Antimicrobial Susceptibility Trends of *Streptococcus pneumoniae* by Age Groups Over Recent 10 Years in a Single Hospital in South Korea

Hyunjoo Oh[1], Sang Taek Heo[1,2], Misun Kim[1], Young Ree Kim[3], and Jeong Rae Yoo[1,2]

[1]Department of Internal Medicine, Jeju National University Hospital, Jeju;
Departments of [2]Internal Medicine and [3]Laboratory Medicine, Jeju National University School of Medicine, Jeju, Korea.

Purpose: Streptococcus pneumoniae (S. pneumoniae) causes respiratory tract infections. Its non-vaccine serotypes and multidrug-resistant pneumococcal diseases have increased during the post-pneumococcal vaccination era. Therefore, it is important to understand the regional and age-related antimicrobial susceptibility of *S. pneumoniae* to select appropriate empirical antimicrobials.

Materials and Methods: We retrospectively studied trends in the antimicrobial resistance of *S. pneumoniae* to commonly prescribed antibiotics in patient groups of various ages at a single teaching hospital in Jeju Island from 2009 to 2018.

Results: In total, 1460 *S. pneumoniae* isolates were obtained during the study period. The overall antimicrobial resistance rates of *S. pneumoniae* to penicillin, erythromycin, ceftriaxone, levofloxacin, and vancomycin were 16.2%, 84.7%, 25.9%, 3.3%, and 0.0%, respectively, and the MDR rate was 6.7%. Erythromycin and ceftriaxone resistance rates increased by years; however, they were significantly reduced in adult groups. Levofloxacin resistance and MDR rates were also higher in adult groups. Overall, the MDR rate significantly increased during the recent 10 years, as well as in patients with a history of hospitalization within 90 days [odds ratio (OR)=3.58, 95% confidence interval (CI)=1.91−6.71] and sinusitis (OR=4.98, 95% CI=2.07−11.96).

Conclusion: Erythromycin and ceftriaxone resistance rates and the MDR rate of *S. pneumoniae* significantly increased during the recent 10 years; the trends in individual antimicrobial resistance rates significantly differed between the age groups. This study indicates the need for caution when using ceftriaxone as an empirical antimicrobial against pneumococcal infections.

Key Words: Streptococcus pneumoniae, antimicrobial resistance, susceptibility, multidrug resistance, antibiotics, pneumonia

INTRODUCTION

Streptococcus pneumoniae (S. pneumoniae) is one of the most frequently identified pathogens in community-acquired pneumonia, acute bacterial otitis media and sinusitis, and bacterial meningitis.[1,2] The invasive infectious disease caused by *S. pneu-moniae* occurs more commonly in children under 2 years of age due to the high burden of *S. pneumoniae* colonization in their nasopharynx, coupled with their immature immune system against the bacterial capsular polysaccharide antigen.[3] However, people aged over 65 years have also shown a high incidence rate of *S. pneumoniae* infection.

Antimicrobial drug resistance of *S. pneumoniae* has been a concern worldwide for decades, while pneumococcal diseases continue to be a leading public health concern despite an increment in the administration of the pneumococcal vaccine.[4-6]

In South Korea, the 7-valent pneumococcal conjugate vaccine (PCV) 7 was introduced in 2003, and PCV 10 and PCV 13 were introduced in 2010.[1] Although these vaccinations were included in the National Immunization Program of South Korea in 2014, pneumonia still remains the third most common cause of mortality.[7,8] After the introduction of PCV 13, the inci-

dence of *S. pneumoniae* infection caused by PCV 13 serotype decreased. In contrast, the proportion of infections caused by non-PCV 13 serotypes and invasive pneumococcal disease (IPD) caused by non-vaccine type multidrug-resistant *S. pneumoniae* increased.[8-10]

Alterations in serotype distribution and antimicrobial resistance patterns of *S. pneumoniae* vary according to geographic and temporal trends.[4,5,11-14] Moreover, in populations consisting of heterogeneous characteristics, it is challenging to accurately analyze the antimicrobial resistance and recommend adequate empirical antimicrobials. In addition, β-lactam continues to be recommended for use as an empirical antibiotic drug in children and adults in South Korea.[15,16] Therefore, knowledge of antimicrobial susceptibility patterns specified by region, time, and age group will provide adequate empirical antimicrobial recommendations. This study analyzed the changes in antimicrobials susceptibility trends and the proportion of multidrug-resistance (MDR) of *S. pneumoniae* isolates according to age groups in a homogenous population of an isolated island in South Korea over the recent 10 years.

