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Increase in the Prevalence of Carbapenem-Resistant *Acinetobacter* Isolates and Ampicillin-Resistant Non-Typhoidal *Salmonella* Species in Korea: A KONSAR Study Conducted in 2011

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Background: Antimicrobial surveillance is important for providing an up-to-date understanding of the epidemiology of antimicrobial resistance and for creating a forum for rational drug development. In this study, we analyzed antimicrobial test data generated in 2011 by hospitals and commercial laboratories participating in the Korean Nationwide Surveillance of Antimicrobial Resistance program (KONSAR).

Materials and Methods: Data on the results of susceptibility tests conducted in 32 hospitals and two commercial laboratories were analyzed. Data on isolates from patients admitted to an intensive care unit (ICU) and those admitted to other wards were compared. Intermediate susceptibility was not analyzed and duplicate isolates were excluded.

Results: *Escherichia coli* was the most prevalent organism identified in both the hospital and commercial laboratories. Among the hospital isolates, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin G-non-susceptible *Streptococcus pneumoniae*, and ampicillin-resistant *Enterococcus faecium* remained as prevalent as they were in 2009. The proportion of vancomycin-resistant *E. faecium* (VR-EFM) slightly decreased from 29% in 2009 to 23% in 2011. Resistance rates of *Klebsiella pneumoniae* to ceftazidime, cefoxitin, fluoroquinolone, and amikacin were 24%, 14%, 27%, and 8%, respectively. Resistance rates of *Pseudomonas aeruginosa* to fl uoroquinolone, ceftazidime, imipenem, and amikacin were 33%, 20%, 22%, and 16%, respectively, whereas those of *Acinetobacter* spp. resistance were 71%, 66%, 64, and 51%, respectively. The prevalence of oxyimino-cephalosporin-resistant *E. coli* and *K. pneumoniae*, carbapenem-resistant *Acinetobacter* spp. and *P. aeruginosa*, MRSA, and VR-EFM among ICU isolates was higher than those among non-ICU isolates. Extended-spectrum β-lactamase-

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producing *E. coli* and *K. pneumoniae*, imipenem-resistant *P. aeruginosa*, and VR-EFM were more prevalent among isolates from commercial laboratories than those from hospitals. Resistance rates of *K. pneumoniae* to ceftazidime and amikacin decreased from 32% and 24% in 2005 to 24% and 8% in 2011, respectively. The resistance rate of *P. aeruginosa* to amikacin decreased from 22% in 2005 to 16% in 2011. The proportion of imipenem-resistant *Acinetobacter* spp. increased from 16% in 2005 to 64% in 2011.
Conclusions: The prevalence of MRSA, penicillin G-non-susceptible *S. pneumoniae,* and ampicillin-resistant *E. faecium* among clinical isolates tested in laboratories remained high. Multidrug resistance was more prevalent among isolates from ICUs. The prevalence of ceftazidime-resistant and amikacin-resistant *K. pneumoniae* and amikacin-resistant *P. aeruginosa* decreased after 2005, while the prevalence of imipenem-resistant *Acinetobacter* spp. increased.

Key Words: Antimicrobial resistance surveillance; KONSAR; *Staphylococcus; Acinetobacter; Pseudomonas aeruginosa*

Introduction

Over recent years, the increasing prevalence of antimicrobial-resistant bacteria has become a serious problem worldwide. Bacterial surveillance previously conducted in Korea indicated a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin G-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus faecium* (VR-EFM), and extended cephalosporin-resistant Enterobacteriaceae. The recent increase in multidrug-resistant (MDR) *Acinetobacter* spp. and *Pseudomonas aeruginosa*, and carbapenem-resistant *Klebsiella pneumoniae* is of great concern in many countries. The prevalence of resistant bacteria varies substantially from country to country, and even from hospital to hospital, as it is influenced significantly by antimicrobial use and the degree of success of efforts to control the spread of resistant bacteria.

