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Antimicrobial Resistance Surveillance of Bacteria in 1999 in Korea with a Special Reference to Resistance of Enterococci to Vancomycin and Gram-Negative Bacilli to Third Generation Cephalosporin, Imipenem, and Fluoroquinolone

The trend of antimicrobial resistance of bacteria isolated from patients in 30 Korean hospitals in 1999 was analyzed with a particular attention to cefotaxime- or fluoroquinolone-resistant gram-negative bacilli, imipenem-resistant *Pseudomonas aeruginosa*, and vancomycin-resistant enterococci. Adequacy of susceptibility testing, and any change in the frequencies of isolated species were also analyzed. The results showed that only 20% and 30% of hospitals tested the piperacillin-tazobactam and cefoxitin susceptibility of *Enterobacteriaceae*, respectively, only 24% of hospitals the piperacillin-tazobactam susceptibility of *P. aeruginosa*, and 17% of hospitals the fusidic acid susceptibility of staphylococci. Among the isolates 26.3% were glucose-nonfermenting gram-negative bacilli, and 34.7% of *Enterococcus* were *Enterococcus faecium*. Slight decline of cefotaxime-resistance rate to 20% was noted in *Klebsiella pneumoniae*, while fluoroquinolone-resistantce rate was 68% in *Acinetobacter baumannii*. The ceftazidime- and imipenem-resistance rates were 17% and 18%, respectively in *P. aeruginosa*. The vancomycin-resistance rate of *E. faecium* rose significantly to 15.1%, but the rates varied significantly depending on hospitals suggesting presence of different degree of selective pressure or nosocomial spread. In conclusion, the prevalence of imipenem-resistant *P. aeruginosa* and the increase of vancomycin-resistant *E. faecium* were the particularly worrisome phenomena observed in this study.

Key Words : *Antimicrobial Drug Resistance in Korea; Resistance Surveillance; Vancomycin-Resistant Enterococci; Imipenem-Resistant Pseudomonas*

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INTRODUCTION

Antimicrobial resistance surveillance became ever more important with an increase of resistant bacteria (1). Two previous nationwide resistance surveillances in Korea have shown serious trends such as rapid increases in vancomycin-resistant enterococci and fluoroquinolone-resistant gram-negative bacilli and prevalence of extended spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* (2, 3). In another study, emergence of VIM-2 metallo-β-lactamase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii* was noted (4). Since most of the surveillances have been based primarily on hospital isolates, resistance patterns of community isolates are not well known (5). Isolates from smaller city hospitals may contain more community-acquired pathogens.

Besides the trend of resistance, a nationwide surveillance can also reveal adequacy of susceptibility testing as to the kind of antimicrobial agents tested, and trend of isolation of particular species, which may change depending on various factors including antimicrobial resistance. In addition, presence of outbreak of nosocomial infection can be suspected.

The aim of the present surveillance was to determine the trend of resistance in clinical isolates of bacteria, particularly those aforementioned ones, in Korean hospitals which are located either in large or in small cities and with various bed capacities. Adequacy of susceptibility testing, and any change in the frequency of isolated species were compared with the previous results.

MATERIALS AND METHODS

Routine susceptibility test data for clinical isolates of *Escherichia coli*, *K. pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, non-typhoidal *Salmonella*, *A. baumannii*, *Stenotrophomonas maltophilia*, *P. aeruginosa*, *Haemophilus influenzae*, staphylococci, enterococci, and pneumococci in 1999 were collected from 33 of 67 hospitals participating in the program of Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR). The hospital laboratories used National Committee for Clinical Laboratory Standards (NCCLS) disk diffusion test (6) or commercial broth microdilution systems of either Vitek (bioMerieux, Marcy l'Etoile, France) or MicroScan (Dade MicroScan Inc., West Sacramento, CA, U.S.A.). Fusidic acid susceptibility test was interpreted based on the breakpoint established by the European Society of Clinical Microbiology and Infectious Disease (7).

