Further Increase of Vancomycin-Resistant *Enterococcus faecium*, Amikacin- and Fluoroquinolone-Resistant *Klebsiella pneumoniae*, and Imipenem-Resistant *Acinetobacter* spp. in Korea: 2003 KONSAR Surveillance

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Monitoring temporal trends of antimicrobial resistance can provide useful information for the empirical selection of antimicrobial agents to treat infected patients and for the control of nosocomial infections. In this study, we analyzed antimicrobial resistance of clinically relevant bacteria in 2003 at Korean hospitals and at a commercial laboratory. The following organism-antimicrobial agent resistance combinations were very prevalent: oxacillin-resistant *Staphylococcus aureus* (68%), expanded-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (25%), and fluoroquinolone-resistant *Escherichia coli* (33%), *Acinetobacter* spp. (58%), and *Pseudomonas aeruginosa* (40%). Moreover, gradual increases in vancomycin-resistant *Enterococcus faecium* (20%), cefoxitin-resistant *E. coli* (10%) and *K. pneumoniae* (23%), and imipenem-resistant *P. aeruginosa* (20%) and *Acinetobacter* spp. (13%) were also observed. The resistance rates of *Acinetobacter* spp. to most antimicrobial agents at hospitals and at the commercial laboratory were similar. Among the *Acinetobacter* spp. isolated at a tertiary-care hospital, 46.2% were multidrug-resistant to 9-12 of 13 antimicrobial agents, and 18.3% were panresistant. The exclusion of duplicate isolates at a tertiary-care hospital significantly lowered the proportion of oxacillin-resistant *S. aureus,* vancomycin-resistant *E. faecium*, and fluoroquinolone-resistant *E. coli.*

Key Words: Antimicrobial resistance surveillance, Korea, vancomycin resistance, fluoroquinolone resistance, imipenem resistance

INTRODUCTION

Antimicrobial agents have significantly contributed to the improvement of human health and welfare,[1] but alarming rises in the prevalence of resistance to some agents among certain groups of bacteria have been noted. The increasing antimicrobial resistance of bacteria is a worldwide problem, albeit the prevalence varies greatly by country because it is influenced by the differences in antimicrobial usage and spread of resistance. With the increase of resistant bacteria, useful information for the treatment of infected patients can be obtained only by determining the susceptibility. However, isolation of etiologic agents is not always possible. Even when possible, it takes time to obtain the results. Therefore, initial antibiotic therapy is typically empirical. Empirical selection of the most appropriate antibiotic is possible only when the current regional resistance pattern is known.

Necessary steps to manage antimicrobial resistance problem include the use of better surveillance to accurately assess the extent of problems. Antimicrobial resistance surveillance is defined as the systematic collection, analysis, and dissemination of data that can be used to identify resistance trends and to assess the need for interven-

tion.[2] Monitoring temporal trends of resistance is considered most beneficial for the detection of subtle changes in resistance.[3]

The most accurate information can be obtained by collecting clinical isolates from participating hospitals and testing them in a reference laboratory. However, this method cannot analyze many isolates and is costly. Examples of such studies include the Alexander, PROTEKT, and SENTRY program.[4,5] Another commonly used resistance surveillance method is the analysis of routine susceptibility test data at hospitals because it does not require extensive resources,[5,6] although it has inherent inaccuracies due to differences in methodology and interpretation.

Based on a World Health Organization (WHO) recommendation to organize a national surveillance program, the KONSAR study was initiated in 1997.[7] In Korea, two surveillance methods have been used: annual analysis of test data generated by KONSAR-participating hospitals,[8] and the collection and testing of problematic organism-antimicrobial combinations by the coordinating laboratory.[9,10] The latter program showed wide dissemination of metallo-β-lactamase (MBL)-producing *Acinetobacter* spp. and *Pseudomonas* spp., and plasmid-mediated AmpC enzyme-producing *Escherichia coli* and *Klebsiella pneumoniae*.

In the present surveillance, some modifications were made. Recently, the increase of multidrug-resistant (MDR) *Acinetobacter* spp. has become a concern in many countries because relatively few antibacterial drugs remain active against this microbe.[11] Therefore, in addition to analyzing resistance rates, MDR patterns of *Acinetobacter* spp. at the coordinating hospital were also analyzed in this study. The higher resistance rates of nosocomially-acquired strains compared to community-acquired strains necessitate differentiation between the two groups. However, in a large-scale study it is difficult to separate these groups appropriately. In the previous KONSAR surveillance, data were collected from hospitals only. However, in this study, data were also collected from a commercial laboratory, which examined a large number of specimens submitted mostly from primary-care clinics located outside of Seoul.

In the analysis of resistance data, NCCLS[12] recommends excluding duplicate isolates from a single patient, although previous KONSAR surveillances have included duplicate isolates. When duplicate isolates are included, resistance rates increase, particularly in drug-resistant nosocomial pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. However, the elimination of duplicate isolates may mask trends in emerging resistance.[6] In this study, the effect of excluding duplicate isolates on the resistance rates in *S. aureus*, *Enterococcus faecium*, and *E. coli* was analyzed using data from the coordinating hospital.

