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Increasing Prevalence of Vancomycin-Resistant Enterococci, and Cefoxitin-, Imipenem- and Fluoroquinolone-Resistant Gram-Negative Bacilli: A KONSAR Study in 2002

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Continued antimicrobial resistance surveillance can provide valuable information for the empirical selection of antimicrobial agents for patient treatment, and for resistance control. In this 6th annual study for 2002, the susceptibility data at 39 Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) hospitals were analyzed. Resistance rates of *S. aureus* were 67% to oxacillin, and 58% to clindamycin. The ampicillin and vancomycin resistance rates of *E. faecium* were 89% and 16%, respectively. To penicillin, 71% of *S. pneumoniae* were nonsusceptible. Resistance rates of *E. coli* were 11% to cefotaxime, 8% to cefoxitin, and 34% to fluoroquinolone, and those of *K. pneumoniae* were 22% to ceftazidime, and 16% to cefoxitin. Lowest resistance rates to cephalosporins shown by *E. cloacae* and *S. marcescens* were to cefepime, 7% and 17%, respectively. This is the first KONSAR surveillance, which detected imipenem-resistant *E. coli* and *K. pneumoniae*. To imipenem, 22% of *P. aeruginosa* and 9% of *Acinetobacter* spp. were resistant. Trends of resistances showed a slight reduction in MRSA and in penicillin-nonsusceptible *S. pneumoniae*, but an increase in ampicillin-resistant *E. faecium*. Ampicillin-resistant *E. coli* and *H. influenzae* remained prevalent. Compared to the previous study, amikacin- and fluoroquinolone- resistant *Acinetobacter* spp. increased to 60% and 62%, respectively. Ceftazidime-resistant *K. pneumoniae* decreased slightly, and imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp., and vancomycin-resistant *E. faecium* increased. In conclusion, vancomycin-resistant *E. faecium*, cefoxitin-resistant *E. coli* and *K. pneumoniae*, and imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. increased gradually, and imipenem-resistant *E. coli* and *K. pneumoniae* appeared for the first time. Continued surveillance is required to prevent further spread of these serious resistances.

Key Words: Antimicrobial resistance, imipenem resistance, Korean resistance surveillance

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INTRODUCTION

Infections due to antimicrobial-resistant bacteria are difficult to cure.[1] *In vitro* resistance undoubtedly increases morbidity, mortality, and costs.[2] The emergence and spread of antimicrobial resistance constitutes a major risk to human health as resistance limits the therapeutic success of these agents and prevention of infectious diseases.[3] The empirical selection of antimicrobial agents has become increasingly difficult due to an increase in the prevalence of resistant bacteria.

Major reasons for surveillance are to determine the size of the problem, to determine whether resistance is increasing or not, to detect any previously unknown types of resistance, and to determine whether any particular type of resistance is spreading or associated with an outbreak.[1] Recently, various international, and national surveillance programs have been conducted for various purposes.[3] However, the most useful surveillance is the monitoring of resistance trends at the local or hospital level to guide therapy, as resistance rates may differ greatly depending on countries or on hospitals.[4]

The analysis of routine susceptibility test data at hospitals is a commonly used and widely accepted method of resistance surveillance. This method has inherent inaccuracies due to differences in methodology and interpretation, but does not require much resource.[3] Another method, the collection of isolates from participating hospitals and susceptibility testing by a coordinating laboratory is more accurate, but many isolates cannot be analyzed for and are expensive. Two surveillance methods have been used by the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) program: the annual analysis of data tested by participating hospitals, by which presence of problem organism with antimicrobial resistance can be recognized,[5] and then collecting problem organisms from participating hospitals to verify the resistance by testing at the a coordinating hospital.[6,7]

The monitoring of temporal trends of resistance is considered most beneficial for the detection of subtle changes in resistance.[8] Previous nationwide surveillances in Korea have showed the continued high prevalence of oxacillin (methicillin)-resistant staphylococci, the increasing resistance of *Enterococcus faecium* to vancomycin, of *Enterobacteriaceae* to 3rd generation cephalosporins, cephamycins, and fluoroquinolones, and of *Pseudomonas aeruginosa* and *Acinetobacter* spp. to carbapenems.[9] It was hoped that recent efforts to control resistant bacteria by the Korean National Health Insurance Program, which in 2001 abolished over-the-counter sales of antimicrobial agents, and started to scrutinize proper use of antimicrobial agents at hospitals, would reduce the prevalence of resistant bacteria.

