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Five-year report of national surveillance of antimicrobial resistance in *Pseudomonas aeruginosa* isolated from non-tertiary care hospitals in Korea (2002–2006)

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Abstract

A nationwide surveillance of the antimicrobial resistance of *Pseudomonas aeruginosa* isolates from non-tertiary care hospitals was conducted in Korea from 2002 to 2006. Resistance to almost all antimicrobial agents decreased significantly from 2003 ($P < 0.01$). Resistance rates to the major antipseudomonal agents, ceftazidime, imipenem, meropenem, and aztreonam, were 18.8%, 20.5%, 18.7%, and 19.7%, respectively, in 2003. However, they had all decreased to below 10% in 2006. The proportion of multidrug-resistant isolates that were resistant to at least 3 of 5 major antipseudomonal agent decreased from 33.5% in 2003 to 23.1% in 2006 ($P < 0.05$). In this study, we found a decreasing trend in resistance rates and low resistance rates in *P. aeruginosa* from non-tertiary care hospitals compared with those from general hospitals, including tertiary care hospitals, in Korea. Our data provide valuable information for the selection of reliable empiric therapies for *P. aeruginosa* infections in non-tertiary care hospital patients, including outpatients.

Keywords: *Pseudomonas aeruginosa*; Antimicrobial resistance

1. Introduction

Pseudomonas aeruginosa is a notoriously difficult organism to control with antibiotics or disinfectants because of its multidrug resistance to many antibiotics, attributable to both its intrinsic resistance and its ability to acquire resistance genes, including those for β-lactamase and aminoglycoside-modifying enzymes (Hancock, 1998; Lambert, 2002). It is not only of great concern in the control of nosocomial infections, but also in the treatment of community-acquired infections (Hatchette et al., 2000). In 2003, *P. aeruginosa* was the most commonly isolated Gram-negative species causing nosocomial pneumonia and the 3rd most common cause of urinary tract infections in the United States (Gaynes et al., 2005). It also causes several other infections in the community, including community-acquired pneumonia (Hatchette et al., 2000; Kang et al., 2005).

For us to select reliable empiric therapies for *P. aeruginosa* infections in the community, it is necessary to identify the antimicrobial resistance trends in non-tertiary care hospitals, including outpatients. However, there are limited data regarding bacterial antibiotic resistance in non-tertiary care hospitals (Lee et al., 2006a) because recent studies have focused on the susceptibility of *P. aeruginosa* isolated in intensive care units and tertiary care hospitals (Friedland et al., 2003; Lee et al., 2006b, 2006c; Obritsch et al., 2004; Wang and Chen, 2005).

This study was conducted to determine the variation in the resistance rates in *P. aeruginosa* to certain antimicrobial agents in non-tertiary care hospitals over a consecutive 5-year period (2002–2006). The inherent trends were also

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studied. These data will be useful in selection of reliable empiric therapies for *P. aeruginosa* infections in non-tertiary care hospital patients.

2. Materials and methods

A nationwide study of the antimicrobial susceptibility of *P. aeruginosa* in non-tertiary care hospitals was performed for the period 2002 to 2006. Clinical isolates of *P. aeruginosa* were obtained from 2 commercial laboratories at which the microorganisms from specimens received predominantly from non-tertiary care hospitals (including clinics and community hospitals) had been identified. During the surveillance period, 476 non-tertiary care hospitals were represented, which were geographically dispersed across South Korea. The participation rates of community hospitals and clinics in the program were 87.1% to 92.2% and 7.8% to 12.9%, respectively, during 2002 to 2006. Of the isolates from community hospitals, 70.9% were collected by 71 institutions, 76% of which had continuously provided isolates for more than 3 years.