The KONSAR laboratories have been participating in a WHO quality control program. The data from three laboratories were excluded from analysis because their quality was considered unreliable. Likewise, the data from hospitals with less than 10 isolates of non-typhoidal *Salmonella* or less than 20 isolates of other species were not included for analysis. Therefore, the numbers of hospitals whose data were analyzed for the uncommon organisms were 19 with non-typhoidal *Salmonella*, 10 with *H. influenzae*, and 24 with pneumococci.

The resistance rates did not include intermediate category. The hospitals were grouped based on location and bed capacity: either in Seoul or outside Seoul; and either over 1000 beds or less. The mean resistance rates were calculated from the resistance rates in each of the hospitals to minimize the influence of a large number of strains tested in some hospitals on the mean resistance rates. Depending on laboratories, either ciprofloxacin, ofloxacin or levofloxacin was used to determine fluoroquinolone susceptibility. Therefore, the results using these agents were put together to calculate fluoroquinolone resistance rates.

RESULTS

Analysis on the methods of susceptibility testing showed that four out of five large hospital laboratories and 17 of 25 medium laboratories used NCCLS disk diffusion test, while the remaining laboratories used commercial broth microdilution systems of either Vitek or MicroScan.

More than 90% of the laboratories tested susceptibility of *Enterobacteriaceae* to ampicillin, at least one of 3rd generation cephalosporins, gentamicin, and fluoroquinolone. Thirty percent or less of the laboratories tested for cefotetan, cefoxitin, piperacillin-tazobactam, cefoperazone-sulbactam, and tetracycline. Ninety percent or more of 29 laboratories tested antimicrobial susceptibility of *P. aeruginosa* to ceftazidime, imipenem, amikacin, gentamicin, tobramycin and fluoroquinolone. Seven laboratories tested for piperacillin-tazobactam susceptibility. All of the 29 laboratories tested susceptibility of *S. aureus* to oxacillin. Ninety percent or more of the laboratories tested susceptibility to penicillin, clindamycin, erythromycin and vancomycin, while only 5 tested susceptibility to fusidic acid (Table 1).

The resistance rates were analyzed from a total of

Table 1. Number of laboratories which tested susceptibility of bacteria to indicated antimicrobial agents

*Enterobacteriaceae**		*P. aeruginosa*		Staphylococci	
Antimicrobial agent	No. of hospital (n=30)	Antimicrobial agent	No. of hospital (n=29)	Antimicrobial agent	No. of hospital (n=29)
Ampicillin	29	Piperacillin	23	Penicillin	26
Piperacillin	17	Ceftazidime	26	Oxacillin	29
Cephalothin	24	Aztreonam	19	Clindamycin	28
3rd-Gen. Cephalosporin	28	Imipenem	26	Erythromycin	28
Aztreonam	17	Piperacillin-tazobactam	7	Fluoroquinolone	23
Imipenem	26	Ticarcillin-clavulanic acid	15	Gentamicin	19
Aminopenicillin-BLI†	18	Cefoperazone-sulbactam	12	Cotrimoxazole	20
Amikacin	26	Amikacin	29	Tetracycline	19
Gentamicin	29	Gentamicin	29	Fusidic acid	5
Tobramycin	22	Tobramycin	26	Teicoplanin	19
Fluoroquinolone	27	Fluoroquinolone	27	Vancomycin	27
Cotrimoxazole	19				

*Less than 10 hospitals tested susceptibility to cefotetan, cefoxitin, piperacillin-tazobactam, cefoperazone-sulbactam and tetracycline
†Aminopenicillin-BLI, amoxicillin-clavulanic acid or ampicillin-sulbactam

Table 2. Species and number of isolates analyzed for antimicrobial resistance in 1999

