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Korean Nationwide Surveillance of Antimicrobial Resistance of Bacteria in 1997

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Antimicrobial-resistant bacteria are known to be prevalent in tertiary-care hospitals in Korea. Twenty hospitals participated to this surveillance to determine the nationwide prevalence of resistance bacteria in 1997. Seven per cent and 26% of Escherichia coli *and* Klebsiella pneumoniae *were resistant to 3rd-generation cephalosporin. Increased resistance rates, 19% of* Acinetobacter baumannii *to ampicillin/sulbactam, and 17% of* Pseudomonas aeruginosa *to imipenem, were noted. The resistance rate to fluoroquinolone rose to 24% in* E. coli, *56% in* A. baumannii *and 42% in* P. aeruginosa. *Mean resistance rates were similar in all hospital groups: about 17% of* P. aeruginosa *to imipenem, 50% of* Haemophilus influenzae *to ampicillin, 70% of* Staphylococcus aureus *to methicillin, and 70% of pneumococci to penicillin. In conclusion, nosocomial pathogens and problem resistant organisms are prevalent in smaller hospitals too, indicating nosocomial spread is a significant cause of the increasing prevalence of resistant bacteria in Korea.*

Key Words: Antimicrobial resistance, resistance surveillance, resistance in Korea, ESBL, MRSA, VRE, PRP

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A rapid increase of antimicrobial-resistant bacteria has become a serious problem in many countries (Neu, 1992; Chin and Marx, 1994), but the resistance rate may vary significantly depending on the country and even on hospitals due to the extent of antimicrobial selective pressure and the magnitude of cross infection in hospitals (Moellering, 1998). It has been known that antimicrobial-resistant bacteria are relatively more prevalent in Korea (Chong *et al.* 1993). However, as the information is mainly based on the reports from tertiary-care hospitals, it may not reflect the nationwide situation. In a surveillance of antimicrobial resistance of gram-negative bacilli, it was found that the rates in smaller hospitals were not significantly lower than those in larger hospitals (Chong *et al.* 1996).

It has been reported that the extended-spectrum β-lactam-resistance was spreading to species other than *Escherichia coli* and *Klebsiella pneumoniae* (Coudron *et al.* 1997), and that cephamycin-resistant *E. coli* and *K. pneumoniae* (Bauernfeind *et al.* 1997) and imipenem-resistant *Pseudomonas aeruginosa* were increasing (Lee *et al.* 1998b). In the first nationwide surveillance in Korea (Chong *et al.* 1996), *Salmonella* and *Haemophilus influenzae* were not included. Also, despite the problem of methicillin resistance in staphylococci and glycopeptide resistance in enterococci, these organisms were not included.

The aim of this surveillance was to determine the prevalence of resistance among frequently isolated gram-positive and -negative species of bacteria in larger and smaller hospitals located in Seoul and non-Seoul areas in Korea, and to compare some of the results with previous data.

MATERIALS AND METHODS

Routine susceptibility data for strains of *E. coli, K. pneumoniae, Enterobacter cloacae, Serratia marcescens* and nontyphoidal *Salmonella, Acinetobacter baumannii, Stenotrophomonas maltophilia, P. aeruginosa, H. influenzae*, staphylococci, enterococci and pneumococci isolated in 1997 were collected from 20 of 50 hospital laboratories in Korea participating in the program of Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR). The laboratories participated in a group quality control program prior to the collection of the data.

The data were not included for analysis when a hospital tested fewer than 20 isolates of a species, and when the species of enterococci were not identified. Therefore, the number of hospitals whose data for uncommon organisms were analyzed, was: nontyphoidal *Salmonella* 5, *H. influenzae* 7, enterococci 12, pneumococci 13. The hospitals were grouped based on location, bed capacity and number of strains tested: 4 larger hospitals in Seoul and 8 medium-sized ones in Seoul, and 8 hospitals in non-Seoul areas.

The susceptibility testing methods used were MicroScan (Dade MicroScan Inc., West Sacramento, CA), Vitek system (bioMerieux, Marcy-l'Etoile, France), and disk diffusion (NCCLS, 1998). Eight hospitals used broth microdilution tests and 12 used disk diffusion for gram-negative bacilli; 7 used broth microdilution and 13 used disk diffusion for staphylococci. To minimize the influence of a large number of strains tested in larger hospitals to the resistance rates, the mean rates were calculated from the resistance rates in each hospitals. The resistance rates did not include intermediate susceptibility.