Surveillance of antimicrobial resistance provides essential data that increases our understanding of the epidemiology of antimicrobial resistance and aids in optimizing empirical management regimens, driving pharmaceutical companies to develop new antimicrobial agents, and adopting better measures for controlling antimicrobial resistance. Since 1997, the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) program has conducted passive surveillance via the analysis of data from tests conducted by participating laboratories [1]. A study in 2009 showed a continued high prevalence of MRSA, third-generation cephalosporin-resistant *K. pneumoniae*, and fluoroquinolone-resistant *Escherichia coli*, *P. aeruginosa,* and *Acinetobacter* spp. There was a minor increase in the prevalence of imipenem-resistant *P. aeruginosa*, but there was a dramatic increase in the prevalence of imipenem-resistant *Acinetobacter* spp. MDR microorganisms were much more common among isolates from intensive care units (ICUs) than those from non-ICUs.

The aim of this study was to analyze the antimicrobial resistance patterns of clinically significant bacteria isolated in 2011 in Korea. Resistance rates were compared between isolates from ICUs and those from non-ICUs. Resistance patterns of isolates derived from secondary care hospitals and primary care clinics that did not have clinical microbiology laboratories were provided by two commercial laboratories. Resistance patterns of isolates derived from tertiary care hospitals were also analyzed. The prevalence of colistin resistance was also assessed, due to the increasing prevalence of MDR *Acinetobacter* spp. and *P. aeruginosa*.

Materials and Methods

Antimicrobial susceptibility test data generated in 2011 by KONSAR-participating laboratories were collected from 32 hospitals and two commercial laboratories, which processed specimens at the request of secondary care hospitals and primary care clinics. Data from hospitals with poor quality performance, such as those indicating susceptibility to intrinsically resistant antimicrobials, were excluded. Resistance patterns of clinically significant microorganisms isolated from ICU patients were compared to organisms isolated from non-ICU patients using data from 20 hospitals.

Questionnaire responses revealed that one laboratory tested the susceptibility of *E. coli* (representing Gram-negative bacilli) and *S. aureus* (representing gram-positive cocci) using Clinical and Laboratory Standards Institute (CLSI) disk diffusion [2], while 25 laboratories used commercial broth microdilution. One laboratory used both methods. Cefotaxime and ceftazidime susceptibility was interpreted using previous CLSI [2] breakpoints. For *S. pneumoniae,* the oxacillin disk method with meningitis breakpoint was used to screen penicillin G-

non-susceptible isolates [3].

The majority of laboratories used WHONET software [4] to analyze susceptibility data. Duplicate isolates were excluded from the analysis. As in the 2009 study [5], resistance rates did not include intermediate susceptibility and mean resistance rates were calculated by averaging hospital resistance rates to avoid the influence of high numbers of isolates from large hospitals. Hospitals that tested fewer than 10 isolates of an organism were excluded from the analysis to avoid bias [6, 7]. The statistical significance of differences between resistance rates was not determined in this surveillance as this has been a common feature of large-scale and continuous surveillance programs [8, 9].

Among the hospital laboratories that participated in the study, 22 modified the measured susceptibility results of cefotaxime/ceftriaxone, ceftazidime, cefepime, and aztreonam if the *E. coli* and *K. pneumoniae* isolates tested were extended-spectrum β-lactamase (ESBL) producers [2, 3]. We therefore compared unmodified resistance rates for these antibiotics from the remaining five hospital laboratories with data from the previous KONSAR studies in order to maintain data consistency.

Results

1. Prevalence of bacterial species

In 2011, 164,686 bacterial isolates were tested in participating hospitals and 72,119 in participating commercial laboratories (Table 1). The most prevalent bacterial species detected in hospital laboratories were as follows: *E. coli* (22.7%), *S. aureus* (16.6%), coagulase-negative staphylococci (CNS, 11.9%), *K. pneumoniae* (10%), and *P. aeruginosa* (9.1%). The most prevalent bacterial species detected in commercial laboratories were as follows: *E. coli* (27.3%), *P. aeruginosa* (12.7%), *S. aureus* (12.3%), *K. pneumoniae* (11.5%), and CNS (9.1%) (Table 1). The bacterial species most often isolated from the ICUs of 20 hospitals were as follows: *S. aureus* (21.6%), *Acinetobacter* spp. (18.9%), CNS (12.8%), *P. aeruginosa* (10.7%), and *K. pneumoniae* (10.2%) (data not shown).