The aim of surveillance in 2002 was to determine any changing trends in the above-mentioned resistances in particular, besides common resistances at KONSAR hospitals located in different cities/provinces, and to determine possible emergence of new types of resistance.

MATERIALS AND METHODS

Participating hospitals and susceptibility testing

Routine susceptibility test data for major aerobic pathogenic bacteria isolated in 2002 were collected from 39 hospitals located in six cities and six provinces in Korea. Surveillance isolates were not included. For susceptibility testing of gram-positive cocci, the majority of the laboratories used the NCCLS disk diffusion method.[10] For gram-negative bacilli testing, the disk diffusion method, the broth microdilution method (Vitek [bioMerieux, Marcy l'Etoile, France] or MicroScan [Dade MicroScan Inc., West Sacramento, CA, U.S.A.] system), and both methods were used by 14, 17 and 4 hospitals, respectively. Methicillin-resistant staphylococci were detected using oxacillin, and penicillin G-non-susceptible *Streptococcus pneumoniae* were screened mainly by using the oxacillin-disk method.[10] The hospitals used either ciprofloxacin or levofloxacin to test for fluoroquinolone susceptibility.

Analysis of data

The data from one hospital were excluded from the analysis because of poor performance versus the WHO/CDC quality control program, and as was in the previous study,[9] less than 20 isolates of a species from a hospital was excluded from the analysis. In this analysis, resistance rates did not include intermediate susceptibility. Hospitals were divided into three groups according to location and bed capacity ($\geq$1000 beds in Seoul and non-Seoul, $<$ 1000 beds in Seoul, and $<$ 1000 beds in non-Seoul). Mean resistance rates were calculated from the mean resistance rates of each group, to minimize the influence of a large number of isolates at some hospitals.[11] Differences in the resistance rates between hospital groups were not presented as the trends were similar to those of the previous study in 2001.[5] In comparison of resistance trends, statistical significances were not determined, as were the cases in most international studies, because the degree of significance is dependent on the statistical method used,[11] and no specific statistical method has been recommended as yet, and because the objectives of the surveillance include the detection of minor changes due to small epidemics of resistant bacteria.[12]

RESULTS

Number of isolates and the antimicrobial agents used

Of the 206,568 isolates, 117,085 (56.7%) were gram-negative bacilli and 89,483 (43.3%) were gram-positive cocci (Table 1). Compared to 1998, the number of isolates tested increased significantly, but the proportions of the individual species were similar. The five most prevalent species were *Staphylococcus aureus* (20.7%), *Escherichia coli* (17.5%), *P. aeruginosa* (14.7%), coagulase-negative staphylococci (CNS) (10.6%), and *Klebsiella pneumoniae* (8.7%). *Acinetobacter* spp. (9.5%), which was fifth ranked in 1998, became 6th (8.4%) in 2002. The proportion of *E. faecium* among all enterococci increased from 29.6% in 1998 to 43.4% in 2002.

Kind of antimicrobial agents used to test the susceptibilities of *E. coli* and *S. aureus* were analyzed (Table 2). For *E. coli*, less than 70% of the hospitals tested for susceptibility to cephalothin, cefotaxime, cefepime, and cefoxitin, and less than 60% tested for cotrimoxazole and piperacillin. For *S. aureus*, 59% of hospitals tested for susceptibility to cotrimoxazole.

Resistance rates

Antimicrobial resistance rates of gram-positive cocci are shown in Table 3. Resistance rate of *S. aureus* and CNS were: to oxacillin 67% and 73%, to clindamycin 58% and 37%, and to cotrimoxazole 18% and 42%, respectively. To oxacillin, 71% of *S. pneumoniae* were resistant, suggesting penicillin non-susceptibility, and to erythromycin 74% were resistant. Ampicillin and vancomycin resistance rates of *E. faecium* were 89% and 16%, respectively.