For the fluoroquinolone resistance, either ciprofloxacin, ofloxacin, or levofloxacin were used depending on hospitals. Two hospitals used pefloxacin for the testing of staphylococci.

RESULTS

The susceptibility analyzed included the followings: 31,985 isolates of *E. coli, K. pneumoniae, E. cloacae* and *S. marcescens*; 539 nontyphoidal *Salmonella*; 3 species 26,128 glucose nonfermenting gram-negative bacilli; 721 *H. influenzae*; 30,582 staphylococci; 6,702 enterococci; 1,649 pneumococci. Over 90% of laboratories tested susceptibilities to the following antimicrobial agents: for *Enterobacteriaceae* ampicillin, cephalothin, 3rd-generation cephalosporin, amikacin, gentamicin and fluoroquinolone; for *P. aeruginosa* piperacillin, ceftazidime, imipenem, amikacin, gentamicin, tobramycin and fluoroquinolone; for staphylococci oxacillin and erythromycin; for enterococci ampicillin, ciprofloxacin, tetracycline, teicoplanin and vancomycin (Table 1; Data for enterococci not shown).

Among the *E. coli* isolates, over 50% were resistant to ampicillin, piperacillin, cotrimoxazole, and tetracycline, while less than 10% were resistant to 3rd-generation cephalosporin, cefoperazone/sulbactam, cefotetan and amikacin. The resistance rate to fluoroquinolone was 24% (Table 2). Although the resistances of *K. pneumoniae*, *E. cloacae*, *S. marcescens*, *A. baumannii* and *S. maltophilia* to ampicillin, cephalothin or cefoxitin are included in Table 2, some of them are natural resistances. The resistance rates of *K. pneumoniae* were 41% to

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

E. coli		*P. aeruginosa*		Staphylococci	
Antimicrobial agent	No. of Lab	Antimicrobial agent	No. of Lab	Antimicrobial agent	No. of Lab
Ampicillin	20	Carbenicillin	5	Penicillin	16
Piperacillin	12	Piperacillin	18	Oxacillin	19
Ampicillin/sulbactam	7	Ceftazidime	18	Clindamycin	14
Cephalothin	20	Cefoperazone/sulbactam	3	Erythromycin	18
3rd-Gen. cephalosporin	18	Imipenem	18	Fluoroquinolone	14
Cefoperazone/sulbactam	3	Amikacin	20	Cotrimoxazole	8
Cefotetan	8	Gentamicin	19	Tetracycline	8
Cefoxitin	6	Tobramycin	18	Fusidic acid	3
Imipenem	15	Fluoroquinolone	18	Gentamicin	6
Amikacin	19			Teicoplanin	15
Gentamicin	20			Vancomycin	17
Tobramycin	15				
Fluoroquinolone	18				
Cotrimoxazole	12				
Tetracycline	8				

Table 2. Antimicrobial resistance rates of gram-negative bacilli frequently isolated from clinical materials

Antimicrobial agents	% of isolates resistant (No. tested)					
	E. coli (16,971)	*K. pneumoniae* (7,828)	*E. cloacae* (4,607)	*S. marcescens* (2,579)	*A. baumannii* (7,875)	*S. maltophilia* (2,128)
Ampicillin	79	97	95	96	93	99
Piperacillin	57	37	46	47	58	77
Ampicillin/sulbactam	24	30	76	86	19	89
Cephalothin	44	41	96	99	99	99
Cefotaxime	7*	26*	39	34	64	88
Cefoperazone/sulbactam	3	5	20	25	3	14
Cefotetan	3	4	51	29	82	18
Cefoxitin	12	16	95	62	97	96
Amikacin	5	8	16	20	50	72
Gentamicin	33	27	41	55	71	77
Tobramycin	25	29	50	64	73	78
Fluoroquinolone	24	7	13	18	56	15
Cotrimoxazole	57	29	40	46	58	23
Tetracycline	69	29	44	88	70	67

*: Not resistance rate to breakpoint for ESBL-producer, but the highest resistance rate to either cefotaxime, ceftazidime or aztreonam with the use of original breakpoint.

cephalothin, 26% to 3rd-generation cephalosporin, and less than 10% to cefoperazone/sulbactam, cefotetan, amikacin and fluoroquinolone. The resistance rates of *E. cloacae*, *S. marcescens*, *A. baumannii* and *S. maltophilia* were very high to most antimicrobial agents tested. The lowest resistance rates observed were *S. marcescens* to fluoroquinolone, 18%; *A. baumannii* to cefoperazone/sulbactam, 3%; and *S. maltophilia* to cefoperazone/sulbactam, 14%. The resistance rates of nontyphoidal *Salmonella* were 25% to ampicillin, 0.7% to 3rd-generation cephalosporin, 6% to cotrimoxazole and none to fluoroquinolone (Data not shown).