Organism	No. (%) of isolates
*Enterobacteriaceae**	49,511 (31.2)
Non-typhoidal *Salmonella*	760 (0.5)
A. baumannii	14,564 (9.2)
S. maltophilia	3,407 (2.1)
P. aeruginosa	23,855 (15.0)
H. influenzae	502 (0.3)
S. aureus	31,747 (20.0)
Coagulase-negative staphylococci	17,854 (11.2)
E. faecalis	9,692 (6.1)
E. faecium	5,148 (3.2)
S. pneumoniae	1,874 (1.2)
Total	158,914 (100)

*Includes *E. coli*, *K. pneumoniae*, *E. cloacae* and *S. marcescens*

158,914 isolates which included the followings: 49,511 (31.2%) isolates of *E. coli*, *K. pneumoniae*, *E. cloacae* and *S. marcescens*; 760 (0.5%) non-typhoidal *Salmonella*; 41,826 (26.3%) *A. baumannii*, *S. maltophilia* and *P. aeruginosa*; 502 (0.3%) *H. influenzae*; 49,601 (31.2%) staphylococci; 14,840 (9.3%) enterococci; 1,874 (1.2%) pneumococci (Table 2).

Among the *E. coli* isolates, 78% were resistant to ampicillin and 38% to aminopenicillin-β-lactamase inhibitor combinations (Table 3). Resistance rate to cefotaxime by conventional breakpoint was 8%. The resistance rates to cefoxitin, gentamicin and fluoroquinolone were 12%, 33% and 28%, respectively. The resistance rates of *K. pneumoniae* were 24% to ceftazidime, 22% to cefoxitin, 10% to fluoroquinolone. Among the isolates of *E. cloacae* and *S. marcescens*, 41% and 36% were resistant to cefotaxime, 0.7% and 1.4% to imipenem, 15% and 18% to amikacin, and 14% and 24% to fluoroquinolone, respectively. Resistance rates of *A. baumannii* and *S. maltophilia* were 73% and 84% to cefotaxime, 63% and 70% to amikacin, 68% and 28% to fluoroquinolone, respectively. Imipenem-resistance rate of *A. baumannii* was 6.2%. Slight decreases of cefotaxime resistance rates in *E. cloacae*, *S. marcescens* and *A. baumannii* were noted in 1999 compared to those in 1998, but they were higher than those isolated in 1997 (Fig. 1).

The resistance rates of *P. aeruginosa* by hospital groups were 32% to 43% to piperacillin, 17% to 22% to ceftazidime, 18% to 21% to imipenem, 23% to 37% to amikacin, and 38% to 40% to fluoroquinolone (Table 4).

Table 3. Antimicrobial resistance rates of gram-negative bacilli frequently isolated from clinical specimens

Antimicrobial agents	% of resistant isolates (No. of isolates tested)					
	E. coli (25,398)	*K. pneumoniae* (12,973)	*E. cloacae* (6,271)	*S. marcescens* (4,869)	*A. baumannii* (14,564)	*S. maltophilia* (3,407)
Ampicillin	78	93*	95*	97*	95*	95*
Aminopenicillin-BLI†	38	30	75	87	29	80
Cephalothin	38	38	96*	99*	100*	99*
Cefotaxime	8	20	41	36	73	84
Ceftazidime	6	24	46	22	65	43
Aztreonam	7	27	42	20	84	93
Cefoperazone-sulbactam	4	5	10	16	8	17
Cefoxitin	12	22	93*	66	97*	96*
Cefotetan	6	4	48	25	89	29
Piperacillin	60	40	54	41	72	75
Piperacillin-tazobactam	6	16	26	24	61	65
Ticarcillin-clavulanate	15	23	43	49	48	28
Imipenem‡	0	0	0.7	1.4	6.2	96
Amikacin	6	7	15	18	63	70
Gentamicin	33	29	45	48	75	70
Tobramycin	24	31	53	62	75	68
Fluoroquinolone	28	10	14	24	68	28
Cotrimoxazole	59	34	43	51	63	27
Tetracycline	67	24	46	61	43	61

*Intrinsic resistance of *K. pneumoniae*, *E. colacae*, *S. marcescens*, *A. baumannii* and *S. maltophilia* to ampicillin, cephalothin, or cefoxitin were included only for comparison