2. Antimicrobial resistance of hospital isolates

Antimicrobial resistance rates among gram-positive cocci are shown in Table 2. The resistance rates of *S. aureus* were 66% to oxacillin/cefoxitin and 59% to clindamycin. A total of 3% of *E. faecalis* isolates were resistance to ampicillin and 1.2% to vancomycin. Among *E. faecium* isolates, 92% were resistant to ampicillin and 23% to vancomycin. Of 2,750 *S. pneumoniae* isolates, 70% were resistant to penicillin G.

The antimicrobial resistance rates of isolated Gram-negative bacilli are shown in Table 3. Of the *E. coli* isolates, 68% were resistant to ampicillin, 8% to cefoxitin, 6% to piperacillin-tazobactam, 1% to amikacin, 36% to ciprofloxacin/levofloxacin, and 35% to trimethoprim-sulfamethoxazole. Of *E. coli* isolates from the five hospitals where provide unmodified resistance

Table 1. Number, proportion, and rank by frequency of clinically important bacteria isolated in 2011

Bacteria	Hospitals		Commercial laboratories	
	No. (%) of isolates	Rank	No. (%) of isolates	Rank
Escherichia coli	37,308 (22.7)	1	19,654 (27.3)	1
Klebsiella pneumoniae	16,404 (10)	4	8,264 (11.5)	4
Enterobacter cloacae	4,499 (2.7)	9	1,573 (2.2)	11
Serratia marcescens	2,577 (1.6)	12	2,736 (3.8)	8
Stenotrophomonas maltophilia	3,393 (2.1)	10	1,813 (2.5)	10
Acinetobacter spp.	11,671 (7.1)	7	5,431 (7.5)	6
Pseudomonas aeruginosa	15,032 (9.1)	5	9,127 (12.7)	2
Haemophilus influenzae	976 (0.6)	13	23 (0.03)	14
Non–typhoidal *Salmonella*	560 (0.3)	14	99 (0.1)	13
Staphylococcus aureus	27,314 (16.6)	2	8,841 (12.3)	3
Coagulase–negative staphylococci	19,574 (11.9)	3	6,594 (9.1)	5
Enterococcus faecalis	12,916 (7.8)	6	5,394 (7.5)	7
Enterococcus faecium	9,757 (5.9)	8	1,984 (2.8)	9
Streptococcus pneumoniae	2,750 (1.7)	11	586 (0.8)	12
Total	164,686 (100)		72,119 (100)	

Table 2. Antimicrobial resistance rates (number tested) of clinically important Gram–positive cocci isolated at hospitals and tested at commercial laboratories in 2011

Antimicrobial agents	*Staphylococcus aureus*[a]		Coagulase–negative staphylococci[a]		*Enterococcus faecalis*		*Enterococcus faecium*		*Streptococcus pneumoniae*	
	HOSP (27,314)	CM (8,841)	HOSP (19,574)	CM (6,594)	HOSP (12,916)	CM (5,394)	HOSP (9,757)	CM (1,984)	HOSP (2,750)	CM (586)
Penicillin/AMP[a]	96	96	93	93	3	NT	92	90	70[b]	64[c]
Oxacillin/FOX	66	66	73	70	–	–	–	–	85[c]	NT
Gentamicin	47	49	40	28	–	–	–	–	–	–
Ciprofloxacin/LEV	51	50	40	32	28	32	92	89	6	10
Clindamycin	59	56	38	33	–	–	–	–	66	NT
Erythromycin	60	58	56	55	68	75	88	90	74	78
Trimethoprim–sulfamethoxazole	2	NT	28	NT	–	–	–	–	53	NT
Tetracycline	51	50	28	26	85	89	33	30	73	77
Teicoplanin	0.01	0	0.15	1.4	1.2	0.8	18	24	–	–
Vancomycin	0	0	0.01	0	1.2	1.3	23	27	–	–
Quinupristin–dalfopristin	0.04	0.2	0.2	0.2	–	–	1.2	1.5	–	–
Linezolid	0.03	0.5	0.06	0.5	0.5	0.9	0.4	1.2	–	–