Among the *E. coli* isolates, 11%, 8%, and 34% were resistant to cefotaxime, cefoxitin, and fluoroquinolone, respectively, and the resistance rates of *K. pneumoniae* were 22% and 16% to

Table 1. Comparison of Number, Proportion and Rank Order of Isolates in 1998 and 2002

Organism	1998			2002		
	No. (%) of isolates		Rank	No. (%) of isolates		Rank
E. coli	20,604	(16.5)	2	36,197	(17.5)	2
K. pneumoniae	9,079	(7.2)	6	17,956	(8.7)	5
E. cloacae	5,781	(4.6)	8	7,509	(3.6)	9
S. marcescens	3,324	(2.7)	9	5,643	(2.7)	10
Acinetobacter spp.	11,866	(9.5)	5	17,330	(8.4)	6
P. aeruginosa	20,370	(16.3)	3	30,342	(14.7)	3
Nontyphoidal *Salmonella*	962	(0.7)	12	1,170	(0.6)	12
H. influenzae	746	(0.6)	13	938	(0.5)	13
S. aureus	26,042	(20.9)	1	42,798	(20.7)	1
CNS	13,854	(11.1)	4	21,884	(10.6)	4
E. faecalis	7,075	(5.7)	7	11,806	(5.7)	7
E. faecium	2,968	(2.4)	10	9,051	(4.4)	8
S. pneumoniae	2,187	(1.8)	11	3,944	(1.9)	11
Total	124,858	(100)		206,568	(100)	

CNS, coagulase-negative staphylococci.

Table 2. Antimicrobial Agents Used to Test Susceptibility of *E. coli* and *S. aureus* in 1998 and in 2002

Species	NCCLS group and antimicrobial agent	% of hospitals		Species	NCCLS group and antimicrobial agent	% of hospitals	
		1998	2002			1998	2002
E. coli	Group A			*E. coli*	Group B (Cont.)		
	Ampicillin	88	95		Amikacin	96	97
	Cephalothin	96	67		Cotrimoxazole	68	54
	Gentamicin	96	97				
	Group B			*S. aureus*	Group A		
	Ampicillin-sulbactam	48	82		Penicillin G	88	95
	CTX, CAZ, ATM*	100†	95†		Oxacillin	96	100
	Cefepime	NT*	67		Group B		
	Cefoxitin	40	64		Clindamycin	88	97
	Piperacillin	52	39		Erythromycin	96	97
	Piperacillin-tazobactam	24	74		Cotrimoxazole	56	59
	Imipenem	96	92		Vancomycin	92	97

*Abbreviations: CTX, cefotaxime; CAZ, ceftazidime; ATM, aztreonam; NT, not tested.
†Proportion of hospitals using at least one of these antimicrobial agents.

Table 3. Antimicrobial Resistance Rates of Staphylococci, Pneumococci and Enterococci

Antimicrobial agents	Percent of isolates resistant (No. of isolates tested)				
	S. aureus (42,798)	CNS (21,884)	*S. pneumoniae* (3,944)	*E. faecalis* (11,806)	*E. faecium* (9,051)
Oxacillin	67	73	71†	NA*	NA
Ampicillin/penicillin‡	97	93	NT*	3	89
Clindamycin	58	37	NT	NA	NA
Erythromycin	69	58	74	72	89
Cotrimoxazole	18	42	NT	NA	NA
Tetracycline	58	44	NT	84	15
Gentamicin	67	59	NA	NT	NT
Ciprofloxacin	61	38	5	40	88
Teicoplanin	0	0.2	NA	1	9
Vancomycin	0	0	NT	1.7	16

*Abbreviations: NA, not applicable; NT, not tested.
†Penicillin nonsusceptible rate according to the criteria for the isolates from meningitis.
‡Ampicillin for enterococci and penicillin for staphylococci.

ceftazidime and cefoxitin, respectively. Lowest resistance rates to cephalosporins shown by *Enterobacter cloacae* and *Serratia marcescens* were to cefepime, 7% and 17%, respectively. This study showed for the first time that 0.1% of *E. coli* and 0.2% of *K. pneumoniae* were resistant to imipenem. To imipenem and ceftazidime, 22% and 21% of *P. aeruginosa* were resistant, respectively. *Acinetobacter* spp. were often resistant to all antimicrobial agents except cefoperazone-sulbactam and imipenem. The resistance rates of nontyphoidal *Salmonella* to ampicillin and cotrimoxazole were 28% and 4%, respectively (data not shown). Fifty-seven percent of *Haemophilus influenzae* were resistant to ampicillin and 54% produced β-lactamase.

