspergillosis was investigated. **Results:** A total of 1374 patients were identified: 333 patients with invasive pulmonary aspergillosis (IPA) (24.2%), 436 patients with other PA (31.7%), 73 patients with other forms of aspergillosis (5.3%), and 532 patients with unspecified aspergillosis (38.7%). The odds of receiving an antifungal prescription were higher for IPA than for other PA (aOR, 0.233; p<0.001), and higher for hematologic malignancies than for respiratory disorders other than cancer or infections (aOR, 10.018; p<0.001). During each hospitalization period, 56.1% (97/173) and 6.4% (11/173) of IPA hospitalizations received voriconazole and itraconazole monotherapy, respectively, whereas 44.3% (27/61) and 27.9% (17/61) of other PA hospitalizations received itraconazole and voriconazole monotherapy, respectively. Among outpatients with IPA, 67.5% (85/126) and 26.2% (33/126) received voriconazole and itraconazole alone, respectively, whereas among outpatients with other PA, 86.1% (68/79) and 12.7% (10/79) received itraconazole and voriconazole alone, respectively, during the year. **Conclusion:** In Korea, voriconazole monotherapy was preferred in IPA inpatients, and itraconazole monotherapy was preferred in other PA inpatients. In the ambulatory care settings for IPA and other PA, itraconazole monotherapy was preferred.

KEYWORDS: Antifungal agents, aspergillosis, comorbidity

Aspergillosis is a fungal infection caused by *Aspergillus* that is found worldwide. *Aspergillus* species are saprophytic filamentous fungi living in a wide variety of environments, including soil, decaying vegetation, and dust suspended in air.[1-3] Globally, approximately 250,000 cases of invasive aspergillosis (IA) and 3,000,000 cases of chronic pulmonary aspergillosis (CPA) occur annually,[4] with *Aspergillus fumigatus* being the most common cause of human *Aspergillus* infections.[3] *A. fumigatus* sporulates abundantly with conidial heads, each of which produces thousands of conidia that are released into the atmosphere. The diameter of the conidia is small enough (2 to 3 μm) to reach lung alveoli. In immunocompetent individuals,

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inhalation of conidia rarely causes aspergillosis because conidia are relatively efficiently eliminated by innate immune mechanisms.[1] However, inhalation of *Aspergillus* spores is the main route of IA in immunocompromised hosts, including patients with prolonged neutropenia, allogeneic hematopoietic stem cell transplant (HSCT), solid organ transplant (SOT), inherited or acquired immunodeficiency, and corticosteroid users.[1,5,6] Although IA occurs primarily in immunocompromised individuals, invasive pulmonary aspergillosis (IPA) has also been reported in non-immunocompromised patients, such as those with chronic obstructive pulmonary disease (COPD) and alcoholism, although its incidence is low.[7] The high mortality rate of IA remains an important issue. In SOT recipients, the overall 12-week mortality rate of IA has been reported to exceed 20%, and the mortality rates for HIV and COPD patients have been reported to be 38% and 55%, respectively.[6,8-10] To increase survival and response rate, the Infectious Diseases Society of America (IDSA) strongly recommends early initiation of antifungal therapy in patients with strongly suspected IPA. Furthermore, IDSA recommends continuing treatment of IPA for at least 6-12 weeks, depending on the patient's immune and disease status. For IPA, voriconazole is strongly recommended as a primary treatment. For the treatment of symptomatic or progressive chronic cavitary pulmonary aspergillosis (CCPA), the IDSA strongly recommends the use of itraconazole or voriconazole for at least 6 months.[5] Although the primary therapy for IA involves the appropriate use of antifungal agents, the clinical outcomes of antifungal therapy are far from satisfactory and IA still has a high mortality rate. Furthermore, despite efforts to reduce the incidence of IA by using prophylactic antifungal therapy in patients at risk of infection, the incidence of IA increases with the number of patients receiving SOT, allogeneic HSCT, and immunosuppressive drugs.[6,8-10] In the United States, the number of hospitalizations related to IA increased by an average of 3% per year between 2000 and 2013.[11] In South Korea, the number of patients with IA increased by 22%, and the cost reimbursed by the National Health Insurance Service (NHIS) doubled in 2018 compared to 2013.[12]

Given the high mortality rate and increasing number of patients, it is necessary to develop guidelines for the prophylaxis and treatment of aspergillosis in South Korea. Nonetheless, to the best of our knowledge, recent studies reporting antifungal therapy for aspergillosis in South Korea are limited. This study aimed to investigate real-world prescription of antifungal agents, comorbidities, and the factors affecting prescribing of antifungal drugs in patients with aspergillosis using nationwide data over a 10-year period.