Antimicrobial susceptibility was tested using the disk diffusion method for amikacin, aztreonam, ceftazidime, ciprofloxacin, cefepime, gentamicin, imipenem, meropenem, piperacillin, tobramycin, and ticarcillin/clavulanic acid, according to the guidelines of the Clinical and Laboratory Standards Institute (2005). Resistance rates were calculated from consecutive nonduplicate isolates. Multidrug-resistant (MDR) isolates were defined as those resistant to 3 or more of the 5 major antipseudomonal drugs. Annual antimicrobial resistance trends were determined using a χ^2 test. *P* values less than 0.05 were considered statistically significant. Statistical analysis was carried out using SPSS version 12.0 software (SPSS, Chicago, IL).

3. Results

A total of 2527 *P. aeruginosa* isolates were obtained from various infections in patients from non-tertiary care hospitals nationwide from 2002 to 2006. The isolates were from 149 clinics (31%) and 327 community hospitals (69%). In this study, *P. aeruginosa* was most commonly isolated from sputum (50.1%), urine (18.2%), and wounds (14.6%). The resistance rates to common antipseudomonal agents among the isolated *P. aeruginosa* are presented in Table 1. Over the 5-year surveillance period, most resistance rates to antimicrobial agents increased from 2002 to 2003 and then decreased to 2006. Although the resistance rates to gentamicin and ciprofloxacin remained high (over 30%), they showed a decreasing trend from 2004. Resistance rates to ceftazidime, cefepime, imipenem, meropenem, and aztreonam decreased to less than 10% between 2005 and 2006. Longitudinal resistance profiles listed by the year of isolation are shown in Fig. 1. For most antimicrobial agents, sharp decreases in resistance occurred between 2004 and 2005. The resistance rates of the tested antimicrobial agents decreased significantly, except those for ciprofloxacin, piperacillin, and ticarcillin/clavulanic acid. The most significant declines in resistance rates from 2002 to 2006 were noted for ceftazidime ($P < 0.001$; OR = 0.42; 95% confidence interval [CI], 0.21–0.83), imipenem ($P < 0.001$; OR = 0.51; 95% CI, 0.30–0.86), amikacin ($P < 0.001$; OR = 0.22; 95% CI, 0.16–0.30), and gentamicin ($P < 0.001$; OR = 0.61; 95% CI, 0.44–0.84). Resistance rates to aztreonam, meropenem, and cefepime also decreased significantly ($P < 0.01$). Ceftazidime resistance was noteworthy for its continuous decline from 18.8% in 2003 to 4.5% in 2006, a 4-fold decrease.

MDR isolates were defined as those resistant to 3 or more of the 5 major antipseudomonal drugs: piperacillin, ceftazidime, ciprofloxacin, gentamicin, and imipenem. The incidence of multidrug resistance is presented in Fig. 2. The incidence of resistance to more than 1 agent reached 58.7% in 2003 and decreased to 42.9% in 2006. The same trend was observed for the incidence of multidrug resistance; the highest incidence of multidrug resistance was 33.5% in 2003, which decreased to 23.1% in 2006. Coresistance to ciprofloxacin, gentamicin, and piperacillin was found in 84.5% of MDR strains. MDR *P. aeruginosa* were most

Table 1
In vitro susceptibilities to 10 antimicrobial agents for clinical isolates of *P. aeruginosa* collected from non-tertiary hospitals during 2002 to 2006