MATERIALS AND METHODS

Study design

This is a retrospective study on antimicrobial resistance of *S. pneumoniae* isolates obtained from patients in a single teaching hospital from January 2009 to December 2018. The hospital is located in Jeju Island, South Korea [largest island off the coast of the Korean Peninsula (33°0' N, 126°0' E) with a population of 690000], serving approximately 90% of the island's inhabitants. All data, including demographic information, antimicrobial susceptibility and resistance, diagnosis, duration of hospitalization, and death, were retrieved retrospectively from electronic medical records. The study protocol was approved by the Institutional Review Board of Jeju National University Hospital (JNUH 13-10-010). The requirement for informed consent was waived due to the retrospective design.

A total of 1460 *S. pneumoniae* isolates were identified from 1454 patients. The isolates were obtained from the upper airway (including paranasal sinuses, nasal cavity, nasopharynx, and oropharynx), lower airway [including sputum, transtracheal aspiration, and bronchoalveolar lavage (BAL)], blood, cerebrospinal fluid (CSF), abscesses, tissues, and other sources. Multiple isolates were obtained from some patients. Isolates showing the same antimicrobial resistant patterns were excluded from the analysis. For analysis of age-associated trends in antimicrobial resistance, the age groups were categorized as follows: 0 to 18 years, 19 to 64 years, and 65 years or older.

Definition

In this study, MDR was defined as the non-susceptibility of bacteria to three or more antimicrobial drug classes.[4,17] Interme-

diate resistant isolates were considered as resistant isolates. Community onset was defined as the diagnosis of *S. pneumoniae* infection acquired outside of the hospital or in patients who did not meet the definition of healthcare-associated onset, and healthcare-associated onset was defined as a diagnosis of *S. pneumoniae* infection acquired in the following conditions: more than 48 hours after hospitalization, including any patient hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antimicrobial therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.[18] IPD was defined as isolation of *S. pneumoniae* from a normally sterile site such as blood, CSF, joint fluid, pericardial fluid, or peritoneal fluid.

Antimicrobial susceptibility and resistance

Standard microbiological techniques were used for identifying *S. pneumoniae* in the isolates, including colony appearance, hemolysis, gram staining, bile solubility, susceptibility to optochin (1 μg) discs, and the automated VITEK II system (BioMérieux, Durham, NC, USA). *S. pneumoniae* (ATCC 49619) was used for quality control. According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, separate interpretive breakpoints were used to define the resistance of isolates to each antimicrobial agent.[19] We screened several antimicrobials that had been tested for susceptibility to *S. pneumoniae*, including penicillin, amoxicillin, ceftriaxone, cefotaxime, erythromycin, levofloxacin, moxifloxacin, trimethoprim/sulfamethoxazole, and vancomycin. The following five antimicrobial agents, which had been documented for susceptibility test for 10 years, were selected for the analysis: penicillin, erythromycin, ceftriaxone, levofloxacin, and vancomycin. Penicillin susceptibility was analyzed using two different breakpoints: the oral penicillin breakpoint (0.06 μg/mL) and the non-meningitis parenteral breakpoint (2.0 μg/mL). The non-meningitis parenteral breakpoint was used in this study unless otherwise specified. The non-meningitis breakpoint for ceftriaxone (1.0 μg/mL) was used. The MIC breakpoints used for erythromycin, levofloxacin, and vancomycin were ≤0.25 μg/mL, ≤2 μg/mL, ≤1 μg/mL, respectively. Since the susceptibility test to penicillin was not performed from May 2011 to April 2013, and the new CLSI penicillin susceptibility breakpoints for *S. pneumoniae* were adopted from 2013 in our hospital, analysis was performed using the data from 2013 to 2018.

Statistical analysis

The frequency of individual antimicrobial resistance rates and MDR rates of *S. pneumoniae* was reported as the proportion of resistant isolates out of the total identified *S. pneumoniae* isolates. The data are presented as either number (%) or mean± standard deviation. The chi-square test was used to evaluate the association between categorical variables. The multivari-

able logistic regression model was used to examine trends of MDR of *S. pneumoniae* according to variables such as age groups, diagnosis, and location of onset. The results are described as odds ratios (ORs) and 95% confidence intervals (CIs). *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of patients with *Streptococcus pneumoniae*

A total of 1460 *S. pneumoniae* strains were included (Table 1), and the mean age was 34.4 years (range, 0–102). The number of isolates in the age group 0 to 18 years, 19 to 64 years, and 65 years or older were 774 (53%), 213 (14.6%), and 473 (32.4%), respectively.

The most common specimen was the sputum, including TTA and BAL (83.1%), followed by upper airway swabs (10.3%). Pneumonia was the most common diagnosis in all age groups (81.3%). There were significant differences in the source of the specimen (*p*=0.017), diagnosis (*p*<0.001), location of onset (*p*<0.001), and hospital stays (*p*<0.001) among the three groups. However, the 30-day mortality was not significantly different between the three age groups (*p*=0.091).