Methods

Data source

We conducted a cross-sectional study using the National Patient Sample (NPS) database of the Health Insurance Review & Assessment Service (HIRA), which is a repository of claims data collected during healthcare reimbursement that covers almost 98% of South Korea's total population. The HIRA-NPS is annual sample data extracted using a sex- and age-stratified randomized sampling method from the HIRA claims data, which demonstrates a high level of representativeness with a 95% match rate between the estimated population and the actual population. The HIRA-NPS contains information on approximately 1.4 million patients per year during 2009-2018, whereas 1 million patients per year from 2019 onwards, accounting for 3% and 2% of the population in the HIRA data, respectively.[13,14] In this study, HIRA-NPS 2011-2020 were analyzed.

The NPS database consists of five tables: Table 20 (general characteristics of the patients and major/secondary diagnosis), Table 30 (healthcare services provided to patients), Table 40 (information on all diagnoses that the patients had received), Table 53 (outpatient prescriptions), and Table of Providers (information on healthcare service providers). All tables are linkable with a key ID, which is a "billing statement" identification code.[13] This study was approved by the Institutional Review Board of Inje University (IRB File Number: INJE 2022-04-012).

Study subjects

We identified patients with aspergillosis using the Korean Standard Classification of Diseases codes, which are the Korean versions of the International Classification of Disease 10th Revision (ICD-10). During the period of 2011-2020, the KCD codes of KCD-6 and KCD-7 for aspergillosis have been the same and are as follows: B44.0 (invasive pulmonary aspergillosis, IPA), B44.1 (other pulmonary aspergillosis, other PA, including allergic bronchopulmonary aspergillosis), B44.2 (tonsillar aspergillosis), B44.7 (disseminated aspergillosis, including generalized aspergillosis), B44.8 (other forms of aspergillosis), and B44.9 (unspecified aspergillosis). We decided to include

chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), and aspergilloma within chronic pulmonary aspergillosis (CPA).[5,9,15] Patients with an aspergillosis diagnosis in the main or sub-main diagnostic code fields were included in this study. The patients' main or sub-main diagnoses, other than aspergillosis, were analyzed as comorbidities. If different aspergillosis diagnoses were shown in the main and sub-main diagnostic code fields of the same "billing statement," the patients were classified according to the main diagnosis. Patients with tonsillar and disseminated aspergillosis were excluded from the statistical analysis of this study because the number of patients was too small.

Prescription of antifungal drugs

Patients who were prescribed antifungal drugs were identified using the 'major ingredient code' that provides information on active ingredient, preparation type (single or complex), administration route, and dosage form.[16] Patients with the same diagnosis of aspergillosis who received both inpatient and outpatient care during the year were analyzed by each care type. The duration of antifungal treatment during each hospitalization period was examined, and "duration" was defined as the number of days' supply of the antifungal drug that showed the longest days' supply among the prescribed antifungal drugs during each hospitalization period. For outpatients, the total number of days' supply of antifungal drugs per year was investigated. Furthermore, we examined factors affecting prescribing of antifungal drugs in patients with aspergillosis.

Statistical analysis

The characteristics of the patients with aspergillosis were presented using frequency analysis. The differences in categorical variables were determined using the χ^2 test, and Fisher's exact test was used when more than 20% of the cells had expected counts less than 5. Multiple logistic regression analysis was performed to investigate the factors affecting prescribing of antifungal drugs in patients with aspergillosis and examine the relationship between the specific type of aspergillosis and comorbidities. All statistical analyses were performed using R statistical software version 3.5.1. and SPSS version 25 (IBM Corporation, New York, USA), and significance level was set at $p<0.05$.