HOSP, hospital laboratory; CM, commercial laboratory; AMP, ampicillin; FOX, cefoxitin; LEV, levofloxacin; NT, not tested; –, not applicable.
[a] Penicillin G resistance for *Staphylococcus* spp., and ampicillin resistance for *Enterococcus* spp.
[b] Penicillin G resistance by MIC determination with meningitis breakpoint.
[c] Oxacillin disk screening to predict penicillin G resistance with meningitis breakpoint [3].

rates, 17% were resistant to cefotaxime/ceftriaxone, 8% to ceftazidime and cefepime, and 10% to aztreonam. Of the *E. coli* isolates tested in hospitals laboratories, 20% were ESBL producers.

Resistance rates of *K. pneumoniae* were 14% to cefoxitin, 15% to piperacillin-tazobactam, 8% to amikacin, 27% to ciprofloxacin/levofloxacin, and 22% to trimethoprim-sulfamethoxazole. The prevalence of ESBL-producing *K. pneumoniae* was 32%. Table 3 shows that resistance rates of *K. pneumoniae* isolates sampled from five hospitals that adopted the 2010 CLSI guidelines were 24% to cefotaxime/ceftriaxone and ceftazidime, 17% to cefepime, and 25% to aztreonam.

Resistance rates of *Enterobacter cloacae* and *Serratia marcescens* were 31% and 14% to ceftazidime, respectively, 7% and 8% to cefepime, respectively, 3% and 9% to amikacin, respectively, and 8% and 14% to fluoroquinolones (ciprofloxacin or levofloxacin), respectively. The resistance rates of *Acinetobacter* spp. were 55% to ampicillin-sulbactam, 66% to cefepime, 64% to imipenem, 51% to amikacin, and 71% to ciprofloxacin/levofloxacin. The resistance rates of *P. aeruginosa* were 20% to ceftazidime, 22% to imipenem, 16% to amikacin, and 33% to ciprofloxacin/levofloxacin.

The resistance rates of 560 non-typhoidal *Salmonella* isolates were 36% to ampicillin, 1% to ciprofloxacin/levofloxacin, and 2.6% to trimethoprim-sulfamethoxazole (data not shown). Among 928 *H. influenzae* isolates, 53% were resistant to ampicillin. The resistance rates of *Stenotrophomonas maltophilia* were 42% to ceftazidime, 8% to ciprofloxacin/levofloxacin, and 8% to trimethoprim-sulfamethoxazole.

3. Antimicrobial resistance rates of commercial laboratory-tested isolates

The resistance rates of *S. aureus* isolates tested in commercial laboratories were 66% to oxacillin/cefoxitin and 56% to clindamycin (Table 2). The resistance rates of *E. faecium* were 90% to ampicillin and 27% to vancomycin. Of 586 *S. pneumoniae* isolates tested in commercial laboratories, 64% were resistant to penicillin G according to the CLSI meningitis breakpoints.

Resistance rates of *E. coli* were 70% to ampicillin, 10% to cefoxitin, 8% to piperacillin-tazobactam, 2% to amikacin, and 44% to ciprofloxacin/levofloxacin (Table 3). Of the *E. coli* strains isolated in commercial laboratories, 28% were ESBL producers.