MATERIALS AND METHODS

Routine susceptibility test data on the most clinically relevant aerobic bacteria in 2003 were collected from 44 hospitals located in large cities and small provincial in Korea. The data from five of the 44 hospitals were excluded from analysis due to the hospitals' poor performance in the WHO/CDC quality control program. Less than 10 isolates of non-typhoidal *Salmonella* and less than 20 isolates of other organisms from a hospital were also excluded from the analysis.

Hospitals were divided into three groups according to location and bed capacity (≥1000 beds countrywide, <1000 beds in Seoul, and <1000 beds in non-Seoul). Resistance rates did not include intermediate susceptibility. The mean resistance rates in each hospital group were calculated from the resistance rates at each hospital, thus minimizing the influence of a large number of isolates and the high prevalence of resistance at some hospitals.[5,13] Test data obtained at a commercial laboratory were analyzed separately.

The resistance rates were calculated from all isolates, including duplicate isolates. However, the effect of excluding duplicate isolates was analyzed using the data for *S. aureus*, *E. faecium*, and *E. coli* at the coordinating hospital. MDR patterns of *Acinetobacter* spp. at the coordinating hospital were analyzed using the WHONET 5 program.[14] Statistical analysis of resistance surveillance data, which was considered difficult,[2] was not performed in this surveillance, as has been the common practice in large scale and continuous surveillance programs.[4,15]

RESULTS

Rank order of isolates and method appropriateness

The number of isolates in 2003 slightly increased compared to the number in 2002, but the rank order remained identical for 11 of 13 organisms with a large number of isolates (Table 1). The most prevalent species in hospitals was *S. aureus* (20.0%), while in the commercial laboratory it was *E. coli* (27.8%). The proportions of *E. faecium* to *E. faecalis* differed considerably in hospitals compared to the commercial laboratory, at 81.9% vs. 15.8%, respectively.

To test *E. coli*, the NCCLS disk diffusion method, broth microdilution method (Vitek [bioMerieux, Marcy l'Etoile, France] or MicroScan [Dade MicroScan Inc., West Sacramento, CA, U.S.A.] system), or a combination of the two methods were used by 11, 27, and three laboratories, respectively. Oxacillin disks were used to differentiate oxacillin (methicillin)-resistant staphylococci and to screen penicillin G-non-susceptible pneumococci. To test fluoroquinolone susceptibility of gram-negative bacilli, the majority of hospitals used ciprofloxacin, while others used levofloxacin.

The antimicrobial agents used in 2003 to test the susceptibility of *E. coli* and *S. aureus* were similar to those used in 2002 (Table 2). Less than 70% of the hospitals tested the susceptibility of *E. coli* to cephalothin, piperacillin, and cotrimoxazole, and only 50% of the hospitals tested the susceptibility of *S. aureus* to cotrimoxazole. Method analysis of 38 laboratories showed that the types of antimicrobial agents tested were 8-10, 15-20, and 16-21, at 5, 20, and 13 laboratories, respectively (data not shown).

Resistance at hospitals and at a commercial laboratory

The mean resistance rates (Table 3) of *S. aureus* were much higher than those of coagulase-negative staphylococci (CNS) to clindamycin (59% vs. 36%) and to ciprofloxacin (61% vs. 38%), but slightly lower to oxacillin (68% vs. 73%) and to cotrimoxazole (16% vs. 39%). Seventy percent of *Streptococcus pneumoniae* were resistant to oxacillin, suggesting penicillin non-susceptibility. The ampicillin and vancomycin resistance rates of *E. faecium* were 88% and 20%, respectively.

Table 1. Comparison of the Number, Proportion, and Rank of Isolates in 2002 and 2003

Organism	2002 Hospitals		2003 Hospitals		2003 Commercial Lab.*	
	No. (%) of isolates	Rank	No. (%) of isolates	Rank	No. (%) of isolates	Rank
Escherichia coli	36,197 (17.5)	2	40,651 (18.9)	2	7,825 (27.8)	1
Klebsiella pneumoniae	17,956 (8.7)	5	18,635 (8.6)	5	2,535 (9.0)	5
Enterobacter cloacae	7,509 (3.6)	9	7,505 (3.5)	9	794 (2.8)	9
Serratia marcescens	5,643 (2.7)	10	5,474 (2.5)	10	1,306 (4.6)	8
Nontyphoidal *Salmonella*	1,170 (0.6)	12	759 (0.4)	13	232 (0.8)	12
Acinetobacter spp.	17,330 (8.4)	6	15,957 (7.4)	6	1,342 (4.9)	7
Pseudomonas aeruginosa	30,342 (14.7)	3	28,163 (13.1)	3	4,064 (14.4)	2
Haemophilus influenzae	938 (0.5)	13	1,248 (0.6)	12	165 (0.6)	13
Staphylococcus aureus	42,798 (20.7)	1	43,003 (20.0)	1	3,776 (13.4)	3
Coagulase-negative staphylococci	21,884 (10.6)	4	24,567 (11.3)	4	3,044 (10.8)	4
Enterococcus faecalis	11,806 (5.7)	7	13,685 (6.3)	7	2,352 (8.4)	6
E. faecium	9,051 (4.4)	8	11,202 (5.2)	8	371 (1.3)	10
Streptococcus pneumoniae	3,944 (1.9)	11	4,652 (2.2)	11	336 (1.2)	11
Total	206,568 (100)		215,501 (100)		28,343 (100)	