Results

Characteristics of aspergillosis patients

Of the approximately 13.2 million patients in HIRA-NPS 2011-2020, a total of 1374 patients (0.01%) diagnosed with IPA, other PA, other forms of aspergillosis, and unspecified aspergillosis were identified. The total number of patients with aspergillosis doubled from 2011 to 2020 (Fig. 1). Furthermore, we identified three patients with tonsillar aspergillosis and two patients with disseminated aspergillosis, who were excluded from the statistical analysis of this study. Table 1 shows the characteristics of the study subjects. Most patients were aged between 45 and 64 years. The proportion of men with IPA,

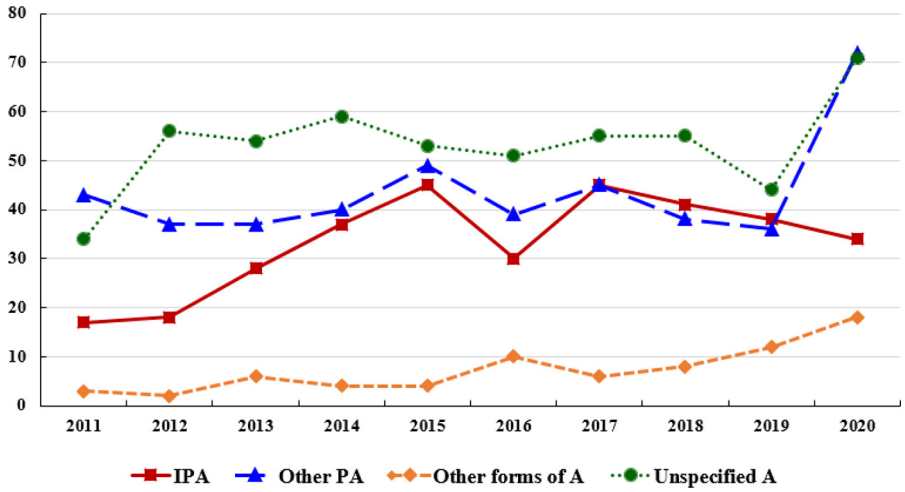


Fig. 1. The number of patients with invasive pulmonary aspergillosis (IPA), other pulmonary aspergillosis (other PA), other forms of aspergillosis, and unspecified aspergillosis in the HIRA-NPS 2011-2020.

Table 1. Characteristics of study subjects

	IPA	Other PA	Other forms of A	Unspecified A	*p* value
	N (%)	N (%)	N (%)	N (%)	
Total	333 (100)	436 (100)	73 (100)	532 (100)	
Age group					0.014
<20	21 (6.3)	8 (1.8)	2 (2.7)	14 (2.6)	
20-44	38 (11.4)	33 (7.6)	5 (6.8)	56 (10.5)	
45-64	158 (47.4)	235 (53.9)	39 (53.4)	253 (47.6)	
65-74	77 (23.1)	103 (23.6)	12 (16.4)	133 (25.0)	
≥75	39 (11.7)	57 (13.1)	15 (20.5)	76 (14.3)	
Sex					0.002
Male	208 (62.5)	285 (65.4)	34 (46.6)	300 (56.4)	
Female	125 (37.5)	151 (34.6)	39 (53.4)	232 (43.6)	
Insurance type					0.316
NHI	311 (93.4)	398 (91.3)	65 (89.0)	498 (93.6)	
MedAid	22 (6.6)	38 (8.7)	8 (11.0)	34 (6.4)	
Type of healthcare provider[a]	Nst=327	Nst=432	Nst=73	Nst=527	0.120
Tertiary care	249 (76.1)	286 (66.2)	50 (68.5)	358 (67.9)	
Secondary care	70 (21.4)	128 (29.6)	21 (28.8)	151 (28.7)	
Primary care	8 (2.4)	18 (4.2)	2 (2.7)	18 (3.4)	
Location of healthcare provider[a]	Nst=328	Nst=432	Nst=73	[c]Nst=527	<0.001
Capital	158 (48.2)	210 (48.6)	35 (47.9)	173 (32.8)	
Metropolitan	84 (25.6)	98 (22.7)	16 (21.9)	123 (23.3)	
Others[b]	86 (26.2)	124 (28.7)	22 (30.1)	231 (43.8)	
Antifungal treatment					
≥1	209 (62.8)	121 (27.8)	22 (30.1)	104 (19.5)	<0.001
0	124 (37.2)	315 (72.2)	51 (69.9)	428 (80.5)	
Comorbidities[a]	[c]Nst=349	[c]Nst=460	[c]Nst=74	[c]Nst=554	<0.001
Respiratory disorders other than cancer and infections[d]	51 (14.6)	185 (40.2)	15 (20.3)	190 (34.3)	
Respiratory infections	57 (16.3)	74 (16.1)	29 (39.2)	132 (23.8)	
Hematologic malignancies	122 (35.0)	16 (3.5)	10 (13.5)	34 (6.1)	
Solid tumors[e]	29 (8.3)	21 (4.6)	0 (0.0)	21 (3.8)	
TB/post-TB	4 (1.1)	20 (4.3)	1 (1.4)	28 (5.1)	
Transplantation recipients[f]	6 (1.7)	1 (0.2)	0 (0.0)	4 (0.7)	