Trend of resistance

Trends of resistance shown by gram-positive cocci, which have been prevalent from previous studies, are shown in Fig. 1. A slight reduction in ORSA and a slight increase in oxacillin-resistant coagulase-negative staphylococci (ORCNS) were noted. Ampicillin-resistant *E. faecium* steadily increased from 70% in 1997 to 89% in 2002, whereas penicillin-nonsusceptible *S. pneumoniae* has decreased slightly since 2000. Trends of previously prevalent resistance in gram-negative bacilli are shown in Fig. 2. Ampicillin-resistant *E. coli* and *H. influenzae* remained prevalent. For nontyphoidal *Salmonella*, an increasing tendency of resistance to ampicillin was noted, but not to cotrimoxazole.

Resistance rates to amikacin of *E. coli* and *K. pneumoniae*, *E. cloacae*, *S. marcescens* and *P. aeruginosa* remained low, and did not change significantly, but that of *Acinetobacter* spp. increased from 50% in 1997 to 60% in 2002 (Fig. 3). Fluoroquinolone resistance rates differed significantly depending on species: i.e., 12% for *K. pneumoniae* and 62% for *Acinetobacter* spp. in 2002, but trends showed no marked changes, except for *E. coli*, in which it increased from 24% in 1997 to 34% in 2002 (Fig. 4).

Serious recent resistance trends are shown in Fig. 5. Notably, a slight decrease in ceftazidime-resistant *K. pneumoniae* was found, while cefoxitin resistance fluctuated between 14% and 22%. Imipenem-resistant *P. aeruginosa* gradually increased from 17% in 1997 to 22% in 2002, while resistant *Acinetobacter* spp. increased from 5% in 2001 to 9% in 2002. Only 4% of *E. faecium* were resistant to

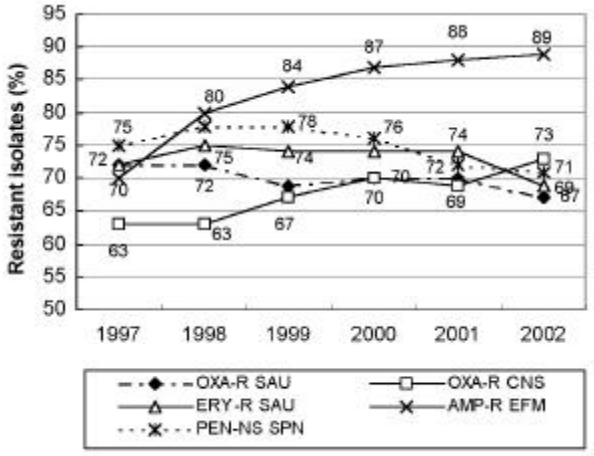

Fig. 1. The trends of some of the common resistant antimicrobial-bacterial combinations. Since around 2001, oxacillin-resistant *S. aureus* and penicillin-nonsusceptible pneumococci slightly decreased, but ampicillin-resistant *E. faecium* further increased to reach 89%. Abbreviations: OXA, oxacillin; ERY, erythromycin; AMP, ampicillin; PEN, penicillin G; R, resistant; NS, nonsusceptible; SAU, *S. aureus*; CNS, coagulase-negative staphylococci; EFM, *E. faecium*; SPN, *S. pneumoniae*.