†Combination of aminopenicillins and β-lactamase inhibitors

‡Rare, but important antibiotic resistance was expressed as decimals to show subtle differences

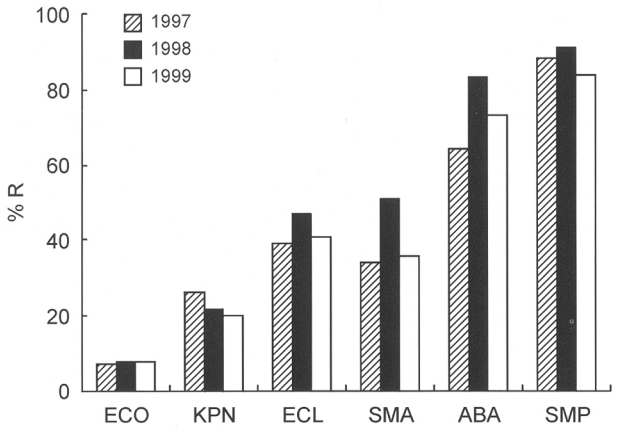

Fig. 1. Trend of cefotaxime resistance rates of gram-negative bacilli. ECO, *E. coli*; KPN, *K. pneumoniae*; ECL, *E. cloacae*; SMA, *S. marcescens*; ABA, *A. baumannii*; SMP, *S. maltophilia*.

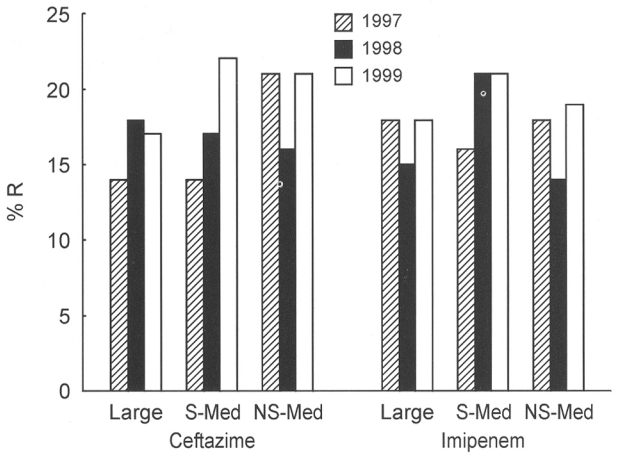

Fig. 2. Rates of ceftazidime and imipenem resistance of *P. aeruginosa* in different groups of hospitals. S-Med, Seoul medium hospitals; NS-Med, non-Seoul medium hospitals.

The resistance rates to ceftazidime and imipenem in 1999 were slightly higher in medium-sized hospitals both in Seoul and in non-Seoul region than in large hospitals. The trend of rise in resistance rates to ceftazidime and imipenem was noted in medium-sized hospitals in Seoul compared to those of the previous years (Fig. 2).

The resistance rates of non-typhoidal *Salmonella* isolates were 21% to 30% to ampicillin and 7% to 9% to cotrimoxazole, depending on hospital groups (Table 4). Among the *H. influenzae* isolates, 65% were resistant to ampicillin, but 45% were β-lactamase positive. β-lactamase positive rate varied significantly depending on hospital groups: 55% in large hospitals, 42% in Seoul medium hospitals and 39% in non-Seoul medium hospitals (Table 4).