A, aspergillosis; COPD, chronic obstructive pulmonary disease; IPA, invasive pulmonary aspergillosis; MedAid, Medical Aid; NHI, National Health Insurance; Nst, subtotal number; PA, pulmonary aspergillosis; TB, tuberculosis. Capital is Seoul, and metropolitan represents Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan.

[a]The percentage was calculated by taking the subtotal number of the patients in each aspergillosis as 100.

[b]Others include Gangwon-do, Gyeonggi-do, Chuncheong-do, Gyeongsan-do, Jeolla-do, and Jeju-do.

[c]Nst was calculated by analyzing all comorbidities if a patient had 2 or more comorbidities.

[d]Respiratory disorders other than cancer and infections include chronic obstructive pulmonary disease (COPD) and asthma.

[e]Solid tumors include breast, liver, stomach, thyroid, and rectal and pulmonary cancer.

[f]Transplantation includes hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT).

Table 2. The relationship between the specific type of aspergillosis and comorbidities

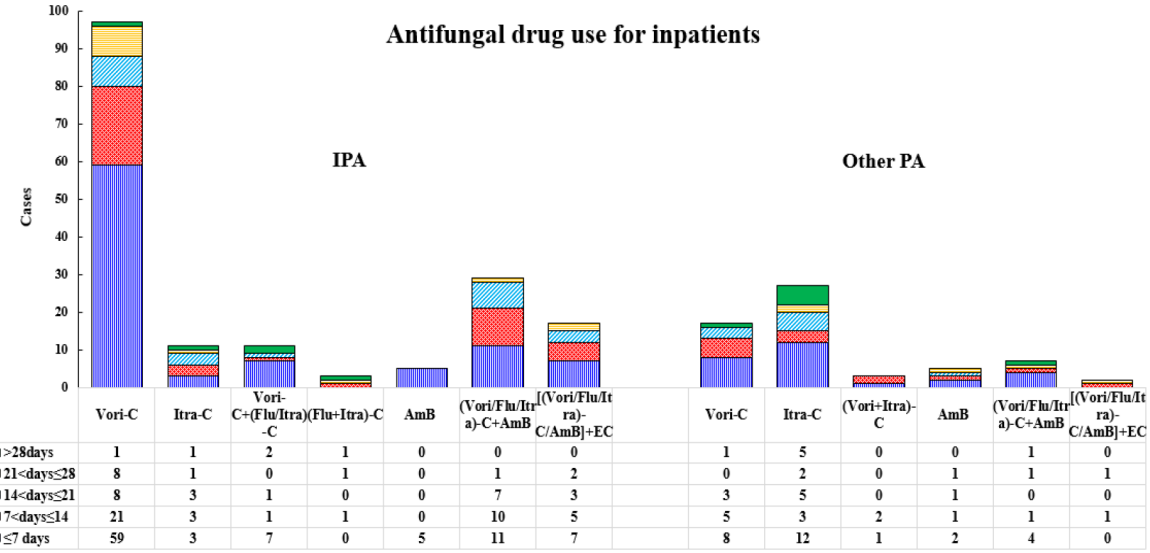
Comorbidities	IPA			Other PA			Other forms of A			Unspecified A		
	aOR	*p* value	95% CI	aOR	*p* value	95% CI	aOR	*p* value	95% CI	aOR	*p* value	95% CI
Respiratory disorders other than cancer and infections	R			R			R			R		
Respiratory infections	1.740	0.005	1.179-2.566	0.484	<0.001	0.359-0.652	3.097	<0.001	1.671-5.740	1.140	0.357	0.863-1.506
Hematologic malignancies	15.086	<0.001	10.155-22.410	0.127	<0.001	0.077-0.210	1.615	0.231	0.737-3.542	0.340	<0.001	0.232-0.498
Solid tumors	6.048	<0.001	3.568-10.252	0.489	0.008	0.287-0.832	-	0.997	-	0.557	0.029	0.329-0.943
TB/post-TB	0.600	0.342	0.209-1.722	0.745	0.318	0.418-1.327	0.552	0.568	0.072-4.245	1.672	0.072	0.955-2.927
Transplantation recipients	10.709	<0.001	3.289-34.863	0.119	0.042	0.015-0.925	-	0.999	-	0.697	0.559	0.207-2.344