The highest resistance rate of *P. aeruginosa* was to carbenicillin, 64%, while the lowest rate was to cefoperazone/sulbactam, 15%. The resistance rates to ceftazidime and imipenem were 16% and 17%, respectively (Table 3). As to *H. influenzae*, some hospitals tested either ampicillin resistance, or β-lactamase production, while others tested both of them. The rates of ampicillin resistance and β-lactamase-production of *H. influenzae* were 58% and 55%, respectively (Table 4).

Among the *S. aureus* isolates tested, 98% were resistant to penicillin and 72% to oxacillin. The resistance rates were 3% to cotrimoxazole, 8% to fusidic acid and 67% to fluoroquinolone (Table 5). The resistance rates of coagulase-negative staphylococci were 91% to penicillin, 63% to oxacillin, 19% to cotrimoxazole, 28% to fusidic acid and 33% to fluoroquinolone. The resistance rates of *E. faecalis* were 4% to ampicillin, 29% to fluoroquinolone and 1% to vancomycin, while the rates of *E. faecium* were 70% to ampicillin, 65% to fluoroquinolone and 2.9% to vancomycin (Table 6). The rates of intermediate plus resistance of pneumococci to penicillin G by screening method was 75% (Table 7).

It was shown that resistance rates to 3rd-gen-

Table 3. Antimicrobial resistance rates of *P. aeruginosa* by hospital group

Antimicrobial agent	% of isolates resistant by hospital group (No. tested):			
	Seoul-Large (6,136)	Seoul-Medium (5,490)	Non-Seoul (4,499)	Total (16,125)
Carbenicillin	60	NT	64	64
Piperacillin	40	39	51	43
Ticarcillin/clavulanic acid	37	NT	61	49
Aztreonam	22	26	43	30
Ceftazidime	14	14	21	16
Cefoperazone/sulbactam	22	16	8	15
Imipenem	18	16	18	17
Amikacin	26	33	38	33
Gentamicin	42	49	53	49
Isepamicin	30	NT	NT	30
Netilmicin	52	56	60	55
Tobramycin	39	49	53	46
Fluoroquinolone	43	44	41	42

NT: not tested.

Table 4. Antimicrobial resistance rates of *H. influenzae* by hospital group

Antimicrobial agent	% of isolates resistant by hospital group (No. tested):			
	Seoul-Large (565)	Seoul-Medium (27)	Non-Seoul (129)	Total (721)
Ampicillin	69	48	57	58
β-lactamase	55	NT	NT	55

NT: not tested.

eration cephalosporins of *E. coli* were lower than those of *K. pneumoniae*, 7% vs 26%. There were cephamycin-resistant strains in both species (Table 2, Fig. 1). Cefoperazone/sulbactam resistance rates of *E. cloacae*, *S. marcescens*, *A. baumannii* and *S. maltophilia* were lower than those to other cepha-

Table 5. Antimicrobial resistance rates of staphylococci by hospital group

Antimicrobial agent	% of isolates resistant by hospital group (No. tested):							
	S. aureus				Coagulase-negative staphylococci			
	SL (9,874)	SM (5,252)	NS (6,923)	Total (22,049)	SL (3,344)	SM (2,804)	NS (2,385)	Total (8,533)
Penicillin	98	97	98	98	90	93	89	91
Oxacillin	70	71	74	72	54	67	65	63
Clindamycin	60	62	65	63	38	42	41	41
Erythromycin	71	69	76	72	56	59	64	60
Fluoroquinolone	65	64	75	67	31	33	36	33
Cotrimoxazole	1	5	2	3	18	15	37	19
Tetracycline	73	80	79	77	52	64	62	60
Fusidic acid	6	13	NT	8	35	13	NT	28
Gentamicin	68	68	76	72	57	71	55	62
Teicoplanin	0	0.3	0.1	0.2	1	2	2	2
Vancomycin	0	0	0	0	0	0.1	0.2	0.1

SL: Seoul Large; SM: Seoul Medium; NS: non-Seoul; NT: not tested.