Table 3. Antimicrobial resistance rates (number tested) of clinically important Gram–negative bacilli isolated at hospitals and tested at commercial laboratories in 2011[a]

Antimicrobial agents	*Escherichia coli*		*Klebsiella pneumoniae*		*Enterobacter cloacae*		*Serratia marcescens*		*Acinetbacter* spp.		*Pseudomonas aeruginosa*	
	HOSP (37,308)	CM (19,654)	HOSP (16,404)	CM (8,264)	HOSP (4,499)	CML (1,573)	HOSP (2,577)	CM (2,736)	HOSP (11,671)	CM (5,431)	HOSP (15,032)	CM (9,127)
Ampicillin	68	70	–	–	–	–	–	–	–	–	–	–
Ampicillin–SUL	34	NT	37	NT	–	–	–	–	55	46	–	–
Cephalothin/CFZ	31	36	38	52	–	–	–	–	–	–	–	–
Cefotaxime/CRO	17	–	24	–	33	11	24	25	70	70	80	98
Ceftazidime	8	–	24	–	31	19	14	8	66	68	20	28
Cefepime	8	–	17	–	7	5	8	6	66	61	20	29
Aztreonam	10	–	25	–	29	14	17	20	80	76	21	28
Cefoxitin	8	10	14	25	–	–	–	–	–	–	–	–
Piperacillin	65	67	99	100	38	33	27	39	67	71	29	42
Piperacillin–TAZ	6	8	15	32	24	15	11	10	66	69	25	40
Imipenem	0.1	0.01	0.4	0.3	0.3	0.3	2	0.6	64	59	22	38
Meropenem	0.04	0.01	0.4	0.3	0.1	0.2	1	0.3	63	58	19	28
Amikacin	1	2	8	20	3	4	9	13	51	13	16	27
Gentamicin	27	32	17	27	11	10	17	29	67	65	25	36
Tobramycin	12	16	22	39	16	20	23	39	57	55	22	33
Ciprofloxacin/LEV	36	44	27	35	8	12	14	10	71	70	33	52
Trimethoprim-sulfamethoxazole	35	NT	22	NT	19	NT	11	NT	63	NT	–	–
Tetracycline	43	NT	18	NT	12	NT	56	NT	40	NT	–	–
Minocycline	–	–	–	–	–	–	–	–	3	3	–	–
Colistin	–	–	–	–	–	–	–	–	1.9	2.6	1.8	5

HOSP, hospital laboratory; CM, commercial laboratory.; SUL, sulbactam; CFZ, cefazolin; CRO, ceftriaxone; TAZ, tazobactam; LEV, levofloxacin; NT, not tested; –, not applicable.

[a] Number of isolates tested are shown in parentheses.

Additional data: ESBL–positive rates for *E. coli*: 20% for hospitals and 28% for commercial laboratory isolates; ESBL–positive rates for *K. pneumoniae*: 32% for hospitals and 46% for commercial laboratory isolates.

The resistance rates of *K. pneumoniae* were 52% to cephalothin/cefazolin, 25% to cefoxitin, 32% to piperacillin-tazobactam, 20% to amikacin, and 35% to ciprofloxacin/levofloxacin (Table 3). Of *K. pneumoniae* isolates, 46% were ESBL-positive. The resistance rates of *E. cloacae* and *S. marcescens* were 19% and 8% to ceftazidime, respectively, 5% and 6% to cefepime, respectively, 4% and 13% to amikacin, respectively, and 12% and 10% to ciprofloxacin/levofloxacin, respectively.

The resistance rates of *Acinetobacter* spp. were 46% to ampicillin-sulbactam, 61% to cefepime, 59% to imipenem, 13% to amikacin, and 70% to ciprofloxacin/levofloxacin. The resistance rates of *P. aeruginosa* were 28% to ceftazidime, 38% to imipenem, 27% to amikacin, and 52% to ciprofloxacin/levofloxacin.