Antimicrobial agents	2002 (n = 481)			2003 (n = 600)			2004 (n = 667)			2005 (n = 532)			2006 (n = 247)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Piperacillin	69.0	0	31.0	61.0	0	39.0	63.6	0	36.4	69.5	0	30.5	72.9	0	27.1
Ticarcillin/clavulanic acid	73.0	0	27.0	64.0	0	36.0	67.8	0	32.2	70.9	0	29.1	71.3	0	28.7
Ceftazidime	82.5	7.5	10	73.8	7.3	18.8	79.5	8.2	12.3	86.5	4.7	8.8	91.5	4.0	4.5
Cefepime	81.5	8.7	9.8	71.7	11.8	16.5	74.2	13.2	12.6	85.0	7.9	7.1	87.9	5.7	6.5
Aztreonam	65.5	22.2	12.3	55.3	25.0	19.7	66	20.4	13.6	64.8	23.5	11.7	73.7	18.2	8.1
Imipenem	80.7	4.6	14.8	76.3	3.2	20.5	78.9	5.2	15.9	91.4	1.5	7.1	89.1	2.8	8.1
Meropenem	83.4	4.8	11.9	76.8	4.5	18.7	81.4	4.0	14.5	89.8	2.3	7.9	89.5	1.2	9.3
Amikacin	70.1	3.7	26.2	64.8	5.7	29.5	63.4	5.5	31	77.6	4.5	17.9	79.8	2.4	17.8
Gentamicin	56.8	1.5	41.8	54.5	3.2	42.3	53.7	2.8	43.5	65.8	1.1	33.1	66.4	3.2	30.4
Ciprofloxacin	60.1	4.4	35.6	52.3	4.8	42.8	48.3	5.5	46.2	58.8	5.8	35.3	59.1	6.9	34.0

S = susceptible; I = intermediate; R = resistant.

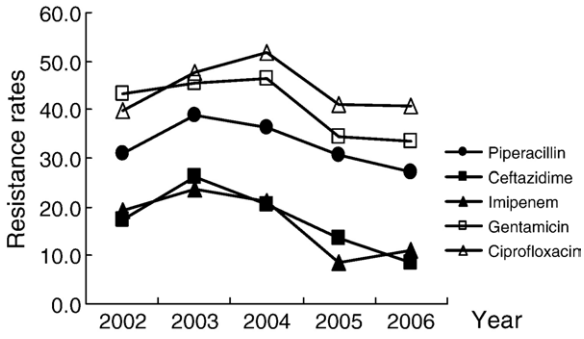

Fig. 1. Temporal changes of piperacillin, ceftazidime, imipenem, gentamicin, and ciprofloxacin resistance in *P. aeruginosa*.

frequently isolated in urine specimens (50.2%), followed by sputum (27.3%) and wounds (20.1%). Resistance to ciprofloxacin, gentamicin, and piperacillin was the most common type of multidrug resistance in all specimens.

4. Discussion

Many surveillance studies, including the SENTRY program, the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC), and the European Antimicrobial Resistance Surveillance System (EARSS), have reported trends in antimicrobial resistance for major Gram-positive and Gram-negative pathogens, including *P. aeruginosa* from intensive care units, cystic fibrosis units, and general wards (Andrade et al., 2003; Cavallo et al., 2007; EARSS, 2005; Rossi et al., 2006). In Korea, antimicrobial resistance strain surveillance by the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) group has been conducted in general hospitals, including tertiary care hospitals, since 1997 (Lee et al., 2006b, 2006c). Although monitoring resistance is necessary for the empiric selection of the most appropriate antimicrobial agents with which to treat infected patients and many *P. aeruginosa* strains have been isolated from non-tertiary care hospitals, there has been little surveillance of those isolates (Lee et al., 2006a). Therefore, we performed a nationwide antimicrobial resistance surveillance of *P. aeruginosa* isolated in non-tertiary care hospitals since 2002 and compared the results with those of KONSAR (2002–2004) and those from 12 tertiary care hospital surveillance groups that participated in KONSAR (2005–2006).