*The majority of the specimens were collected from primary care clinics outside of Seoul.

Table 2. Proportion of Hospitals Which Used Antimicrobial Agents for the Susceptibility Testing of *E. coli* and *S. aureus* in 2002 and 2003*

Species	CLSI group and antimicrobial agents	% of hospitals 2002	% of hospitals 2003	Species	CLSI group and antimicrobial agents	% of hospitals 2002	% of hospitals 2003
E. coli	Group A			*E. coli*	Group B (Control)		
	Ampicillin	95	95		Cotrimoxazole	54	43
	Cephalothin	67	61		Fluoroquinolone	100	100
	Gentamicin	97	100				
	Group B			*S. aureus*	Group A		
	Ampicillin-sulbactam	82	80		Penicillin G	95	89
	CTX, CAZ, ATM	95	95		Oxacillin	100	100
	Cefepime	67	73		Group B		
	Cefoxitin	64	70		Clindamycin	97	93
	Piperacillin	39	36		Erythromycin	97	95
	Piperacillin-tazobactam	74	77		Cotrimoxazole	59	50
	Imipenem	92	98		Vancomycin	97	95
	Amikacin	97	98				

*The number of participating laboratories was 39 in 2002 and 44 in 2003.
CTX, cefotaxime; CAZ, ceftazidime; ATM, aztreonam; CLSI, clinical laboratory standards institute.

The cefotaxime and fluoroquinolone resistance rates of *E. coli* were 11% and 33%, respectively, and those of *K. pneumoniae* to ceftazidime and cefoxitin were 25% and 23%, respectively (Table 4). The lowest resistance rates shown by *Enterobacter cloacae* and *S. marcescens* to cephalosporins were to cefepime and were 8% and 19%, respectively. Imipenem-resistant *K. pneumoniae*, *E. cloacae*, and *Serratia marcescens* isolates existed, although their rates were very low.

Lower resistance rates were shown by *P. aeruginosa* to ceftazidime (19%) and imipenem (20%) and by *Acinetobacter* spp. to imipenem (13%) and cefoperazone-sulbactam (15%). The resistance rates of non-typhoidal *Salmonella* to ampicillin, cotrimoxazole, and fluoroquinolone were 29%, 4%, and 0.3%, respectively (data not shown). The ampicillin resistance rate of *Haemophilus influenzae* was 54%, and a test of part of the isolates showed that 52% produced β-lactamase (data not shown).

The resistance rates of staphylococci to all antimicrobial agents, except for cotrimoxazole resistance of *S. aureus* (Table 3), were much lower at the commercial laboratory than at the hospitals. The ampicillin resistance rates of *E. faecium* were equal at the hospitals and the commercial laboratory (88%), but the vancomycin resistance rates were 20% at the hospitals and 7% at the commercial laboratory. Compared to the resistance rates at the hospitals, the rates at the commercial laboratory were: similar in cefotaxime and fluoroquinolone resistance of *E. coli* (12% and 31%, respectively); slightly lower in cefoxitin resistance of *K. pneumoniae* (18%); much lower in cefotaxime, ticarcillin-clavulanic acid, amikacin, and fluoroquinolone resistance of *E. cloacae* and *S. marcescens*; slightly lower in ceftazidime and imipenem resistance of *P. aeruginosa* (15% and 17%, respectively); and much lower in ampicillin-sulbactam and imipenem resistance of *Acinetobacter* spp. (22% and 5%, respectively) (Table 4).