Antimicrobial resistance patterns of *Streptococcus pneumoniae* according to the age groups

According to the CLSI (2017) breakpoint of non-meningitis parenteral breakpoint, penicillin resistance was 16.2%. The proportion of resistance to erythromycin, ceftriaxone, levofloxacin, and vancomycin was 84.7%, 25.9%, 3.3%, and 0.0%, respectively. The proportion of *S. pneumoniae* isolates that were classified as MDR during the study period was 6.7% (98/1460) (Fig. 1). The results of overall individual antimicrobial re-

Table 1. Characteristics of Patients with *Streptococcus pneumoniae* by Age Groups (2009–2018)

Variables	All ages (n=1460)	0–18 years (n=774)	19–64 years (n=213)	≥65 years (n=473)	*p* value
Age	34.4±33.7	4.3±2.7	50.9±11.4	76.4±7.2	<0.001
Source of specimen					0.017
Sputum/TTA/BAL	1213 (83.1)	604 (78.0)	167 (78.4)	442 (93.4)	
Upper airway swabs*	150 (10.3)	128 (16.5)	13 (6.1)	9 (1.9)	
Ear discharge	30 (2.1)	15 (1.9)	9 (4.2)	6 (1.3)	
Blood	26 (1.8)	6 (0.8)	14 (6.6)	6 (1.3)	
Adenoid tissue	16 (1.1)	15 (1.9)	0 (0.0)	1 (0.2)	
Wound/abscess	16 (1.1)	4 (0.5)	6 (2.8)	6 (1.3)	
CSF	2 (0.1)	1 (0.1)	1 (0.5)	0 (0.0)	
Others†	7 (0.5)	1 (0.1)	3 (1.4)	3 (0.6)	
Diagnosis					<0.001
Pneumonia	1187 (81.3)	615 (79.5)	160 (75.1)	412 (87.1)	
Pharyngitis/tonsilitis	69 (4.7)	62 (8.0)	2 (0.9)	5 (1.1)	
Otitis	47 (3.2)	40 (5.2)	4 (1.9)	3 (0.6)	
Sinusitis	42 (2.9)	18 (2.3)	15 (7.0)	9 (1.9)	
Meningitis	8 (0.5)	5 (0.6)	3 (1.4)	0 (0.0)	
Deep-seated infection‡	8 (0.5)	1 (0.1)	6 (2.6)	1 (0.2)	
Primary bacteremia	7 (0.5)	3 (0.4)	4 (1.9)	0 (0.0)	
Others§	92 (6.3)	30 (3.9)	19 (8.9)	43 (9.1)	
IPD	33 (2.3)	7 (0.9)	19 (8.9)	7 (1.5)	0.184
Community-onset	1182 (81.0)	672 (86.8)	169 (79.3)	341 (72.1)	<0.001
Patient status					
Hospitalization	1314 (90.0)	724 (93.5)	163 (76.5)	427 (90.3)	0.012
ICU	140 (10.7)	15 (2.1)	38 (23.3)	87 (20.4)	<0.001
Hospital days	14.31±29.54	7.13±11.72	27.38±45.90	21.56±38.16	<0.001
30-days mortality	40 (2.7)	15 (1.9)	8 (3.8)	17 (3.6)	0.091

SD, standard deviation; TTA, transtracheal aspiration; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; IPD invasive pneumococcal disease; ICU, intensive care unit.
Values are presented as mean±SD or number (%) or number/total number (%).
*These specimens included nasal cavity, nasopharyngeal, and oropharyngeal swabs, †These specimens included joint fluid, pleural fluid, ascites, bile, and urine, ‡This diagnosis included empyema, intraabdominal abscess, spontaneous bacterial peritonitis, and septic arthritis, §This diagnosis included cellulitis, conjunctivitis, and colonization of *S. pneumoniae*.

sistance rates and MDR rates in the three age groups are shown in Table 2 and Fig. 2. There were no significant differences in the comparison of penicillin resistance rates of the three age groups (p=0.376). However, the resistance rates to erythromycin (p<0.001) and ceftriaxone (p=0.002) in the 0 to 18 years age group were significantly higher than those in the 19 to 64 years and 65 year or older age groups. However, the resistance rates of levofloxacin was significantly higher in the age groups of 19 to 64 years and 65 years or older compared to the age group of 0 to 18 years (p<0.001). The MDR rates of *S. pneumoniae* was also significantly higher in the other age groups than in the 0 to 18 years age group (Table 3 and Fig. 3).