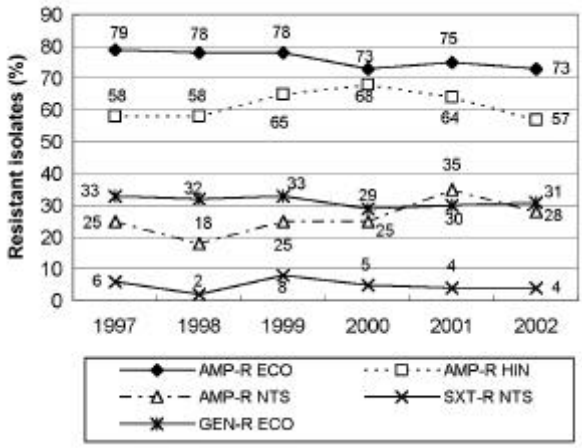

Fig. 2. The trends of ampicillin-resistant *E. coli*, nontyphoidal *Salmonella* and *H. influenzae*, and gentamicin-resistant *E. coli* and cotrimoxazole-resistant nontyphoidal *Salmonella*. Ampicillin resistance remained prevalent in *E. coli*, increased slightly in nontyphoidal *Salmonella*, and decreased slightly in *H. influenzae*. Cotrimoxazole-resistant nontyphoidal *Salmonella* remained rare. Abbreviations: GEN, gentamicin; SXT, cotrimoxazole; ECO, *E. coli*, NTS, nontyphoidal *Salmonella*; HIN, *H. influenzae*.

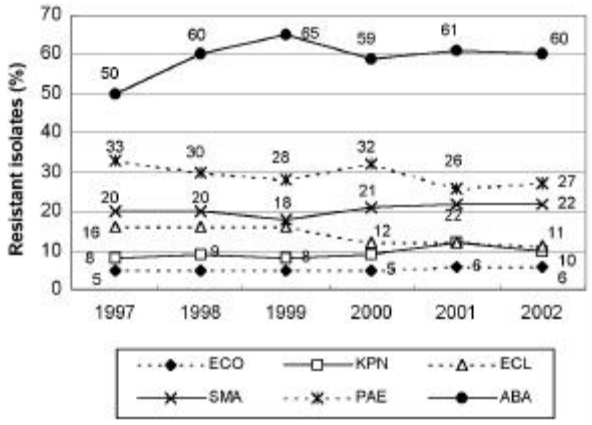

Fig. 3. Trends of amikacin resistance. Amikacin resistance rates of *E. coli*, *K. pneumoniae*, *E. cloacae*, and *S. marcescens* were relatively low, but the resistance rate of *Acinetobacter* spp. was higher than that of *P. aeruginosa*. Abbreviations: KPN, *K. pneumoniae*; ECL, *E. cloacae*; SMA, *S. marcescens*; ABA, *Acinetobacter* spp.; PAE, *P. aeruginosa*.

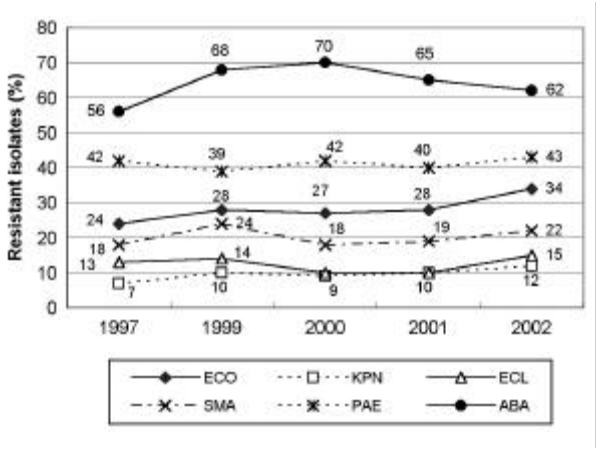

Fig. 4. Trends of fluoroquinolone resistance. The resistance rates of *K. pneumoniae*, *E. cloacae* and *S. marcescens* were relatively low, but the rate of *E. coli* showed slightly increasing tendency. Resistance of *Acinetobacter* spp. was more prevalent than *P. aeruginosa*. *Abbreviations* see Fig. 2 and 3.

vancomycin in 1997, but this rate increased to 16% in 2002.