Trends of significant resistance

The trends of significant resistance in staphylococci, enterococci, *K. pneumoniae*, and *Acinetobacter* spp. are shown in Fig. 1-3. As in 2002, the oxacillin resistance rate was slightly higher in CNS than in *S. aureus* in 2003 (Fig. 1). Not only did the ampicillin resistance of *E. faecium* remain highly prevalent, but vancomycin resistance reached 20% in 2003. The ceftazidime and cefoxitin resistance rates of *K. pneumoniae* in 2003 were higher than those in 2002, and a gradual increase in the

Table 3. Antimicrobial Resistance Rates of Staphylococci, Pneumococci, and Enterococci Tested at Hospitals and at a Commercial Laboratory

Antimicrobial agents	Percent of isolates resistant (No. of isolates tested)									
	S. aureus		CNS		*S. pneumoniae*		*E. faecalis*		*E. faecium*	
	Hospitals (43,003)	C-Lab (3,800)	Hospitals (24,567)	C-Lab (3,100)	Hospitals (4,652)	C-Lab (336)	Hospitals (13,685)	C-Lab (2,350)	Hospitals (11,202)	C-Lab (370)
Oxacillin	68	55	73	69	70*	NT	NT	NT	NT	NT
Penicillin/ampicillin[†]	97	95	93	92	NT	NT	0.6	1	88	88
Clindamycin	59	42	36	19	NT	NT	NT	NT	NT	NT
Erythromycin	69	60	58	45	72	77	NT	NT	NT	NT
Cotrimoxazole	16	21	39	32	NT	NT	NT	NT	NT	NT
Tetracycline	56	50	40	45	NT	NT	81	84	17	15
Gentamicin	66	58	56	46	NT	NT	NT	NT	NT	NT
Ciprofloxacin	61	48	38	25	NT	NT	35	28	88	81
Teicoplanin	0.03	NT	0.2	NT	NT	NT	0.8	0	17	2
Vancomycin	0	0	0.03	0	NT	NT	0.9	0	20	7

*Indicates proportion of penicillin-nonsusceptible isolates.
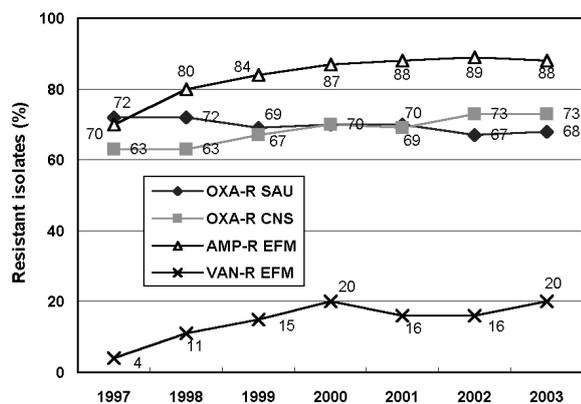[†] Penicillin for staphylococci and ampicillin for enterococci.
C-Lab, commercial laboratory; CNS, coagulase-negative staphylococci; NT, not tested.

Table 4. Antimicrobial Resistance Rates of *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter* spp. Tested at Hospitals and at a Commercial Laboratory

Antimicrobial agents	Percent of isolates resistant (No. of isolates tested)											
	E. coli		*K. pneumoniae*		*E. cloacae*		*S. marcescens*		*P. aeruginosa*		*Acinetobacter* spp.	
	Hospitals (40,651)	Clinics (7,900)	Hospitals (18,635)	Clinics (2,500)	Hospitals (7,508)	Clinics (790)	Hospitals (5,474)	Clinics (1,300)	Hospitals (28,163)	Clinics (4,100)	Hospitals (15,957)	Clinics (1,400)
Ampicillin	71	NT	-	-	-	-	-	-	-	-	-	-
Ampicillin-Sulb	33	26	34	30	-	-	-	-	-	-	47	22
Cephalothin	39	33	36	36	-	-	-	-	-	-	-	-
Cefotaxime	11	12	20	18	36	15	31	16	61	NT	67	64
Ceftazidime	10	NT	25	NT	38	NT	23	NT	19	15	55	NT
Aztreonam	9	NT	24	NT	34	NT	25	NT	26	16	73	NT
Cefepime	8	NT	14	NT	8	NT	19	NT	21	NT	41	NT
CFP-Sulb	5	NT	10	NT	16	NT	37	NT	20	NT	15	NT
Cefoxitin	10	6	23	18	-	-	-	-	-	-	-	-
Cefotetan	4	NT	12	NT	-	-	-	-	-	-	-	-
Piperacillin	52	NT	39	NT	46	NT	40	NT	38	39	60	NT
Piperacillin-Tazo	5	NT	14	NT	23	NT	25	NT	25	NT	42	NT
Ticarcillin-Clv	15	5	25	14	48	22	42	28	45	44	37	34
Imipenem	0.1	0	0.3	0	0.2	0	1.2	0	20	17	13	5
Meropenem	0.1	NT	0.5	NT	0.1	NT	0.8	NT	20	NT	25	NT
Amikacin	5	5	13	19	10	6	24	10	25	28	54	55
Gentamicin	28	25	21	27	26	25	42	19	42	45	64	64
Tobramycin	21	NT	32	NT	36	NT	47	NT	39	41	65	NT
Fluoroquinolone	33	31	19	19	12	6	22	9	40	46	58	65
Cotrimoxazole	53	44	31	30	31	29	25	38	94	NT	57	56
Tetracycline	56	NT	23	NT	31	NT	72	NT	95	NT	51	NT

*-, not applicable because of natural resistance.
NT, not tested; CFP, cefoperazone; Sulb, sulbactam; Tazo, tazobactam; Clv, clavulanic acid.