aOR, adjusted odds ratio; A, aspergillosis; IPA, invasive pulmonary aspergillosis; PA, pulmonary aspergillosis; TB/post-TB, tuberculosis/post-tuberculosis

Table 3. Factors affecting prescribing of antifungal drugs in patients with aspergillosis

Explanatory variable		Prescribing antifungal drugs		
		aOR	P value	95% CI
Diagnosis				
	Invasive pulmonary aspergillosis (R)			
	Other pulmonary aspergillosis	0.233	<0.001	0.176-0.308
	Other forms of aspergillosis	0.215	<0.001	0.126-0.366
	Unspecified aspergillosis	0.146	<0.001	0.110-0.194
Type of patient care				
	Inpatients (R)			
	Outpatients	0.494	<0.001	0.398-0.614
Comorbidity				
	Respiratory disorders other than cancer and infections (R)			
	Respiratory infections	1.073	0.664	0.782-1.471
	Hematologic malignancies	10.018	<0.001	6.877-14.592
	Solid tumors	4.911	<0.001	2.971-8.115
	Tuberculosis/post-tuberculosis	1.070	0.835	0.564-2.031
	Transplantation recipients	3.134	0.052	0.992-9.902

aOR, adjusted odds ratio; COPD, chronic obstructive pulmonary disease



	Vori-C	Itra-C	Vori-C+(Flu/Itra)-C	(Flu+Itra)-C	AmB	(Vori/Flu/Itra)-C+AmB	[(Vori/Flu/Itra)-C/AmB]+EC	Vori-C	Itra-C	(Vori+Itra)-C	AmB	(Vori/Flu/Itra)-C+AmB	[(Vori/Flu/Itra)-C/AmB]+EC
>28days	1	1	2	1	0	0	0	1	5	0	0	1	0
21<days≤28	8	1	0	1	0	1	2	0	2	0	1	1	1
14<days≤21	8	3	1	0	0	7	3	3	5	0	1	0	0
7<days≤14	21	3	1	1	0	10	5	5	3	2	1	1	1
≤7 days	59	3	7	0	5	11	7	8	12	1	2	4	0

Fig. 2. Antifungal drug use for inpatients stratified by the duration of antifungal drug use during each hospitalization period. A, aspergillosis; IPA, invasive pulmonary aspergillosis; PA, pulmonary aspergillosis; Vori-C, voriconazole; Itra-C, itraconazole; Flu-C, fluconazole; AmB, amphotericin B; EC, echinocandin