Table 6. Antimicrobial resistance rates of enterococci by hospital group

Antimicrobial agent	% of isolates resistant by hospital group (No. tested):							
	E. faecalis				*E. faecium*			
	SL (2,808)	SM (1,202)	NS (1,059)	Total (5,069)	SL (1,048)	SM (475)	NS (110)	Total (1,633)
Ampicillin	4	5	4	4	74	63	89	70
Fluoroquinolone	22	27	37	29	67	59	78	65
Tetracycline	79	85	87	84	44	58	74	57
Teicoplanin	0.3	0.1	0.4	0.2	2.3	0.7	6.0	2.1
Vancomycin	0	0.4	2.7	1.0	1.5	2.1	7.0	2.9

SL: Seoul Large; SM: Seoul Medium; NS: non-Seoul.

Table 7. Antimicrobial resistance rate of pneumococci by hospital group

Antimicrobial agent	% of isolates resistant by hospital group (No. tested):			
	Seoul-Large (981)	Seoul-Medium (454)	Non-Seoul (214)	Total (1,649)
Cotrimoxazole	63	69	83	69
Erythromycin	72	75	65	71
Penicillin G*	76	78	71	75
Tetracycline	64	90	57	78

*: Includes intermediate.

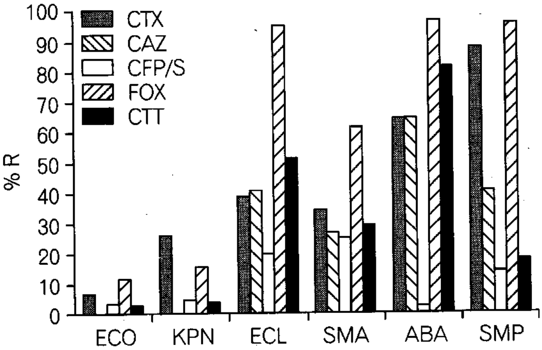

Fig. 1. Comparison of resistance rates of gram-negative bacilli to 3rd-generation cephalosporin, cephamycin and cefoperazone/sulbactam. The resistance rates of E. coli *and* K. pneumoniae *to cefotaxime indicates the highest resistance rates to either cefotaxime, ceftazidime or aztreonam, with use of the original breakpoint for interpretation. Abbreviations: ECO:* E. coli; *KPN:* K. pneumoniae; *ECL:* E. cloacae; *SMA:* S. marcescens; *ABA:* A. baumannii; *SMP:* S. maltophilia; *CTX: cefotaxime; CAZ: ceftazidime; CFP/S: cefoperazone/sulbactam; FOX: cefoxitin; CTT: cefotetan.*

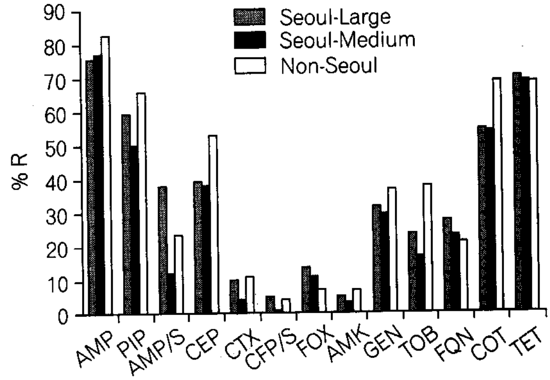

Fig. 2. Comparison of resistance rates of E. coli *by hospital group. The strains isolated in smaller hospitals in Seoul showed slightly lower resistance rates than those isolated in larger hospitals to piperacillin, ampicillin/sulbactam, cefotaxime, and cefoperazone/sulbactam. The strains isolated in non-Seoul hospitals showed slightly higher resistance rates to ampicillin, piperacillin, cephalothin, gentamicin, tobramycin and cotrimoxazole. Abbreviations: AMP: ampicillin; PIP: piperacillin; AMP/S: ampicillin/sulbactam; CEP: cephalothin; AMK: amikacin; GEN: gentamicin; TOB: tobramycin; FQN: fluoroquinolone; COT: cotrimoxazole; TET: tetracycline. For others see Fig. 1.*

losporins and cephamycins.

The mean resistance rates of *E. coli* in the Seoul-larger hospital group were slightly lower than those in the non-Seoul hospital group for ampicillin, piperacillin, cephalothin, gentamicin, tobramycin and cotrimoxazole, while they were slightly higher for ampicillin/sulbactam, cefoxitin, and fluoroquinolone. The rates were similar for cefotaxime, cefoperazone/sulbactam, amikacin and tetracycline (Fig. 2). The resistance rates to piperacillin, ampicillin/sulbactam, cefotaxime, cefoperazone/sulbactam and tobramycin in the Seoul-medium hospital group were lower than those in the other groups.