Oxacillin resistance rate of *S. aureus* was 66% to 72% depending on hospital groups (Table 5). Resistance rates to clindamycin, erythromycin, gentamicin, fluoroquinolone and tetracycline ranged from 60% to 74% and the rates were similar in all hospital groups. Fusidic acid

Table 4. Antimicrobial resistance rates of *P. aeruginosa*, non-typhoidal *Salmonella*, and *H. influenzae* by hospital group

Antimicrobial agents	% of resistant isolates (No. of isolates tested)			
	Large	Seoul-Medium	Non-Seoul-Medium	Mean
P. aeruginosa	(7,042)	(4,172)	(12,641)	(23,855)
Piperacillin	39	32	43	38
Piperacillin-tazobactam	32	22	33	29
Ticarcillin-clavulanate	51	41	45	46
Aztreonam	24	21	26	24
Ceftazidime	17	22	21	20
Cefoperazone-sulbactam	25	19	35	26
Imipenem	18	21	19	19
Amikacin	23	37	31	30
Gentamicin	43	45	49	46
Tobramycin	40	39	44	41
Fluoroquinolone	39	38	40	39
Non-typhoidal *Salmonella*	(226)	(38)	(496)	(760)
Ampicillin	21	24	30	25
Ceftazidime	0	0	0	0
Cotrimoxazole	7	9	7	8
Fluoroquinolone	0	0	1	<1
H. influenzae	(183)	(78)	(241)	(502)
Ampicillin	73	66	55	65
β-lactamase	55	42	39	45

Table 5. Antimicrobial resistance rates of staphylococci, enterococci and pneumococci by hospital group

Antimicrobial agents	% of resistant isolates (No. of isolates tested)			
	Large	Seoul-Medium	Non-Seoul-Medium	Mean
S. aureus	(9,579)	(5,330)	(16,838)	(31,747)
Penicillin	98	98	97	98
Oxacillin	72	69	66	69
Clindamycin	63	61	57	60
Erythromycin	75	74	74	74
Fluoroquinolone	66	65	64	65
Cotrimoxazole	5	4	6	5
Gentamicin	70	73	72	72
Tetracycline	69	74	67	70
Fusidic acid	23	19	14	19
Teicoplanin	0	0.3	<0.1	0.1
Vancomycin	0	0	0	0
Coagulase-negative staphylococci	(4,124)	(2,685)	(11,045)	(17,854)
Penicillin	93	93	89	92
Oxacillin	70	67	65	67
Clindamycin	40	38	36	38
Erythromycin	60	58	58	59
Fluoroquinolone	36	31	29	32
Cotrimoxazole	48	40	40	43
Gentamicin	50	65	61	59
Tetracycline	41	50	51	47
Fusidic acid	61	66	73	67
Teicoplanin	0.2	0.8	0.1	0.4
E. faecalis	(3,295)	(995)	(5,402)	(9,692)
Ampicillin	3	2	3	3
Fluoroquinolone	39	35	43	39
Tetracycline	82	87	86	85
Teicoplanin*	0.5	0.7	0.5	0.2
Vancomycin*	0.7	0.6	1.1	0.8
E. faecium	(1,966)	(703)	(2,479)	(5,148)
Ampicillin	87	80	85	84
Fluoroquinolone	86	52	82	73
Tetracycline	42	47	56	48
Teicoplanin*	11.0	9.0	10.0	10.0
Vancomycin*	18.0	14.4	13.0	15.1
S. pneumoniae	(276)	(508)	(1,090)	(1,874)
Penicillin†	81	82	72	78
Erythromycin	80	88	68	79
Cotrimoxazole	84	79	65	76
Fluoroquinolone	12	5	3	7
Tetracycline	86	89	69	81

*Rare, but important antibiotic resistance was expressed as decimals to show subtle differences
†Nonsusceptible rate to penicillin. Includes oxacillin-disk screening positive

resistance rate was 14% in non-Seoul medium hospitals, while it was 23% in large hospitals. In general, rates of resistance in coagulase-negative staphylococci were somewhat lower than those of *S. aureus*, but the rates to cotrimoxazole and fusidic acid were higher (43% vs 5% and 67% vs 19%, respectively).