Fig. 1. The resistance trends of staphylococci to oxacillin, and *E. faecium* to ampicillin and vancomycin. Continued high prevalence of oxacillin-resistant staphylococci, ampicillin-resistant *E. faecium*, and a gradual increase of vancomycin-resistant *E. faecium* were observed. OXA, oxacillin; AMP, ampicillin; VAN, vancomycin; R, resistant; SAU, *S. aureus*; CNS, coagulase-negative staphylococci; EFM, *E. faecium*.
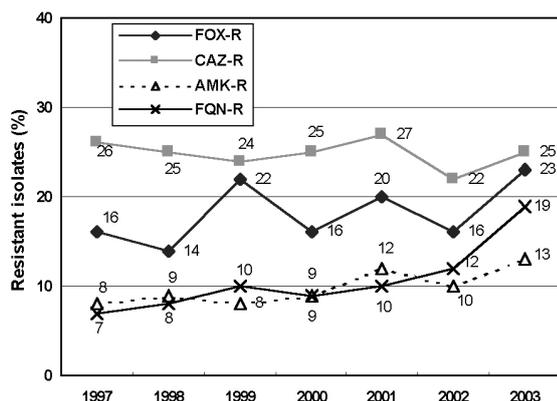
Fig. 2. The resistance trend of *K. pneumoniae* to cefoxitin, ceftazidime, amikacin, and fluoroquinolone. The ceftazidime resistance rate remained high, while a tendency of increasing resistance to other antimicrobial agents was observed. FOX, cefoxitin; CAZ, ceftazidime; AMK, amikacin; FQN, fluoroquinolone.

fluoroquinolone and amikacin resistance rates is apparent in the last several years (Fig. 2). A slight decline of *Acinetobacter* spp. resistance to amikacin, fluoroquinolone, and ceftazidime was noted, but the rates remained over 50% (Fig. 3). Imipenem-resistant *Acinetobacter* spp. gradually increased, reaching 13% in 2003.

Comparing the resistance rates between hospital groups, vancomycin-resistant *E. faecium*, fluoro-quinolone-resistant *E. coli*, and cefoxitin-resistant
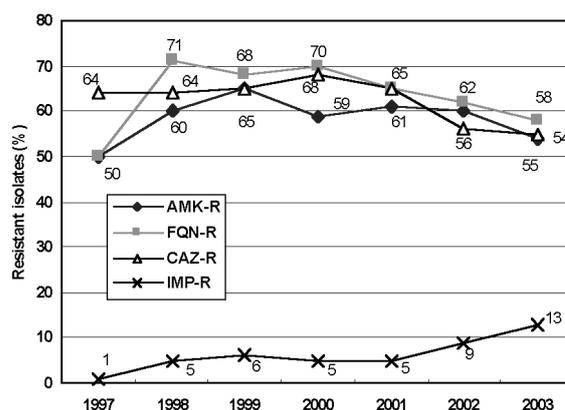
Fig. 3. The resistance trend of *Acinetobacter* spp. to amikacin, fluoroquinolone, and ceftazidime remained high, and a tendency for increasing imipenem-resistance was observed. AMK, amikacin; FQN, fluoroquinolone; CAZ, ceftazidime; IMP, imipenem.

K. pneumoniae were more prevalent at larger hospitals. Large differences in resistance rates were observed between the large hospital group and the commercial laboratory for vancomycin-resistant *E. faecium* (25% and 7%, respectively), and for imipenem-resistant *Acinetobacter* spp. (11% and 5%, respectively) (Fig. 4).
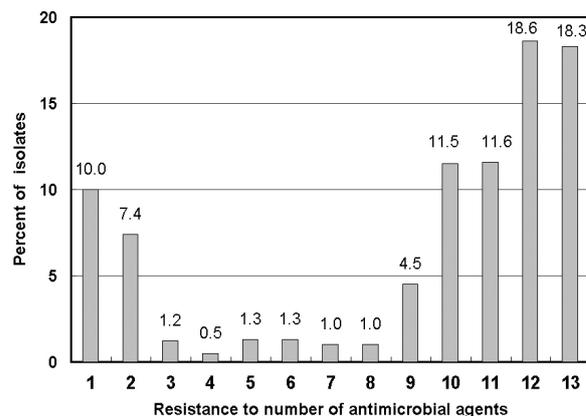
MDR *Acinetobacter* spp.

MDR patterns of *Acinetobacter* spp. to 13 antimicrobial agents were determined excluding duplicate isolates and isolates with less than a 1% pattern (Fig. 5). Among the 925 isolates analyzed, 11.5% were resistant to none of the antimicrobial agents (data not shown), but 18.3% were resistant to all of the drugs, and 11.5%, 11.6% and 18.6% showed MDR to 10, 11, and 12 antimicrobial agents, respectively.