Changes in antimicrobial resistance trend of *Streptococcus pneumoniae*

The proportion of penicillin-resistant *S. pneumoniae* isolates
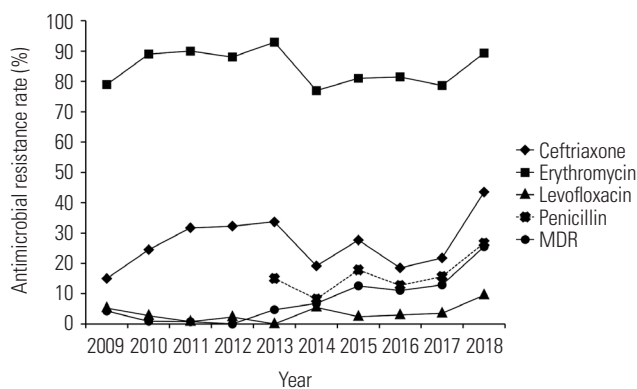

Fig. 1. Trend in antibiotics resistance to *Streptococcus pneumoniae* during 2009–2018. Since the susceptibility test to penicillin was not performed from May 2011 to April 2013 and the new CLSI penicillin susceptibility breakpoints for *S. pneumoniae* was adopted from 2013 at our hospital, the analysis was performed using the data from 2013 to 2018. MDR, multidrug-resistance.

was 15% in 2013 and 26.7% in 2018, but there was no significant increment between the years (p=0.145). However, the erythromycin resistance rates increased significantly through the study period, from 79.0% in 2009 to 89.4% in 2018 (p=0.030), and the ceftriaxone resistance rates also significantly increased from 15.0% in 2009 to 43.6% in 2018 (p<0.001). The levofloxacin resistance rates showed a trend of increment in 2018 (9.6%) compared with that in 2009 (5.3%) (p=0.166). The MDR rates of *S. pneumoniae* increased significantly from 0.9% in 2009 to 25.5% in 2018 (p<0.001). The trends in the individual antimicrobial resistance rates and MDR rate of *S. pneumoniae* during 2009–2018 by age groups are shown in the Fig. 3.
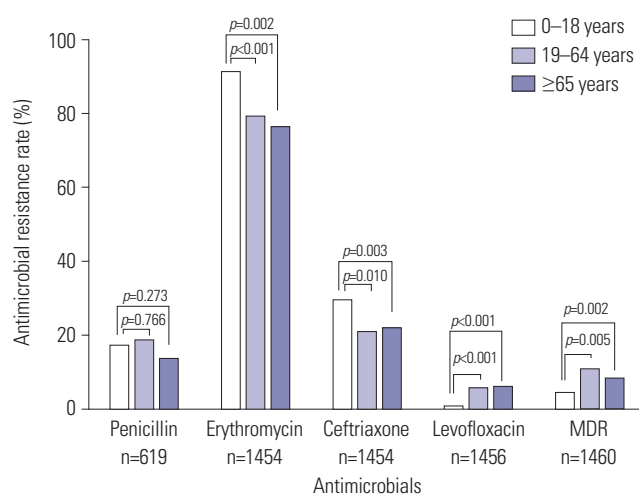

Fig. 2. Comparison of overall antibiotic resistance rates among the three age groups during 2009–2018. Chi-square test was used to compare the antibiotics resistance rates among the three age groups. Since the susceptibility test to penicillin was not performed from May 2011 to April 2013 and the new CLSI penicillin susceptibility breakpoints for *S. pneumoniae* was adopted from 2013 at our hospital, the analysis was performed using the data from 2013 to 2018. MDR, multidrug-resistance.

Table 2. Distribution and OR of Antimicrobial Resistance Rate of *Streptococcus pneumoniae* according to Age Groups (2009–2018)

Antimicrobials*	Age (years)	Resistance rate (%)	OR (95% CI)	p value
Penicillin[†] (n=619)	0–18	39/224 (17.4)	reference	
	19–64	25/134 (18.7)	1.09 (0.63–1.90)	0.766
	≥65	36/261 (13.8)	0.76 (0.46–1.24)	0.273
Erythromycin (n=1454)	0–18	702/770 (91.2)	reference	
	19–64	169/213 (79.3)	0.37 (0.25–0.56)	<0.001
	≥65	360/471 (76.4)	0.34 (0.23–0.44)	<0.001
Ceftriaxone (n=1454)	0–18	230/773 (29.8)	reference	
	19–64	44/212 (20.8)	0.62 (0.43–0.89)	0.010
	≥65	103/469 (22.0)	0.66 (0.51–0.87)	0.003
Levofloxacin (n=1456)	0–18	7/772 (0.9)	reference	
	19–64	12/213 (5.6)	6.53 (2.54–16.79)	<0.001
	≥65	29/471 (6.2)	7.17 (3.12–16.50)	<0.001

OR, odds ratio; CI, confidence interval.
Values are presented as number/total number (%) or OR (95% CI).
*Missing data occurred because susceptibility tests were not performed, [†]Since the susceptibility test to penicillin was not performed from May 2011 to April 2013 and the new CLSI penicillin susceptibility breakpoints for *S. pneumoniae* was adopted from 2013 at our hospital, the analysis was performed using the data from 2013 to 2018.