E. faecalis showed resistance rates of 3% to ampicillin and 0.8% to vancomycin (Table 5). The mean resistance rate of *E. faecium* to ampicillin was 84%, while the rates to vancomycin were 13% in non-Seoul medium hospitals and 18% in large hospitals. Significant increase in vancomycin resistance was noted in large hospitals and non-Seoul medium hospitals (Fig. 3). Rate of vancomycin resistance in *E. faecium* was more variable depending on

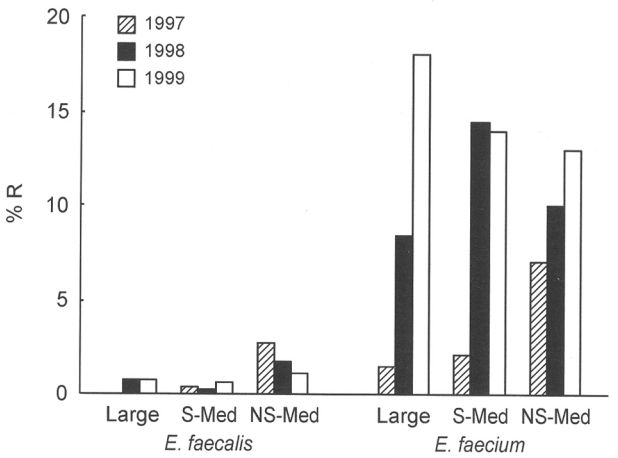

Fig. 3. Rates of vancomycin resistance of enterococci in different groups of hospitals. Abbreviations: see Fig. 2.

hospitals even in the same hospital group, compared to imipenem resistance in *P. aeruginosa*.

The penicillin-nonsusceptible rate of pneumococci was 78%. The resistance rates to erythromycin, cotrimoxazole and tetracycline ranged from 76% to 81% and the rates were similar in all hospital groups (Table 5).

DISCUSSION

It became ever more complicated to decide which antimicrobial agents to include for susceptibility testing due to the growing number of antimicrobial agents in the NCCLS guideline (6). Commercial broth microdilution test systems have many advantages, but with these systems selection of antimicrobial agents is almost impossible (8). Also, interpretation of test result needed modifications due to the emergence of new mechanisms of resistance (9). Therefore, laboratories are confronted with various problems to provide adequate susceptibility test data to clinicians.

Class of antimicrobial agents used for the test by the participating laboratories are shown in Table 1. With an increase of β-lactamase-producing *E. coli*, combination of β-lactam and β-lactamase inhibitor have been useful in treating patients (10), but a significant proportion of the laboratories did not include them in susceptibility testing. Also, with increases of ESBL-producing *E. coli* and *K. pneumoniae*, cephamycin should be useful, but many laboratories did not include either cefoxitin or cefotetan. Cephamycin, especially cefotetan was considered as an attractive option as a second-line therapy for infections caused by ESBL producer (10). Almost all laboratories tested imipenem susceptibility. Carbapenem is recommended for severe infections caused by ESBL-producing *Enterobacteriaceae*, but it was considered that 4th generation cephalosporin, and combination of β-lactam and β-lactamase inhibitor were not suitable as a first-line therapy (10). Imipenem also might be useful when the isolates were AmpC β-lactamase hyperproducers. However, reporting that the isolate is imipenem susceptible might render the clinicians to an over use of the agent.

In general, the relative proportions of each of the species or organisms in 1999 were similar to those in 1997 and 1998 (2, 3). However, slight increases in the proportions of *A. baumannii*, coagulase-negative staphylococci and *E. faecium* were noted (Table 2). These finding might be related to the increased resistances in these organisms.

The resistance rates of *E. coli* in 1999 were quite similar to those in 1998. ESBL-mediated resistance has become a major health problem in most countries (11). The resistance rate to cefotaxime was 8% by conventional breakpoint, suggesting a persistence of ESBL-producing strains (Table 3). However, it is interesting that cefotaxime resistance rate of *K. pneumoniae* has been slightly declining since 1997 (Fig. 1).