Fluoroquinolone resistance rates in the Seoul-larger hospital group were slightly higher for *E. coli* and *S. maltophilia*, slightly lower for *E. cloacae* and *A. baumannii*, and similar for *K. pneumoniae* and *P. aeruginosa* (Fig. 3).

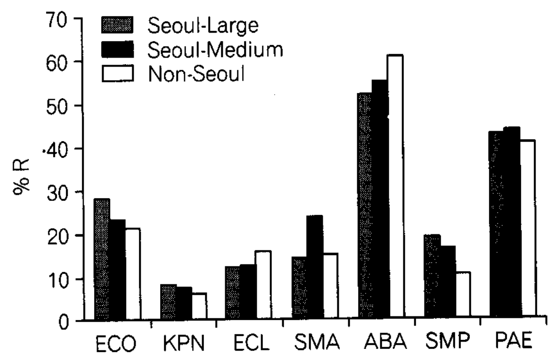

Fig. 3. Comparison of fluoroquinolone-resistance rates by hospital group. The resistance rates of E. coli *and* S. maltophilia *in the Seoul larger hospital group were slightly higher than those in other hospital groups. The resistance rates of* E. cloacae *and* A. baumannii *were slightly higher in the non-Seoul hospital group. Abbreviations: PAE:* P. aeruginosa; *For others see Fig. 1.*

DISCUSSION

A limitation in the surveillance of antimicrobial resistance involving many levels of hospitals is that the resistance rate may be affected due to various factors other than susceptibility test methods used.

All of the hospitals participating in this study used recognized methods of microdilution and disk diffusion, but there should have been some subtle error. It is known that some methods have difficulty in detecting strains with certain mechanisms of resistance (Murray, 1994). The inoculum density particularly affects susceptibility to cell wall active agents (Doern *et al.* 1997).

In the United States, a recent movement to centralize or regionalize the service was predicted to fail if the driving force and single focus was saving money (Mortensen, 1994). Discussions for an organizational change started to appear in Korea, too. However, in Korea, only large tertiary-care hospitals have been providing quality bacteriology service, requiring expansion of the service in smaller hospitals, which can actually reduce medical costs. As more antimicrobial agents became available and as multiresistant bacteria became more prevalent, laboratories should have been able to provide more useful information to clinicians by increasing the kind of antimicrobial agents to be tested (Acar and Goldstein, 1996). However, it was found in this study that among the 20 laboratories surveyed, less than one half tested the susceptibility of *E. coli* to cefoperazone/sulbactam, cephamycin and tetracycline, and of staphylococci to cotrimoxazole, tetracycline and fusidic acid (Table 1). This may have been due partly to cost-saving policies and the use of commercial microbroth dilution test systems produced in foreign countries, which do not include some drugs used in Korea.

The resistance rates of *Enterobacteriaceae, A. baumannii* and *S. maltophilia* to most antimicrobial agents were similar to those in 1994-1995 (Chong *et al.* 1996). When a >5% rise in the resistance rate together with a >10% rise over the rate in 1994-1995 were arbitrarily considered as significant ones, significant rises observed were: *E. coli* to cephalothin; *K. pneumoniae* to cephalothin, 3rd-generation cephalosporin, and cotrimoxazole; *E. cloacae* to gentamicin, cotrimoxazole and tetracycline; *S. marcescens* to cefotaxime and cefoxitin; *A. baumannii* to ampicillin/sulbactam, cefotaxime, gentamicin, tobramycin, fluoroquinolone, cotrimoxazole and tetracycline; *S. maltophilia* to amikacin. A significant rise of resistance rates of *P. aeruginosa* to carbenicillin, ticarcillin/clavulanic acid, aztreonam, imipenem, amikacin and fluoroquinolone was also observed.

ESBL-producing *E. coli* and *K. pneumoniae* started to be recognized in Korea in the late 1980s (Lee *et al.* 1994; Pai *et al.* 1997). The MICs of extended-spectrum β-lactams for ESBL-producing bacteria are often low. Therefore, the original breakpoints underestimate the presence of ESBL-producing strains. In this study, when the original breakpoint was used, the resistance rates were 7% and 26%, respectively for *E. coli* and *K. pneumoniae*. However, in a hospital, the rates were 16% and 38%, respectively.