DISCUSSION

It was stressed that resistance surveillance is an important part of modern clinical microbiology.[8] Analysis of isolation ranks based on the first isolate from a patient is recommended by the

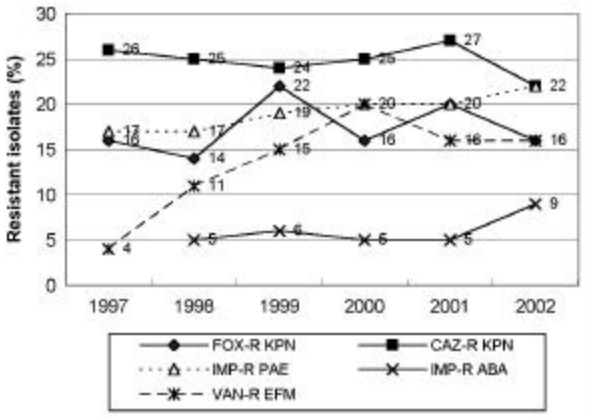

Fig. 5. Trend of more serious resistance. Ceftazidime-resistant *K. pneumoniae* slightly declined, but cefoxitin resistance fluctuated. Imipenem-resistant *P. aeruginosa* gradually increased, while imipenem-resistant *Acinetobacter* isolates suddenly increased in 2002. Vancomycin-resistant *E. faecium* increased gradually to reach 20% in 2000 and then slightly decreased. FOX, cefoxitin; IMP, imipenem; CAZ, ceftazidime; VAN, vancomycin; for others see Fig. 1 and 3.

NCCLS for reporting surveillance laboratory data with the primary aim of guiding empirical therapy selection by clinicians.[13] However, a study showed that even in the United States, not all participating hospitals followed this guideline.[14] When first isolates only are included, selection of resistance that occurs within the observation period cannot be detected.[3] In the present study, duplicate isolates were not excluded, which probably resulted somewhat higher resistance rates for some nosocomial pathogens.

The proportions of individual species in this study were very similar to those in 1997, i.e., *S. aureus*, *E. coli*, *P. aeruginosa* and CNS remained in the same rank order of 1 to 4, respectively, but that of *E. faecium* changed from 10th to 8th, which was probably due to an increase in the prevalences of ampicillin- and vancomycin-resistant isolates (Table 1, Figs. 1 and 5). This belief is supported by a study at a French hospital, in which vancomycin-resistant enterococci were rare, and where the prevalence of ampicillin-resistant *E. faecium* was considered to be caused partly by clonal spread.[15] Antimicrobial resistance surveillance can also reveal laboratories with poor performance in species identification and susceptibility testing, for example, an ampicillin resistance

Table 4. Antimicrobial Resistance of *Enterobacteriaceae, P. aeruginosa* and Acinetobacters

Antimicrobial agents	Percent of isolates resistant (No. of isolates tested)					
	E. coli (36,197)	*K. pneumoniae* (17,956)	*E. cloacae* (7,509)	*S. marcescens* (5,643)	*P. aeruginosa* (30,342)	*Acinetobacter* spp. (17,330)
Ampicillin	73	NA*	NA	NA	NA	NA
Ampicillin-sulbactam	31	29	NA	NA	NA	50
Cephalothin	38	33	NA	NA	NA	NA
Cefotaxime	11	16	30	32	59	69
Ceftazidime	9	22	37	19	21	56
Cefepime	6	6	7	17	22	58
Aztreonam	8	21	33	24	29	76
Cefoperazone-sulbactam	2	6	9	19	17	10
Cefoxitin	8	16	NA	NA	NA	NA
Cefotetan	4	10	NA	NA	NA	NA
Piperacillin	60	37	45	46	38	62
Piperacillin-tazobactam	5	10	23	25	26	42
Ticarcillin-clavulanate	11	21	35	42	50	34
Imipenem	0.1	0.2	0.6	3	22	9
Amikacin	6	10	11	22	27	60
Gentamicin	31	23	32	40	43	68
Tobramycin	24	28	35	48	39	68
Fluoroquinolone†	34	12	15	22	43	62
Cotrimoxazole	49	24	32	32	NT*	88
Tetracycline	41	19	15	89	NT	76

*Abbreviations: NA, not applicable; NT, not tested.
†Mostly tested by using ciprofloxacin, but a few hospitals used ofloxacin or levofloxacin.

rate of 3% for *E. faecalis* was considered to indicate probable misidentification of *E. faecium* in an United Kingdom study.[1]