The cefoxitin resistance rates of *E. coli* and *K. pneumoniae* were 12% and 22%, respectively. In Korea, plasmid-mediated CMY-1 β-lactamase-producing *E. coli* and *K. pneumoniae* are widespread (12), and the emergence of CMY-1-producing strains with an increased resistance to ceftazidime has also been reported (13). Resistance rates of *E. coli* and *K. pneumoniae* to cefotetan were much lower than those to cefoxitin, but the clinical significance of this is not clear.

E. cloacae, *S. marcescens*, *A. baumannii* and *S. maltophilia* are frequently encountered nosocomial pathogens and are often resistant to multiple antimicrobial agents (14). Cefotaxime-resistance rates of these organisms were very high (Fig. 1). These results suggest a prevalence of derepressed AmpC-β-lactamases-producing strains (15). Future surveillance on the susceptibility to 4th-generation cephalosporin, such as cefepime and cefpirome, may provide valuable information on these nosocomial pathogens (16).

An increase of carbapenemase-producing gram-negative bacilli was predicted previously (17). Recently, VIM-2 metallo-β-lactamase-producing isolates were detected among imipenem-resistant *P. aeruginosa*, *A. baumannii*, *E. cloacae* and *S. marcescens* in Korea (unpublished data). *A. baumannii* is also a typical nosocomial pathogen with a frequent multi-resistance (18). In this study, imipenem resistance rate was 6.2% (Table 3). It was found that in a tertiary care hospital approximately 50% of the imipenem-resistant isolates were producing metallo-β-lactamase. Most of the metallo-β-lactamases was of VIM-2 type, but one isolate with IMP-1 type was also detected.

S. maltophilia rarely causes infection, but in recent

years, this has been increasingly reported as a cause of life-threatening infections, particularly in compromised patients (19). In this study, the number of *S. maltophilia* isolates tested was only slightly less than that of *S. marcescens*. *S. maltophilia* is naturally resistant to carbapenem and most isolates were reported to be resistant to aminoglycosides, β-lactams, and ciprofloxacin, while cotrimoxazole and ticarcillin-clavulanic acid had a borderline activity (19). In this study, the isolates showed relatively low resistance rates of less than 30% to fluoroquinolone, cefotetan, and cefoperazone-sulbactam, besides to cotrimoxazole and ticarcillin-clavulanic acid.

In *P. aeruginosa*, mean ceftazidime-resistance rate further rose from 16% in 1997 to 20% in 1999. It is interesting that the rates were higher in medium-sized hospitals than those in large hospitals. A slight increase in imipenem resistance rate was noted, that is, 17% in 1997 and 19% in 1999. Imipenem-resistant isolate was present in every hospitals, although the rates varied significantly. This suggests a wide dissemination of imipenem-resistant *P. aeruginosa* in Korea. It was found that among the strains collected from KONSAR group hospitals in 1999, 12% were producing VIM-2 metallo-β-lactamase (20). The VIM-2 gene was located in class 1 integron. Some strains transferred the resistance by conjugation. This may partially explain the prevalence of VIM-2 metallo-β-lactamase-producing strains.

Non-typhoidal *Salmonella* enteritis may not require antimicrobial treatment, but in case the organism invades extraintestinal sites, antimicrobial therapy is necessary. Antimicrobial resistance of non-typhoidal *Salmonella* is a problem in many countries. Ampicillin resistance rate of non-typhoidal *Salmonella*, 25% in this study, was significantly higher than that of 13% in 1998. As was in 1998, the rate was higher in non-Seoul medium hospitals. Most surveillance studies have been based primarily on hospital isolates (5). Therefore, it is considered that prevalence of resistance in community pathogens are difficult to estimate. However, *Salmonella* infections are mostly community acquired. Therefore, the present data may reflect resistance of non-typhoidal *Salmonella* in the community. In this study, fluoroquinolone resistance rate remained low, 0.3%, suggesting that its resistance is not problematic. It was reported that 13.3% of the *Salmonella* serovar Typhimurium isolated in 1995-1996 in France were resistant to nalidixic acid, but all were susceptible to ciprofloxacin. This indicates that ciprofloxacin susceptibility may fail to detect the low level quinolone resistance or to predict clinical efficacy in the treatment of non-typhoidal *Salmonella* infection (21).