Resistance rates excluding duplicate isolates

Resistance rates were lowered by more than 20% after the exclusion of duplicate isolates from the coordinating laboratory data of the following: clindamycin and cotrimoxazole resistance of *S. aureus*, teicoplanin and vancomycin resistance of *E. faecium*, and ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, cefotaxime, ceftazidime, aztreonam, cefoperazone-sulbactam,
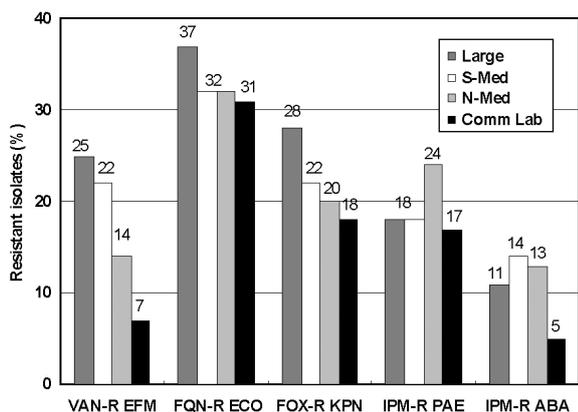
Fig. 4. Antimicrobial resistances of strains isolated at three hospital groups and tested at a commercial laboratory. Resistance rates were generally higher in the large hospital group. Vancomycin-resistant *E. faecium* and imipenem-resistant Acinetobacter spp. were much less prevalent among the commercial laboratory tested strains. S-med, Seoul-medium; N-med, non-Seoul-medium; Comm Lab, commercial laboratory; VAN, vancomycin; FQN, fluoroquinolone; FOX, cefoxitin; IPM, imipenem; EFM, *E. faecium*; ECO, *E. coli*; KPN, *K. pneumoniae*; PAE, *P. aeruginosa*; ABA, *A. baumannii*.

Fig. 5. Multi-resistance of *Acinetobacter* spp. isolated at a tertiary-care hospital. Among the isolates 11.5% were resistant to none of the 13 antimicrobial agents tested, but 18.3% were resistant to all of the agents tested.

cefoxitin, cefotetan, amikacin tobramycin, and ciprofloxacin resistance of *E. coli* (Table 5).

Table 5. Comparison of Resistance Rates Calculated from All Isolates and from the First Isolates per Patient per Year at a Tertiary-care Hospital*

Species	Antimicrobial agent	Resistant isolates (%)		Species	Antimicrobial agent	Resistant isolates (%)	
		All	1st			All	1st
S. aureus		n = 3,723	n = 1,793	*E. coli*	Piperacillin	62	57
	Oxacillin	71	58	(Control)	Ampicillin-sulbactam	31	24
	Penicillin	95	94		Ticarcillin-clavulanate	11	8
	Clindamycin	60	48		Piperacillin-tazobactam	6	4
	Erythromycin	71	61		Cephalothin	40	34
	Cotrimoxazole	18	12		Cefotaxime	11	7
	Tetracycline	52	46		Ceftazidime	8	5
	Ciprofloxacin	66	53		Aztreonam	8	5
					Cefepime	3	3
E. faecium		n = 1,864	n = 1,032		Cefoperazone-sulbactam	3	2
	Ampicillin	97	95		Cefoxitin	10	6
	Tetracycline	9	11		Cefotetan	5	3
	Ciprofloxacin	95	93		Amikacin	9	5
	Teicoplanin	22	15		Gentamicin	31	25
	Vancomycin	29	21		Tobramycin	27	20
					Cotrimoxazole	46	41
E. coli		n = 3,138	n = 2,206		Tetracycline	58	56
	Ampicillin	74	69		Fluoroquinolone	33	25

*Vancomycin- and teicoplanin-resistant *S. aureus* and imipenem- and meropenem-resistant *E. coli* isolates were absent.

DISCUSSION

It is stressed that surveillance is an important part of modern clinical microbiology, because only resistance surveillance can provide the necessary information for empirical selection. For example, it has been suggested that when resistance to a particular drug occurs in >10-20% of isolates, the drug should not be used for empirical treatment.[6] Isolation rank based on the first isolate in a patient has been recommended by NCCLS[12] for reporting laboratory surveillance data, with the primary aim of guiding clinicians in the selection of empirical therapy. However, when only the first isolates are included, resistance selection occurring within the observation period cannot be detected.[6] In our present study, duplicate isolates were included, as in the previous surveillances, because we considered the information gained by including duplicate isolates to be useful for the control of nosocomial infections.

The proportions of each species were very similar in 2002 and 2003: *S. aureus, E. coli, P. aeruginosa,* CNS, and *K. pneumoniae* remained in the same rank order of 1 to 5, respectively. However, at the commercial laboratory, *E. coli, P. aeruginosa,* and *S. aureus* were ranked 1 to 3, respectively. It is difficult to compare the rank orders without knowledge of the specimens, but it can be assumed that the difference was probably due to a relatively low prevalence of nosocomial pathogens at clinics (Table 1).