Table 3. Multivariable Logistic Regression Analysis for MDR of *Streptococcus pneumoniae*

Variables	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age (yr)				
0–18	reference	0.001	reference	<0.001
19–64	2.56 (1.48–4.43)	0.001	2.77 (1.52–5.03)	0.001
≥65	1.95 (1.22–3.12)	0.005	2.32 (1.41–3.84)	0.001
Diagnosis				
Pneumonia	reference	<0.001	reference	0.001
Pharyngitis/tonsilitis*	1.25 (0.57–3.12)	0.499	2.11 (0.85–5.22)	0.107
Otitis	1.00 (0.30–3.28)	0.996	1.50 (0.44–5.16)	0.516
Sinusitis	4.57 (1.86–8.46)	<0.001	4.98 (2.07–11.96)	<0.001
Meningitis†	N/A	0.999	N/A	0.999
Deep-seated infection†‡	N/A	0.999	N/A	0.999
Primary bacteremia†	N/A	0.999	N/A	0.999
Others§	0.50 (0.16–1.63)	0.253	0.43 (0.13–1.42)	0.167
IPD	0.89 (0.21–3.79)	0.880	1.53 (0.31–7.66)	1.606
Hospitalization	0.64 (0.36–1.17)	0.146	0.80 (0.40–1.62)	0.535
Healthcare-associated onset	1.33 (0.82–2.17)	0.249	0.49 (0.25–0.99)	0.046
Hospitalized within 90-day	2.22 (1.42–3.48)	<0.001	3.58 (1.91–6.71)	<0.001

MDR, multidrug-resistance; N/A, not available; IPD, invasive pneumococcal disease; OR, odds ratio; CI, confidence interval.
Values are presented as OR (95% CI).
*This diagnosis included empyema, intraabdominal abscess, spontaneous bacterial peritonitis, and septic arthritis, †MDR was not detected in these diagnoses, ‡This diagnosis included empyema, intraabdominal abscess, spontaneous bacterial peritonitis, and septic arthritis, §This diagnosis included cellulitis, conjunctivitis, and colonization of *S. pneumoniae*.

Risk evaluation for MDR and antimicrobial resistance of *Streptococcus pneumoniae*

Of all aged isolates, the penicillin resistance rates (OR=2.01, 95% CI=1.28–3.14, *p*=0.002), levofloxacin resistant rates (OR=1.92, 95% CI=1.01–3.64, *p*=0.042), and the rates of MDR (adjusted OR=3.58, 95% CI=1.91–6.71, *p*<0.001) increased significantly in patients with a history of hospitalization within the previous 90 days. According to the diagnosis, the MDR rate in sinusitis was significantly higher than the MDR rate of pneumonia (adjusted OR=4.98, 95% CI=2.07–11.96, *p*<0.001). The MDR rates were not significantly different between IPD and non-IPD isolates: 6.1% (2/33) and 6.7% (96/1427), respectively (*p*=1.000). Table 3 shows the results of multivariable logistic regression analysis for evaluating the risk factors of multidrug-resistant *S. pneumoniae*. We additionally analyzed the differences in antimicrobial susceptibilities between the erythromycin-resistant strains. The penicillin resistance rate and ceftriaxone resistance rate were significantly higher in the erythromycin-resistance strains than in the erythromycin-susceptible strains (OR=26.7, 95% CI=3.68–193.52, *p*=0.001 and OR=6.71, 95% CI=3.78–11.91, *p*<0.001, respectively). The levofloxacin resistance rate did not show a significant difference between the erythromycin-resistance strains and erythromycin-susceptible strains (OR=0.66, 95% CI=0.32–1.35, *p*=0.258).

Antimicrobial resistance rates of IPD
A total of 33 isolates of IPD were identified; seven were in the under 18 years old group, 19 in the 18–64 years old group, and seven in the over 65 years old group. The antimicrobial resistance rates of individual antimicrobials and the MDR rate did not differ significantly between IPD and non-IPD isolates. However, in multiple logistic regression analysis, the 19 to 64 years age group had independent risk factors for IPD (OR=6.38, 95% CI=2.27–17.96, *p*<0.001). Although ages of under 2 years or 65 years are considered risk factors of IPD, in the comparison by separating the under 2 years old age group from the 0 to 19 years old age group, IPD was significantly higher in the 19 to 64 years age group.