The resistance rates of 99 non-typhoidal *Salmonella* isolates tested in commercial laboratories were 45% to ampicillin and 0% to ciprofloxacin/levofloxacin (data not shown). Among 23 *H. influenzae* isolates, 48% were resistant to ampicillin. The resistance rates of *S. maltophilia* were 22% to ceftazidime and 15% to ciprofloxacin/levofloxacin.

4. Resistance rates of isolates from ICU and non-ICU patients

The prevalences of antimicrobial-resistant microorganisms isolated from ICU patients vs. non-ICU patients from 20 hospitals are shown in Figure 1. Prevalences of cefotaxime-resistant *E. coli*, ceftazidime-resistant *K. pneumoniae*, imipenem-resistant *Acinetobacter* spp., imipenem-resistant *P. aeruginosa*, oxacillin-resistant *S. aureus*, and VR-EFM from ICU patients was

almost two-fold higher than those from non-ICU patients.

5. Resistance rates of isolates sampled from both hospital and commercial laboratories

Figure 2 shows the resistance rates of bacterial isolates tested in both hospital and commercial laboratories. ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, imipenem-resistant *P. aeruginosa*, and VR-EFM were more prevalent among isolates tested by commercial laboratories than those tested by hospitals. However, imipenem-resistant *Acinetobacter* spp. was more prevalent in hospital isolates than in commercial laboratory isolates. The proportion of *S. aureus* isolates that were oxacillin-resistant was 66% in both hospital and commercial laboratories.

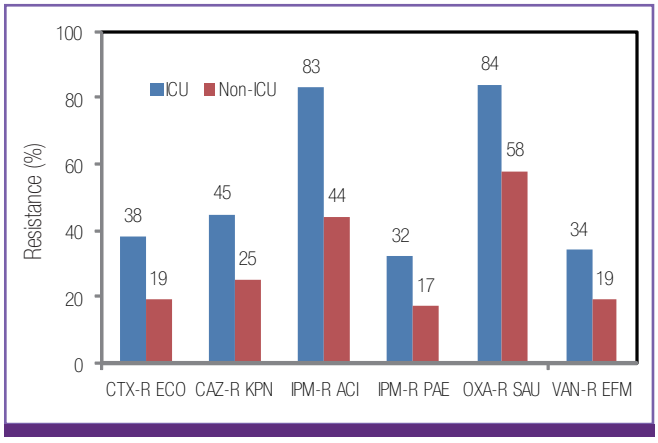

Figure 1. Prevalence of antimicrobial-microorganism combinations detected in isolates from ICU and non-ICU patients in 20 hospitals.
CTX-R ECO, cefotaxime-resistant *E. coli*; CAZ-R KPN, ceftazidime-resistant *K. pneumoniae*; IPM-R ACI, imipenem-resistant *Acinetobacter* spp.; IPM-R PAE, imipenem-resistant *P. aeruginosa*; OXA-R SAU, oxacillin/cefoxitin-resistant *S. aureus*; VAN-R EFM, vancomycin-resistant *E. faecium*.

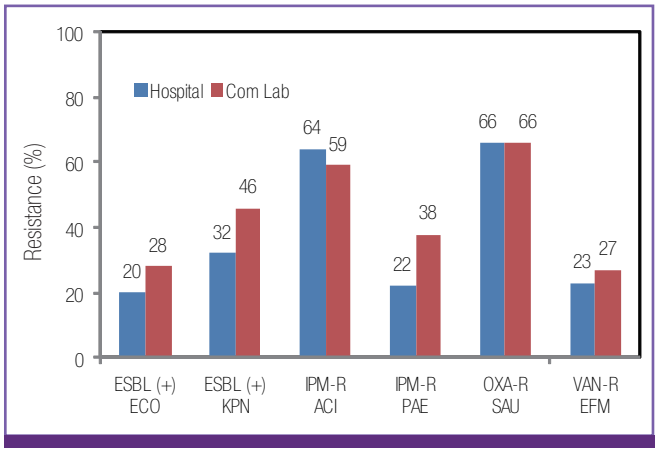

Figure 2. Resistance rates of isolates tested by hospitals and commercial laboratories.
ESBL (+) ECO, ESBL-producing *E. coli*; ESBL (+) KPN, ESBL-producing *K. pneumoniae*; IPM-R ACI, imipenem-resistant *Acinetobacter* spp.; IMP-R PAE, imipenem-resistant *P. aeruginosa*; OXA-R SAU, oxacillin-resistant *S. aureus*; VAN-R EFM, vancomycin-resistant *E. faecium*.