The resistance rates of *E. coli* and *K. pneumoniae* to cefoperazone/sulbactam and cefotetan were very low, although few laboratories tested the resistance. These drugs are active against ESBL-producing strains. However, persistence of cephamycinase-producing *E. coli* and *K. pneumoniae* were reported in Korea (Bauernfeind *et al.* 1997; Kwon *et al.* 1998). It has recently been reported that plasmid-mediated ESBL resistance was spreading to *E. cloacae* (Lee *et al.* 1998a; Lim *et al.* 1998). Class C β-lactamase-producing gram-negative bacilli, such as *E. cloacae,* are susceptible to 4th-generation cephalosporins, cefpirome and cefepime, but the strains also producing ESBL can be resistant to both 3rd- and 4th-generation cephalosporins. *A. baumannii* strains are often multiresistant with various mechanisms, but are usually susceptible to ampicillin/sulbactam (Livermore, 1995). In this study, the resistance rate to ampicillin/sulbactam became significantly higher than before. Carbapenem is a drug very active even against gram-negative bacilli which are resistant to other β-lactams. Therefore, the emergence of imipenem resistance has been a great concern. In this study, the imipenem resistance rate of *P. aeruginosa* was 17%, which was similar to those to ceftazidime, 16%, and cefoperazone/sulbactam, 15%.

The resistance rates of *E. coli* and *K. pneumoniae* to amikacin remained relatively low, but the rates of *A. baumannii* and *S. maltophilia* were high. Few laboratories tested the resistance of *P. aeruginosa* to isepamicin or netilmicin. The rates were similar to those to amikacin and gentamicin.

Although fluoroquinolones are very active against gram-negative bacilli, a gradual increase of resistance became evident in Korea as well as in other countries (Chong and Lee, 1998). Among the *Enterobacteriaceae* species, *E. coli* were more often resistant to fluoroquinolone. The mean resistance rate was 24% in this study, but in a tertiary-care hospital, the rate was 39%, which was a significant rise from 5% in 1991. An increase in fluoroquinolone-resistant nontyphoidal *Salmonella* was reported in Britain (Threfall *et al.* 1997), but in this study a resistant strain was not present. The fluoroquinolone-resistance rates of *A. baumannii* and *P. aeruginosa* were 56% and 42%, respectively, indicating the drug could not be used reliably without prior susceptibility testing.

In this study, it was found that in some hospitals resistance rates of *Enterobacteriaceae* and glucose-nonfermenting gram-negative bacilli to certain antimicrobial agents were significantly higher than in other hospitals. However, it was evident that resistant bacteria were also prevalent even in smaller hospitals. Also, the ampicillin-resistance rate of *H. influenzae* was not significantly different and it can be estimated that over 50% of the isolates were β-lactamase producers (Table 4).

Prevalence of MRSA varies greatly depending on countries (Voss *et al.* 1994). MRSA has been very prevalent in Korea (Lee and Chong, 1996). In this study, the proportion of methicillin-resistant *S. aureus* and coagulase-negative staphylococci were around 70% and 60%, respectively, in all hospital groups indicating the widespread nature of resistance at all levels of hospitals. In Korea, vancomycin-intermediate *S. aureus* has not yet been reported, but the data from some hospitals showed the presence of glycopeptide-resistant staphylococci, which require investigation for accuracy. Ampicillin-resistant *E. faecalis* was reported from some hospitals, again requiring confirmation. In Italy, ampicillin resistance rates of *E. faecalis* were reported to be 0% to 6.5% depending on hospitals (Fontana *et al.* 1998). The vancomycin-resistance rate was less than 1% until 1997, in Korea (Cheong *et al.* 1998), but a rise of over 2% in the rate in *E. faecium* in this study may indicate a gradual spread of the resistance. Penicillin-nonsusceptible pneumococci has been known to be very prevalent in Korea (Baquero, 1995; Lee *et al.* 1995; Song *et al.* 1997). The rates were over 70% in all hospital groups in this study, again showing widespread resistance.

In conclusion, such nosocomial pathogens as *S. marcesens*, *A. baumannii* and *S. maltophilia*, as well as such problem organisms as 3rd-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, imipenem-resistant *P. aeruginosa*, methicillin-resistant staphylococci, penicillin-nonsusceptible pneumococci are prevalent in smaller Korean hospitals, too. As the nosocomial spread of resistant bacteria should be a significant cause of the prevalence of resistant bacteria in Korea, prudent use of antimicrobial agents alone may not be effective to reduce resistant bacteria, requiring concomitant efforts to prevent the nosocomial spread of resistant bacteria.

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