Antimicrobial resistance rates and MDR rates in the age group of 0 to 18 years
Comparison of individual antibiotic resistance rates showed no significant difference between the under 2 years old age group and the 2–18 years old age group. However, in the comparison of MDR rate, the age group of under 2 years showed a significantly higher proportion (OR=3.08, 95% CI=1.49–6.38, *p*=0.002). For risk evaluation, logistic regression analysis was performed using the source of specimen, diagnosis, hospitalized within 90 days as variables, and hospitalized within 90 days was significantly higher in the under 2 years old age group (OR=1.67, 95% CI=1.03–2.70, *p*=0.036).
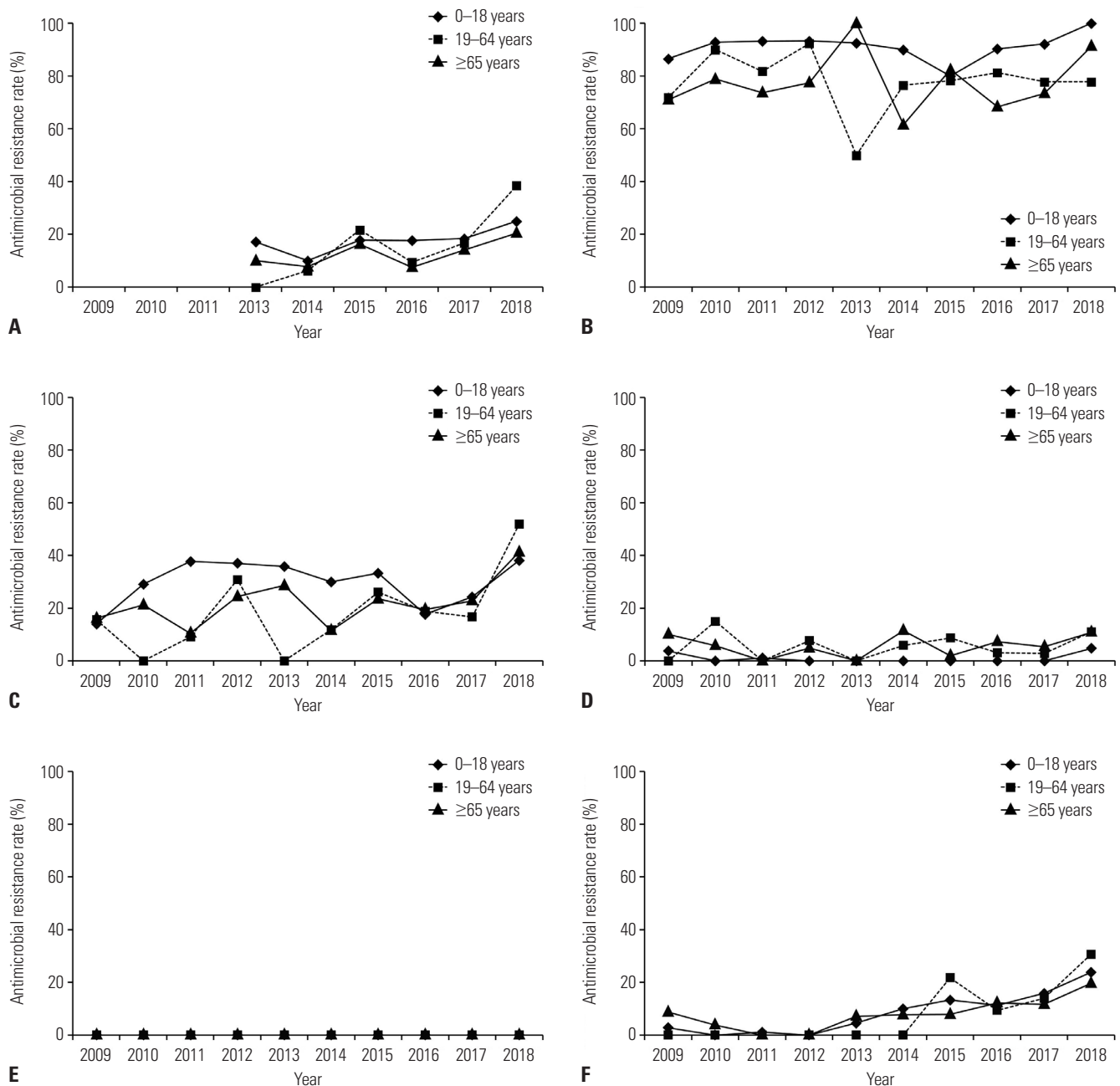
Fig. 3. Trends in antibiotic resistance rates of *Streptococcus pneumoniae* during 2009–2018 by age groups. (A) Penicillin. (B) Erythromycin. (C) Ceftriaxone. (D) Levofloxacin. (E) Vancomycin. (F) MDR. Since the susceptibility test to penicillin was not performed from May 2011 to April 2013 and the new CLSI penicillin susceptibility breakpoints for *S. pneumoniae* was adopted from 2013 at our hospital, the analysis was performed using the data from 2013 to 2018. MDR, multidrug-resistance.