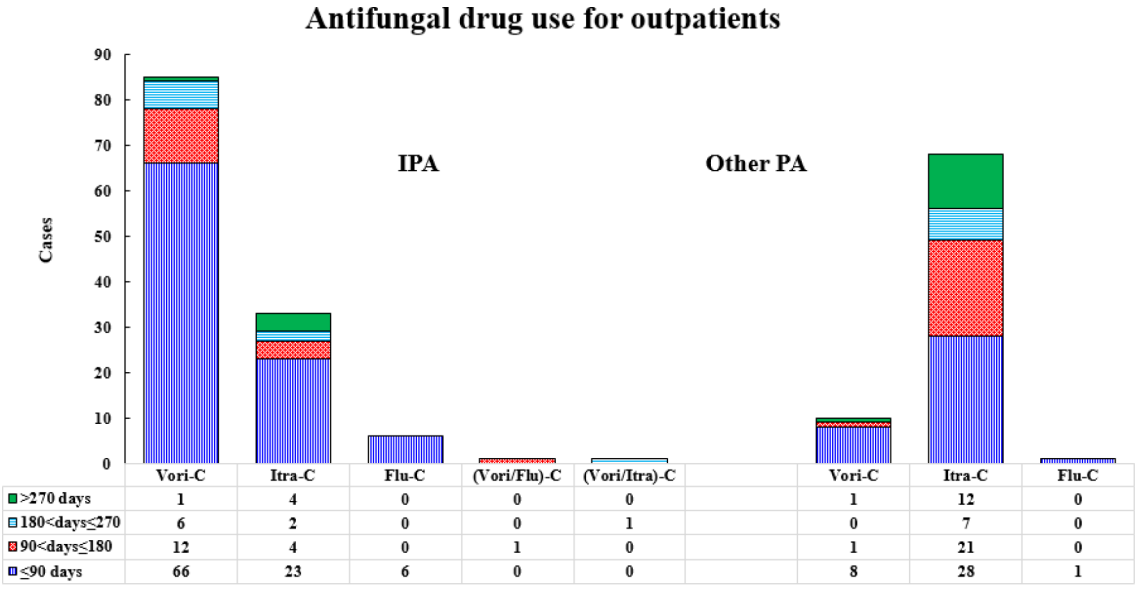
other PA, and unspecified aspergillosis was higher than that of men with "other forms of aspergillosis." Most cases of aspergillosis were treated by healthcare providers in tertiary care settings. The proportion of patients treated in provinces other than the capital and metropolitan areas was higher for unspecified aspergillosis than for IPA, other PA, or "other forms of aspergillosis." The proportion of patients that received at least one antifungal prescription was highest for IPA (62.8%) compared with other PA (27.8%), "other forms of aspergillosis" (30.1%), and unspecified aspergillosis (19.5%). The most common comorbidity in patients with IPA was hematologic malignancies, including lymphoid and myeloid leukemia and Hodgkin lymphoma, whereas "respiratory disorders other than cancer and infections," including chronic obstructive pulmonary disease (COPD) and asthma were the most common in patients with other PA. COPD was found in 7 and 45 patients with IPA and other PA, respectively. Among solid tumors, pulmonary cancer was found in 15, 7, and 9 patients with IPA, other PA, and unspecified A, respectively. Table 2 shows the relationship between specific type of aspergillosis and comorbidities. Patients with hematologic malignancies, transplantation, solid tumors, and respiratory infections showed a higher risk of IPA than patients with respiratory disorders other than cancer and infections (adjusted odds ratio [aOR], 15.086, 10.709, 6.048, and 1.740, respectively; p<0.005). Patients with respiratory disorders other than cancer and infections had a higher risk of other PA than the patients with solid tumors, respiratory infections, hematologic malignancies, and transplantation recipients (aOR, 0.489, 0.484, 0.127, and 0.119, respectively; p<0.005).

Prescribing antifungal drugs in patients with aspergillosis

Among the diagnoses of aspergillosis, IPA was the most likely to receive antifungal prescription (aOR: 0.233, 0.215, and 0.146 for other PA, "other forms of aspergillosis," and unspecified aspergillosis, respectively, p<0.001). Outpatients had a lower probability of receiving antifungal prescription than inpatients (aOR, 0.494; p<0.001). Patients with hematologic malignancies and solid tumors were more likely to be treated with antifungal drugs than the patients with respiratory disorders other than cancer and infections (aOR: 10.018 for hematologic malignancies and 4.911 for solid tumors, p<0.001) (Table 3).