One of the important reasons for the susceptibility testing of clinical isolates is to guide clinicians in the proper selection of antimicrobial agents. Therefore, if a laboratory tested bacterial susceptibility to limited kind of antimicrobial agents, the result would not be very useful. The NCCLS guideline[10] suggests the primary testing of antimicrobial agents in groups A and B. As resistant bacteria are highly prevalent in Korea, the primary testing of group C antimicrobial agents would also be helpful. Table 2 shows, as an example, the proportion of hospitals using groups A and B antimicrobial agents to test the susceptibilities of *E. coli* and *S. aureus*. The susceptibility testing of *E. coli* to cephalothin and β-lactamase inhibitor combinations is needed because of increased ampicillin resistance, and to cefoxitin and cefepime because of increased resistance due to plasmid-mediated AmpC β-lactamases. However, a significant proportion (18-34%) of the hospitals did not test for susceptibility to these agents. For the optimal detection of ESBL-producing *E. coli* and *K. pneumoniae*, use

of both ceftazidime and cefotaxime is recommended.[10] Given the increasing prevalence of CTX-M type ESBLs, the testing of cefotaxime susceptibility became important in Korea,[16] as in other countries.[17] However, some (8%) of the laboratories performed susceptibility testing for one of these only. These testing limitations with respect to antimicrobial kinds are probably due to the use of commercial broth microdilution methods, which include predetermined sets of drugs. Seventeen laboratories used only broth microdilution methods.

The resistance of some antimicrobial-species of bacteria combinations has been very prevalent for sometime in Korea. Present surveillance showed that the oxacillin-resistance rate of *S. aureus* and CNS remained high, at approximately 70% (Fig. 1). Kim et al.[18] reported that 64% of *S. aureus* collected in 1999-2001 from eight university hospitals were methicillin resistant, and that most of the MRSAs were multiresistant. However, none of the isolates were resistant to quinupristin-dalfopristin (synercid) or linezolid, and superior in vitro activity was shown by rifampin, fusidic acid, cotrimoxazole, and arbekacin. MRSA has also been prevalent in Japan, and in a surveillance in 2000-2002 involving 22 to 29 hospitals, the proportion slightly decreased from 62% to 56%.[19] Only three isolates of true vancomycin-resistant *S. aureus* were reported worldwide in 2002 and 2004,[20] and in the present study, no such isolate was detected as expected.

In the present study, penicillin-nonsusceptible *S. pneumoniae* remained prevalent, as has been reported previously.[5] However, it should be noted that the proportion was based on a breakpoint for the treatment of meningitis.[10] Among the Korean isolates which were mainly from sputum, 24.3% of pneumococci were intermediate to penicillin G.[21] Infections due to such isolates may respond to penicillin G therapy.[22] The macrolide resistance rate, 74% in our present study was only slightly lower than that in another Korean study 85%.[23] Overall, > 90% of penicillin-resistant isolates were also resistant to macrolide according to Song et al,[23] whereas all Korean pneumococcal isolates were susceptible to telithromycin in a another study.[24]

In the present study, the high prevalence of ampicillin-resistant *E. coli* and *H. influenzae* did not change (Fig. 2), and the ampicillin resistance rate of *H. influenzae* (57%) was similar to the β-lactamase positive rate (54%). It was interesting that among type b isolates from meningitis in Japan, 70.8% were resistant to ampicillin, but only 26.3% were β-lactamase positive.[25] Nontyphoidal *Salmonella* infections are more often community-acquired than nosocomial. Increasing number of ampicillin-resistant nontyphoidal *Salmonella* isolates may also indicate an increasing prevalence of this resistance in the community. However, resistance rates were much lower than those of *Salmonella enterica* serovar Typhimurium DT104 isolates, which were 34% to both ampicillin and cotrimoxazole.[26]

E. coli and *K. pneumoniae* often acquire ESBLs. In this study, 11% of *E. coli* and 22% of *K. pneumoniae* were resistant to ceftazidime or cefotaxime, suggesting the production of ESBLs. Cefotaxime resistance rates of *E. cloacae* and *S. marcescens* were 30% and 32%, respectively, suggesting the prevalence of AmpC enzyme-hyperproducing strains. A significant proportion of these species were also resistant to cefepime, which is a cephalosporin stable to AmpC enzymes. Carbapenem is active against ESBL and AmpC β-lactamase-producing gram-negative bacilli. In the 2001 surveillance,[5] none of the *E. coli* and *K. pneumoniae* isolates were resistant to imipenem, but in the present study, 0.1% and 0.2% of these species, respectively, were resistant. A study is needed to determine the possible presence of metallo-β-lactamase (MBL)-producing isolates among these isolates, as the resistance can be spread by horizontal gene transfer. VIM-2 MBL-producing isolates of *K. pneumoniae* were detected in the KONSAR coordinating laboratory in 2004 (unpublished data).