DISCUSSION

This study highlights the changes in trends and distribution of antimicrobial resistance of *S. pneumoniae* strains by age groups obtained from a single center located in Jeju Island, which is a geographically isolated region in South Korea. We found a significant increase in the MDR rates and antimicrobial resistance rates (erythromycin and ceftriaxone) for *S. pneumoniae* isolates obtained from this hospital over a 10-year period (2009–2018). However, the resistance of *S. pneumoniae* isolates to penicillin

and levofloxacin did not change significantly during the study period. Furthermore, we observed that the resistance trend of *S. pneumoniae* was significantly different among the age groups.

Since the first report of reduced susceptibility of *S. pneumoniae* to penicillin emerged in 1965, the frequency of infections of penicillin-resistant *S. pneumoniae* increased in worldwide, and reports of MDR strains and decreased susceptibility of pneumococci to fluoroquinolone were emerging.[4] However, susceptibility patterns and drug resistance can differ regionally or temporally.[20,21] Therefore, it is important to have an insight

into the changing patterns and trends of antibiotic susceptibility in homogenous populations and geographically isolated areas. There have been reports of antimicrobial resistance patterns and serotype distribution of pneumococcal isolates by region and age group.[13,22-25] Increasing antimicrobial resistance in *S. pneumoniae* is primarily attributable to resistance to β-lactams and macrolides.[4,26] The prevalence of penicillin-resistant *S. pneumoniae* in South Korea, using the CLSI new non-meningitis intravenous breakpoints, ranges from 9.1% to 21.2%.[21,27] In the current study, the overall penicillin resistance rate in *S. pneumoniae* was 16.2%, which did not differ from those in previous studies. It was reported that between 1990s and 2000s, under the former CLSI breakpoint criteria, the penicillin non-susceptibility rate of *S. pneumoniae* in South Korea was 79.7%.[20] Similarly, the penicillin non-susceptibility rates of pneumococci in our hospital from 2009 to 2011 was 72.5%, with the former CLSI breakpoint criteria. After the adaptation of new CLSI breakpoint criteria, the resistance rate decreased to 15% in 2013. Although the resistance rate slightly increased to 26.7% in 2018, it was not significant between the two periods. Moreover, there was no significant difference in penicillin resistance rate among the age groups. Since the penicillin non-susceptibility rates in *S. pneumoniae* have remained relatively low by years, β-lactam antibiotics would be suggested as an initial empirical antimicrobial drugs in suspected pneumococcal infections, including community-acquired pneumonia.

According to the previous studies, high resistance rate to macrolide ranged from 75.6% to 88.3% in Asian countries, 90.8% in China, and 76.7–85.1% in South Korea.[28,29] Of 1460 isolates in this study, 1231 (84.7%) were resistant to erythromycin, which is similar to the antimicrobial resistance rate of *S. pneumoniae* in mainland South Korea. The resistance to macrolide may not be a major issue for *S. pneumoniae*, due to the reduced clinical utility of macrolide against infections caused by *S. pneumoniae*. However, pneumococcal isolates that are resistant to erythromycin are often resistant to other antimicrobials.[30] Therefore, it is noteworthy that the resistance rate to erythromycin remained high over 10 years and increased significantly between 2009 and 2018.

Of 1460 pneumococcal isolates, 377 (25.9%) were resistant to ceftriaxone during the study period. The change in overall resistance rate to ceftriaxone ranged from 15.0% to 43.6%. The resistance rate of *S. pneumoniae* isolates to ceftriaxone increased significantly between 2009 and 2018. In Asian countries, the resistance rate to ceftriaxone in adults was reported to be low, except in China (22.2%).[29] Recent research from South Korea reported the non-susceptibility rate to ceftriaxone to range between 16.4% and 30.7%.[31,32] The result in present the study shows a remarkable discrepancy from other reports of ceftriaxone-resistant *S. pneumoniae* in South Korea. Furthermore, the ceftriaxone resistance rate in the 0 to 18 years age group was significantly higher than those in the 19 to 64 years and 65 year or older age groups. Broad-spectrum cephalosporins, such as

ceftriaxone, are usually recommended to treat *S. pneumoniae* infection empirically. However, this study found that ceftriaxone should be selected cautiously against pneumococcal infection, and it may be necessary to change the Korean guidelines for pediatric pneumonia according to recent changes in the resistance rates of *S. pneumoniae*.