The rates of ampicillin-resistance and β-lactamase production in *H. influenzae* were significantly different. This may be due to the presence of isolates with β-lactam resistance by other mechanisms than β-lactamase production, or be due to the difficulties in accurate susceptibility testing of this organism (22).

Resistance rates of *S. aureus* were similar to those in 1998 with the exception of increased resistance to fusidic acid from 4% in 1998 to 19% in 1999. The resistance to fusidic acid is a matter of great concern, in that it is one of the antimicrobial agents active against MRSA. Oxacillin resistance rate of *S. aureus*, 69%, was similar to that in 1998. MRSA has been a serious problem in almost all levels of hospitals in Korea. Since the first detection in Japan, the recent concern is vancomycin-intermediate *S. aureus* (VISA). Previously, Kim et al. (23) reported a case of VISA infection in Korea. It may be impossible to detect presence of VISA by this type surveillance, since the detection method is sophisticated. However, it seems not necessary to use special methods to detect VISA at the moment, considering the fact that great efforts by some investigators failed to detect any more VISA in Korea (24). Mori et al. in Japan (25) reported that heteroresistant VISA was not detected among the MRSAs isolated in 1998-1999. Their opinion was that heteroresistant VISA was no more responsible for the therapeutic failure of vancomycin treatment than ordinary MRSA. Burnie et al. (26) reported that after exposure to vancomycin, vancomycin-susceptible MRSA gave rise to a subpopulation with reduced susceptibility to this antimicrobial agent, whereas the treatment with rifampin reduced the mortality of the patients.

The resistance rate of enterococci to ampicillin differs significantly depending on the species. Ampicillin resistance rate of *E. faecalis* remained very low, while the rate of *E. faecium* has risen further from 70% in 1997 to 80% in 1998, and then to 84% in 1999. Vancomycin resistance in enterococci is a great concern in many countries, particularly in the United States (27). Vancomycin-resistant *E. faecium* increased from 2.9% in 1997 to 10.9% in 1998, and then to 15.1% in 1999. The rise was of significantly greater degree in large hospitals than in non-Seoul medium hospitals (Table 5). However, the rates varied significantly depending on hospitals in the same hospital group. This suggests a presence of different degree of selective pressure or nosocomial infection. According to the experience with MRSA and penicillin-non-susceptible pneumococci in Korea, once the resistant strain started to increase, then the resistance is uncontrollable. In this regard, it is a great concern that VRE started to increase in many hospitals in Korea. Donskey et al. (28) reported that it was difficult to control the spread of VRE by infection control measure alone.

Penicillin-nonsusceptible pneumococci remained prevalent (Table 5). The resistance rates to erythromycin, cotrimoxazole, and tetracycline were also high, indicating

these antimicrobial agents have a limited value for the treatment of infections even other than meningitis, too. Fluoroquinolone resistance rate was relatively low in this study. MICs of newer fluoroquinolones are lower against gram-positive bacteria (29), but it has been suggested that bacteria in general show cross resistance to various fluoroquinolones (30).

In conclusion, many hospitals need to test susceptibility of gram-negative bacilli to the combination of β-lactam and β-lactamase inhibitor and to cephamycin, and of staphylococci to fusidic acid. A significant proportion of the isolates were glucose-nonfermenters among gram-negative bacilli, and *Enterococcus faecium* among enterococci. A slight decline of cefotaxime resistance was noted in gram-negative bacilli, while a rise was observed in fluoroquinolone resistance in some species of gram-negative bacilli and in ceftazidime or imipenem resistance in *P. aeruginosa*. In addtion a significant rise of vancomycin resistance in *E. faecium* was noted. The prevalence of imipenem-resistant *P. aeruginosa* and increase of vancomycin-resistant *E. faecium* were the particularly worrisome phenomena observed in this study.

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