Hong et al. (2003) reported that resistance rates were generally higher among isolates from hospitals with more than 1000 beds. In accordance with a previous report, our study showed much lower resistance rates in non-tertiary care hospitals in Korea, especially for carbapenems and ceftazidime. However, they were higher than those for outpatients in the United States (Flamm et al., 2004). In 2002, the resistance rates to piperacillin, ceftazidime, amikacin, and ciprofloxacin in the Unites States were 8.9%, 6.9%, 7.0%, and 27.1%, respectively, whereas the corresponding resistance rates we observed were 31%, 10%, 26.2%, and 35.6%, respectively. Remarkably, a decline in the resistance rates to all tested antipseudomonal agents since 2003 was observed in our study. Moreover, the rates of multidrug resistance were also reduced. In 2003, antimicrobial resistance rates to most antimicrobial agents were as high as those found in general hospitals. However, resistance rates declined continuously in our study, although no decreasing trends were observed in the surveillance of tertiary care hospitals. In our study, the resistance rates to ceftazidime and imipenem were 18.8% and 20.5%, respectively, in 2003, and were 19% and 20%, respectively, in tertiary care hospital surveillance for the same period. However, in 2006, these were 4.5% and 8.1%, respectively, in our study, but 22% and 29%, respectively, in tertiary care hospital surveillance (Lee et al., 2006c, 2007). The cause of the high resistance rates for these drugs in general hospitals, including tertiary care hospitals, has been attributed to their preference for carbapenem and 3rd- or 4th-generation cephalosporins as therapeutic agents because of the low resistance rates to those antibiotics, identified in our survey. Our nationwide surveillance provides valuable information related to emerging trends in the resistance of *P. aeruginosa* to major antipseudomonal antibiotics in non-tertiary care hospital isolates. A possible reason for this decrease in the resistance rates is that antimicrobial agents have been defined as prescription drugs in Korea since 2000. Lee (2002) reported that a reduction in the use of antimicrobial agents tended to lead to a decrease in the resistance rates of *Escherichia coli* and *Staphylococcus aureus* in the community (comparing data from 2000 with those from 2001), although this is a controversial correlation. In the EARSS (2006) annual report, the proportion of MDR isolates with resistance to 5 classes of antimicrobial agents (piperacillin, carbapenem, fluoroquinolone, aminoglycoside, and ceftazidime) was 7.4% in 2005. In our study, resistance to 5 classes of antimicrobial agents increased from 2.1% in 2002 to 7.5% in 2003 and then decreased continuously to 1.2% in 2006. Our multidrug resistance rate is low compared with those of other surveillance reports. The multidrug resistance rate was 9.9% in the Unites States in 2003 and 20.5% in China in

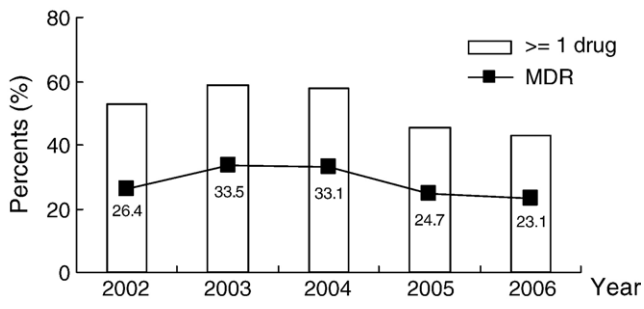

Fig. 2. Proportions of antimicrobial resistant *P. aeruginosa* more than 1 antibiotic from 2002 to 2006. Resistance to at least 3 of these drugs was considered multidrug resistance.

2002 (Karlowsky et al., 2005; Wang and Chen, 2005). MDR *P. aeruginosa* were most frequently isolated in urine specimens (50.2% of urine specimens). The proportion of urine samples among all specimen types was 18%. Sputum specimens were the 2nd most frequent source of *P. aeruginosa* in this study, with 50.1% MDR isolation rate. Our results differ from those of the SENTRY program (1997–2001), where the MDR profiles were mainly from patients with lower respiratory tract infections (55.4%) (Andrade et al., 2003).

In conclusion, the resistance rates of *P. aeruginosa* to antipseudomonal agents in non-tertiary care hospitals in Korea decreased from 2002 to 2006, together with the multidrug resistance rate. The resistance rates were much lower than those of general hospitals, including tertiary care hospitals, over the same period. Moreover, there were no declining trends in resistance rates in tertiary care hospitals. Our study is crucial to clinicians in the selection of reliable empiric therapies for *P. aeruginosa* infections in non-tertiary care hospital patients.

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