Antifungal drug use for patients with aspergillosis

In 161 inpatients with IPA, 173 hospitalizations treated with antifungal drugs were identified, of which 53.2% (92/173) received antifungal treatment for up to 7 days during each hospitalization period. Of the 173 hospitalizations, 56.1% (97/173) received voriconazole monotherapy, and 6.4% (11/173) received itraconazole monotherapy. Overall 38 hospitalizations (22.0%) received liposomal amphotericin B (L-AmB) monotherapy



	Vori-C	Itra-C	Flu-C	(Vori/Flu)-C	(Vori/Itra)-C	Vori-C	Itra-C	Flu-C
>270 days	1	4	0	0	0	1	12	0
180<days≤270	6	2	0	0	1	0	7	0
90<days≤180	12	4	0	1	0	1	21	0
≤90 days	66	23	6	0	0	8	28	1

Fig. 3. Antifungal drug use for outpatients stratified by the total number of days' supply per year per outpatient. A, aspergillosis; IPA, invasive pulmonary aspergillosis; PA, pulmonary aspergillosis; Vori-C, voriconazole; Itra-C, itraconazole; Flu-C, fluconazole

or combination therapy with voriconaozle, fluconazole, itraconazole, or caspofungin during each hospitalization period. L-AmB was used in 20% (1/5) and 69.7% (23/33) of the amphotericin B (AmB) monotherapy and combination therapy groups, respectively. Of the 17 hospitalizations treated with echinocandins, 15 received caspofungin and 2 received micafungin. In 149 inpatients with other PA, 61 hospitalizations treated with antifungal drugs were identified, of which 44.3% (27/61) received antifungal treatment for up to 7 days during each hospitalization period. Of the 61 hospitalizations, 44.3% (27/61) and 27.9% (17/61) received itraconazole and voriconazole monotherapy, respectively (Fig. 2). In 41 inpatients with "other forms of aspergillosis," 10 hospitalizations treated with antifungal drugs were identified. In 167 inpatients with unspecified aspergillosis, 70 hospitalizations treated with antifungal drugs were identified, of which 37.1% (26/70) and 21.4% (15/70) received voriconazole and itraconazole monotherapy, respectively. Caspofungin and micafungin were used in 6 and 2 hospitalizations, respectively.

Of the 241 outpatients with IPA, 52.3% (126/241) received at least one antifungal prescription during the year, of which 75.4% (95/126) were prescribed antifungal drugs for up to 90 days per year. Of 126 patients, 67.5% (85/126) and 26.2% (33/126) received voriconazole and itraconazole alone, respectively. Of the 363 outpatients with other PA, 21.8% (79/363) received at least one antifungal prescription, of whom 46.8% (37/79) were prescribed antifungal drugs for up to 90 days per year. Of 79 patients, 86.1% (68/79) and 12.7% (10/79) received itraconazole and voriconazole alone, respectively, during the year (Fig. 3). Of the 37 outpatients with "other forms of aspergillosis," 11 (29.7%) received at least one antifungal prescription. Of the 439 outpatients with unspecified aspergillosis, 16.9% (74/363) received antifungal drugs, of whom 71.6% (53/74) were prescribed the drugs for up to 90 days per year. Of 74 patients, 35 each received voriconazole and itraconazole monotherapy.

Discussion

In this study, 1374 patients with aspergillosis were included, of whom 24.2 and 31.7% were patients with IPA and other PA, respectively. This proportion is similar to that found in a previous study conducted in Poland, where IPA and other PA were 29.0 and 31.9%, respectively.[17] In this study, male patients were dominant in all forms of aspergillosis, except for "other forms of aspergillosis." This finding was in line with the results of previous studies conducted with inpatients in Poland and France, where the male proportion was 64.7% for all forms of aspergillosis and 63.5% for CPA, respectively.[17,18] There was no difference in insurance type as a socioeconomic factor among the aspergillosis diagnoses. However, the proportion of patients covered by MedAid was slightly higher for