With the increase in MDR bacteria, limiting susceptibility testing only to a few classes of antimicrobial agents cannot provide sufficient information for patient treatment. However, as in 2002, some laboratories tested susceptibility to only a small number of antimicrobial agents (Table 2). For optimal detection of extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae,* the use of both ceftazidime and cefotaxime is recommended.[16] Due to the increasing prevalence of CTX-M type ESBLs, the concomitant testing of cefotaxime susceptibility is now important in Korea,[17] as in other countries.[18] However, some laboratories tested susceptibility to only one expanded-spectrum cephalosporin, as was the case in 2002. A previous study with collected strains showed a high prevalence of plasmid-mediated AmpC enzyme DHA-1-producing *K. pneumoniae,*[10] indicating the need for susceptibility testing to cefoxitin and cefepime. However, many laboratories did not test for these drugs in 2002 or 2003.

The present surveillance showed that the oxacillin-resistant *S. aureus* (ORSA) and oxacillin-resistant CNS remained very high, at approximately 70% (Fig. 1). This trend is similar to that in Japan.[19] ORSA is now a worldwide problem: the proportions were more than 40% in Greece, Italy, and the United Kingdom in 1999-2002.[20] In the present surveillance, penicillin-non-susceptible pneumococci (based on the breakpoint for the treatment of meningitis) also remained very prevalent as was observed in other Asian countries.[21] Increases in penicillin resistance were also reported in the United States in the 1990s.[22]

The gradual increase of vancomycin-resistant *E. faecium* continued and reached 20% in the hospital groups in 2003 (Fig. 2). The rate was much higher in the large hospital group (25%) than in the smaller non-Seoul hospital group (14%), and was only 7% in the commercial laboratory (Table 4), suggesting the influence of nosocomial dissemination. The higher rate observed at a tertiary-care hospital was partly due to the inclusion of duplicate isolates (Table 5). Difficulties in the control of vancomycin-resistant enterococci were shown by their high prevalence in a U.S. hospital.[23] *E. faecium* increased from 12.7% to 22.2% from 1993 to 2002 among all enterococcal isolates, which included one isolate per patient per month, and vancomycin-resistant isolates increased from 28.9% to 72.4%, respectively.

The high prevalence of ampicillin-resistant *E. coli* (71%) in our study was similar to the rate in Taiwan (78%).[24] The ampicillin resistance rate of *H. influenzae* (53%) was similar to the β-lactamase positive rate of 52% (data not shown). This result suggests that β-lactamase-negative ampicillin-resistant (BNAR) *H. influenzae* remains rare in Korea, although it is a prevalent type in Japan.[25]

The increase in isolates of ampicillin-resistant non-typhoidal *Salmonella* may indicate an increasing prevalence of this resistance in the community, as the infections are more often community-acquired rather than nosocomially-acquired. However, the resistance rates were much

lower than those of *Salmonella enterica* serovar Typhymurium DT104 isolates, which were 34% for both ampicillin and cotrimoxazole.[26] The ciprofloxacin resistance rate was only 0.3%, but this rate probably cannot be used to predict clinical efficacy in the treatment of extraintestinal infections because low-level quinolone resistance cannot be detected by using fluoroquinolones.[16]

E. coli and *K. pneumoniae* often acquire ESBL genes. In this study, 11% of *E. coli* and 25% of *K. pneumoniae* were resistant to cefotaxime and ceftazidime, respectively, suggesting ESBL production. In Korea, TEM-, SHV-, and CTX-M-type ESBLs were previously reported.[17,27] Cefoxitin-resistant *E. coli* (10%) and *K. pneumoniae* (23%) may be partly due to plasmid-mediated AmpC enzymes, such as DHA-1 and CMY-1-like, which are prevalent in Korea.[10] Carbapenems are the only class of β-lactam agents active against strains producing ESBLs and hyperproducing AmpC enzymes.[28] Therefore, the increasing carbapenem resistance in *P. aeruginosa* and *Acinetobacter* spp. is the most serious problem. The imipenem resistance rate of *Acinetobacter* spp. (13%) was lower than that of *P. aeruginosa* (20%), but interestingly, the rate of the former has increased rapidly since 2002 (Fig. 3), while that of the latter remained similar (data not shown). Among the isolates in 2000 and 2001, VIM-2 and IMP-1 MBL genes were detected in *Acinetobacter* isolates, but only the VIM-2 gene was detected in *P. aeruginosa* isolates.[9] Kim et al.[29] tested 116 imipenem-resistant *P. aeruginosa* isolates from 2000 to 2003 at a tertiary-care hospital, and detected 19 (16.4%) VIM-2 gene-positive isolates. These data indicate a wide dissemination of MBL-producing *P. aeruginosa* and *Acinetobacter* spp. A study with 3,233 strains of *P. aeruginosa* isolated at 37 medical institutes in Japan showed an imipenem resistance rate of 19.0%, which was similar to our results, but the rates to all other antimicrobial agents were lower than our results.[30] Jeong et al.[31] reported a VIM-2-producing *E. cloacae* isolate in 2003. In the present study, imipenem-resistant isolates were also present in *K. pneumoniae*, although the proportion was very low.