Amikacin is the most active aminoglycoside against various gram-negative bacilli. Although resistance rates of species of *Enterobacteriaceae* were relatively low (6-22%) in the present study, that of *P. aeruginosa* was relatively high (27%), and that of *Acinetobacter* spp. gradually increased to reach 60% in 2002 (Fig 3). Fluoroquinolones became increasingly used, as they are one of the three major broad-spectrum classes of antimicrobial agents, and this use led to the consequent

emergence of resistance.[27] The resistance rate of *Acinetobacter* spp. to fluoroquinolone remained high, i.e., over 60% since 1999, and that of *E. coli* gradually increased from 24% in 1997 to 34% in 2002.

A recent concern in Korea and elsewhere, is an increase in problem organisms with relatively new resistance, i.e., *E. faecium* with vancomycin resistance,[5] *E. coli* and *K. pneumoniae* with ESBL production or cephamycin resistance,[28] and *P. aeruginosa* and *Acinetobacter* spp. with carbapenem resistance[7] (Fig. 5). Huh et al.[29] reported that 20 isolates of vancomycin-resistant *E. faecium*, collected from 9 different university hospitals in 2000 to 2002, had largely heterogeneous PFGE patterns and 3 types of Tn*1546*-like elements, indicative of an endemic nature. Ceftazidime-resistant *K. pneumoniae*, most of which probably produces ESBL, slightly decreased in 2002, but a significant proportion (16%) of these isolates were resistant to cefoxitin. Cephamycins such as cefoxitin and cefotetan, are active against ESBL- producing *E. coli* and *K. pneumoniae*. A recent increase in cefoxitin-resistant *E. coli* and *K. pneumoniae* in Korea were mostly due to plasmid-mediated AmpC β-lactamase production.[28] CMY-1 has been present since 1988 in Korea, and then CMY-1b (CMY-10) appeared.[30] Recently, inducible plasmid-mediated DHA-1 enzyme-producing *K. pneumoniae* started to spread in Korea.[28] For AmpC β-lactamase-producing isolates, the only active cephalosporins are cefepime and cefpirome.

Carbapenems are the only class of β-lactams active against ESBL- and AmpC β-lactamase-producing gram-negative bacilli.[31] In the present study, the carbapenem resistance rate of *P. aeruginosa* increased slightly to 22%, but that of *Acinetobacter* spp. increased significantly from 5% in 2001 to 9% in 2002 (Fig. 5). The imipenem-resistance rate of *Acinetobacter* spp. was lower than that of *P. aeruginosa*, but VIM-2 and IMP-1 MBL genes were detected in 10.1% and 4.1% of them, respectively, in 2000-2001.[6] Even higher imipenem-resistance rates of *P. aeruginosa* 28% and *Acinetobacter* spp. 18% have been reported, in 2003 at the KONSAR coordinating laboratory,[32] which suggests that this resistance may spread further. It is a concern that *Acinetobacter* spp. are often resistant to all available antimicrobial agents.

In conclusion, ORSA, ORCNS, penicillin-non-susceptible *S. pneumoniae*, expanded-spectrum cephalosporin-resistant *K. pneumoniae*, and fluoroquinolone-resistant *E. coli*, *Acinetobacter* spp., and *P. aeruginosa* are highly prevalent. And, it is a concern that vancomycin-resistant *E. faecium*, cefoxitin-resistant *E. coli* and *K. pneumoniae*, and imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. are gradually increasing, and that imipenem-resistant *E. coli* and *K. pneumoniae* have appeared, for which continued surveillance is required to prevent further spread of these serious resistances.

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