apergillosis patients (6.4-11.0%) than for the total population. In South Korea, approximately 3% of the total population is covered by the MedAid plan, a form of medical insurance providing affordable medical care to low-income families.[14] Most patients were treated at tertiary and secondary hospitals in the capital and metropolitan areas. This finding may be partly explained by the limited availability of medical facilities for diagnosing aspergillosis in primary care settings. Furthermore, in South Korea, approximately 73% of tertiary and secondary hospitals are in Seoul and 6 metropolitan areas.[19] Here, patients with hematologic malignancies and transplantation recipients were at high risk for IPA. A high incidence of IA in these patients (23-24%) has been reported previously.[20] Furthermore, patients with respiratory disorders other than cancer and infections, such as COPD and asthma, were at highest risk for other PA. This result is supported by a previous study conducted in France, where 44% of patients hospitalized for CPA had COPD as a comorbidity.[18] This study found that among aspergillosis diagnoses, the proportion of patients who received at least one antifungal prescription was the highest for IPA. This result is consistent with recent guidelines recommending early initiation of antifungal therapy in patients with strongly suspected IPA. Furthermore, guidelines recommend that for patients with CPA, antifungal therapy can be determined according to the type of disease, clinical phenotype, and eligibility for surgical treatment; patients with CCPA without pulmonary symptoms and dysfunction can be observed without antifungal therapy and followed up every 3-6 months.[5,15] Here, among the IPA hospitalizations treated with antifungal drugs, voriconazole monotherapy was the most frequent, which is in accordance with recent guidelines that recommend voriconazole as the gold standard for the treatment of IA. Clinical studies have demonstrated that in IA patients, initial therapy with voriconazole achieved a higher survival rate and better response at week 12 than initial therapy with AmB deoxycholate.[21,22] In another study conducted on patients with pulmonary and tracheobronchial IA, 60% showed good responses following voriconazole treatment.[23] However, itraconazole therapy has shown only mild efficacy in IA.[24] For CPA, itraconazole and voriconazole are preferred according to recent guidelines.[5,15] In accordance with the guidelines, in this study, 44.3 and 27.9% of hospitalizations for other PA were treated with itraconazole and voriconazole monotherapy, respectively. Moreover, 86.1% of outpatients with other PA were prescribed itraconazole alone. However, among outpatients with other PA, 46.8% were prescribed for up to 90 days and only 25.3% were prescribed for more than 180 days per year. Considering that the duration of antifungal treatment in 44.3 and 65.6% of the inpatients was up to 7 and 14 days, respectively, it was difficult to evaluate whether the duration of antifungal drug use in other PA patients met the guidelines. Recent guidelines recommend at least six months of antifungal therapy for patients with symptomatic or progressive CPA.[5,15] The lower cost of itraconazole compared to voriconazole might make itraconazole a valid option for chronic aspergillosis.[25]

This study had some limitations. Because we used the newly collected HIRA-NPS each year, it was not possible to follow individual patients for more than one year. Furthermore, it was impossible to accurately determine the number of days of continuous administration of antifungal drugs in outpatients and whether individual patients were cured or diagnosed with other aspergillosis. Moreover, in the diagnosis of aspergillosis, the detailed diagnosis of other PA and “other forms of aspergillosis” was unknown. The HIRA-NPS is sample data extracted from the HIRA claims data; it is possible that not all actual patients with aspergillosis were analyzed. The duration of antifungal treatment during each hospitalization period reported here may be shorter than the actual duration of antifungal treatment in some hospitalizations. For some “billing statements” containing more than one antifungal drugs on the same “billing statement,” the order of administration of the drugs and whether the drugs were co-administered were unknown. Finally, antifungal treatment was not subdivided according to the dose of antifungal drugs. Despite these limitations, to the best of our knowledge, this is the first study to investigate prescribing of antifungal drugs in patients with aspergillosis in South Korea over a 10-year period.

Conclusion

In South Korea, voriconazole monotherapy was preferred in IPA inpatients, and itraconazole monotherapy was preferred in other PA inpatients. In the ambulatory care settings for IPA and other PA, itraconazole monotherapy was preferred.

Acknowledgments

This study was performed using HIRA-NPS 2011-2020 (S20220518007), but the results of this study have no concern

with the Ministry of Health and Welfare and HIRA.

Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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