The resistance of *E. coli* and *K. pneumoniae* to gentamicin and tobramycin in this study were not very high (21% and 32%, respectively). Previously,

amikacin-resistant gram-negative bacilli were very rare. However, the resistance rates of gram-negative bacilli other than *E. coli* were high at 10% to 54% (Table 4), making empirical use of the drug difficult. Fluoroquinolones are frequently used, as they are one of the three major broad-spectrum classes of antimicrobial agents.[32] The fluoroquinolone resistance rate of *E. coli* in 2003 (33%) was similar to that in 2002. We found similar fluoroquinolone resistance rates of *E. coli*, *P. aeruginosa* and *Acinetobacter* spp. at the commercial laboratory and at the hospitals (Table 4), which also suggests the prevalence of this resistance in the community.

It is concerning that *Acinetobacter* spp. isolates are often MDR. Abbo et al.[33] reported that they were unable to clearly define the mode of spreading and the reason for the emergence of MDR *A. baumannii*. Analysis of *Acinetobacter* spp. isolated at the coordinating laboratory showed that 46.2% of the isolates were MDR to 9 to 12 of the 13 antimicrobial agents tested, and 18.3% were panresistant (Fig. 5). MDR and panresistant *Acinetobacter* has been reported in other countries as well.[33,34] In Brazilian hospitals, resistance rates of *Acinetobacter* spp. to carbapenem have reached 12% or higher.[35] Thus, more toxic agents, such as polymyxin, have been used. Consequently, it was found that 5 of 100 *Acinetobacter* blood isolates were resistant to this drug.

Ideally, multi-center surveillance should be representative of all types and sizes of institutions; however, current surveillance tends to include only larger university-affiliated hospitals, which may overrepresent the prevalence of resistance due to the types of patients treated at large hospitals.[36] Accurate resistance surveillance of a community-acquired pathogen was considered to be difficult because of sampling bias. For example, physicians' requests for urine culture have decreased recently, and cultures have been performed relatively more often for patients with failed antimicrobial therapy.[36] In the analysis of surveillance data, making the distinction between nosocomial and community-acquired infections is also difficult.[15] In the present study, as in previous studies, we did not separate community-acquired from nosocomially-acquired strains due to the difficulty of separation. Instead, the resistances of

strains at a commercial laboratory, which were mostly from primary-care clinic patients, were compared to those at hospitals. Our results showed that resistance rates at the commercial laboratory were generally lower, but it was difficult to generalize the resistance patterns.

It is well known that excluding duplicate isolates lowers resistance rates. Lee et al.[37] reported an overestimation of MRSA when duplicate isolates were included. In our analysis of data from a tertiary-care hospital, including only the first isolate/patient/year reduced proportions of ORSA by 18%, vancomycin-resistant *E. faecium* by 28%, and fluoroquinolone-resistant *E. coli* by 24% (Table 5). However, the effect was minimal in the resistance rates to old antimicrobial agents, i.e., penicillin-resistant *S. aureus*, ampicillin-resistant *E. faecium*, and ampicillin- and fluoroquinolone-resistant *E. coli*. When duplicate isolates are excluded from analysis, the emergence of resistance that occurs within the observation period may not be seen, thereby giving an overly optimistic view of the percentage of susceptible strains.[3,6] Also, there could be a question as to the removal period, i.e., 5 days, 30 days, or 365 days.

In conclusion, oxacillin-resistant staphylococci, expanded-spectrum cephalosporin-resistant *K. pneumoniae*, and fluoroquinolone-resistant *E. coli*, *Acinetobacter* spp., and *P. aeruginosa* remain very prevalent in Korea. Vancomycin-resistant *E. faecium*, cefoxitin-resistant *E. coli* and *K. pneumoniae*, and imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. have gradually increased. The resistance rates of *Acinetobacter* spp. to most antimicrobial agents tested at hospitals and at a commercial laboratory were similar, suggesting dissemination of this problematic organism in Korea. Analysis of the data from a tertiary-care hospital showed the prevalence of MDR and panresistant *Acinetobacter* spp. The exclusion of duplicate isolates lowered the proportion of ORSA, vancomycin-resistant *E. faecium*, and fluoroquinolone-resistant *E. coli* significantly. In future surveillances, more useful information could be obtained by determining the resistance trends of problematic antibiotic-bacteria combinations at both hospitals and commercial laboratories. Also, more information could be gained by presenting resistance data that both includes and excludes duplicate isolates.

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