The resistance rate to levofloxacin was as low as 3.3%, which was either similar or lower than those reported in previous studies.[29,31] The resistance rate was significantly higher in the adult age groups than in the 0 to 18 years age group.

Antimicrobial resistance is closely related to the consumption of antimicrobial agents. β-lactam and macrolide are most frequently prescribed antimicrobials for respiratory tract infection. Children are more likely to use antimicrobials and be the carriers of *S. pneumoniae* for a longer duration than adults, which leads to increased exposure to antimicrobials and the acquisition of a resistant strain.[33] The fluoroquinolone is not routinely administered as first-line therapy to pediatric patients, but it is frequently used in adults for respiratory tract infection. The increasing use of levofloxacin in adults may have caused the relatively higher resistance rate in the adult groups. All isolates studied remain susceptible to vancomycin.

The overall MDR rate of pneumococcal isolates obtained from the present study was 6.7% during the study period. This result showed a relatively low MDR rate compared to other reported MDR rates, which overall ranged from 56.1% to 78.4% in South Korea.[1,29,31,34] MDR is defined most frequently as resistance to three or more antimicrobial drug classes or resistant to one key antimicrobial. Of the nine screened antimicrobial agents, we included four antimicrobials documented for the antimicrobial susceptibility test results over the recent 10 years as well as penicillin in our analysis; therefore, we defined MDR as resistance to at least three of the five antimicrobials studied. Since there are different definitions of MDR, low prevalence of MDR cannot be directly compared to other reports. Furthermore, the susceptibility test to penicillin was not performed from May 2011 to April 2013, which could have affected the low rate of MDR in present study. MDR strains have been reported to be found frequently in the isolates belonging to serotypes 19F, 19A, 15A, 11A, 6A, 23F, 23A, and 35A.[23,29] A previous study conducted on patients from the same hospital in 2018 revealed that the most frequently found serotypes were 19F, 15A/15F, 19B, and 23A, accounting for 62.5% of all isolates.[8] Therefore, we expected that if we included more antimicrobials in the analysis, the rate of MDR would be even higher.

A strength of this study is that it was conducted on a geographically isolated island where it was difficult to access hospitals in other regions. Additionally, most patients using this hospital were residents of the island; therefore, the characteristics of *S. pneumoniae* strains in this region were expected to be well-preserved. Therefore, we expected the results of this study to reflect the antimicrobial susceptibility patterns and changing trends at the community level. Furthermore, we ana-

lyzed data over a 10-year period; therefore, we expect the data to provide a profound understanding of the changes in trends of antimicrobial resistance in this area. The present study also had some limitations. First, since our data were derived from a single hospital, the results may not provide a comprehensive picture of the nationwide antimicrobial resistance trends of *S. pneumoniae*. Second, the serotypes of *S. pneumoniae* were not included. Third, we did not analyze the association between antimicrobial resistance patterns and antimicrobial prescription or consumption.

In summary, we compared the changes and trends of the antimicrobial resistance of *S. pneumoniae* isolates over a period of 10 years according to age groups in a homogenous population of Jeju Island, a geographically isolated region in South Korea. The erythromycin and ceftriaxone resistance rate and the MDR rate of *S. pneumoniae* significantly increased during the 10-year period. However, the distribution of individual antimicrobial resistance rates and MDR rates of *S. pneumoniae* significantly differed by age groups. This study highlighted that ceftriaxone, as an empirical antimicrobial drug, should be selected cautiously for use against pneumococcal infections.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jeong Rae Yoo. Data curation: Young Ree Kim and Misun Kim. Formal analysis: Hyunjoo Oh. Funding acquisition: Jeong Rae Yoo. Investigation: Hyunjoo Oh and Jeong Rae Yoo. Methodology: Hyunjoo Oh and Jeong Rae Yoo. Project administration: Jeong Rae Yoo. Resources: Young Ree Kim and Jeong Rae Yoo. Software: Misun Kim. Supervision: Jeong Rae Yoo. Validation: Sang Take Heo. Visualization: Jeong Rae Yoo. Writing—original draft: Hyunjoo Oh. Writing—review & editing: Jeong Rae Yoo. Approval of final manuscript: all authors.

ORCID iDs

Hyunjoo Oh   https://orcid.org/0000-0003-4815-2743
Sang Taek Heo   https://orcid.org/0000-0001-8947-5069
Misun Kim   https://orcid.org/0000-0003-3771-6101
Young Ree Kim   https://orcid.org/0000-0003-2454-8815
Jeong Rae Yoo   https://orcid.org/0000-0002-5488-7925

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