6. Trends in resistance

Trends in antimicrobial resistance patterns in hospital isolates were compared between 2005 and 2011 as, since 2005, duplicate isolates have been excluded in resistance rate calculations. MRSA, penicillin G-nonsusceptible *S. pneumoniae*, and ampicillin-resistant *E. faecium* remained highly prevalent among the 2011 samples (Fig. 3). The proportion of VR-EFM

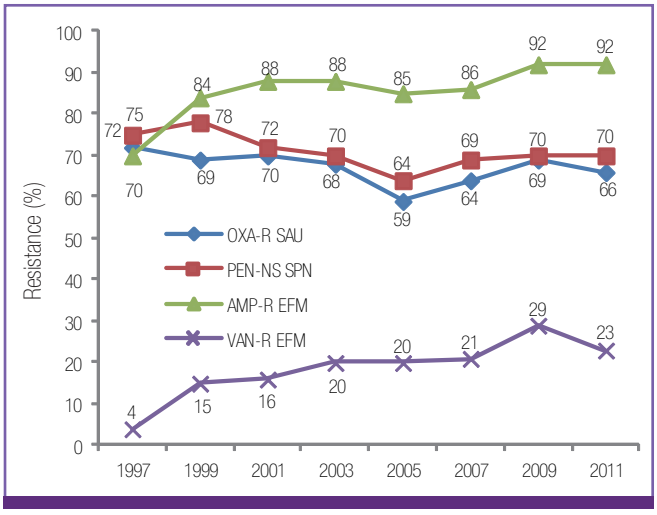

Figure 3. Trends in resistance of clinically significant Gram-positive cocci isolated from 1997 to 2011 from KONSAR-participating hospitals.
OXA-R SAU, oxacillin/cefoxitin-resistant *S. aureus*; PEN-NS SPN, penicillin G-nonsusceptible *S. pneumoniae*; AMP-R EFM, ampicillin-resistant *E. faecium*; VAN-R EFM, vancomycin-resistant *E. faecium*.

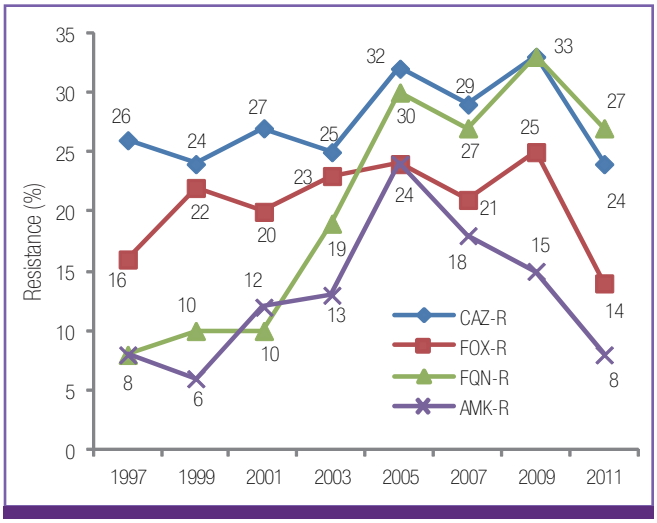

Figure 4. Trends in resistance of *K. pneumoniae* samples isolated from 1997 to 2011 from KONSAR-participating hospitals.
CAZ-R, ceftazidime resistance; FOX-R, cefoxitin resistance; FQN-R, fluoroquinolone resistance; AMK-R, amikacin resistance.

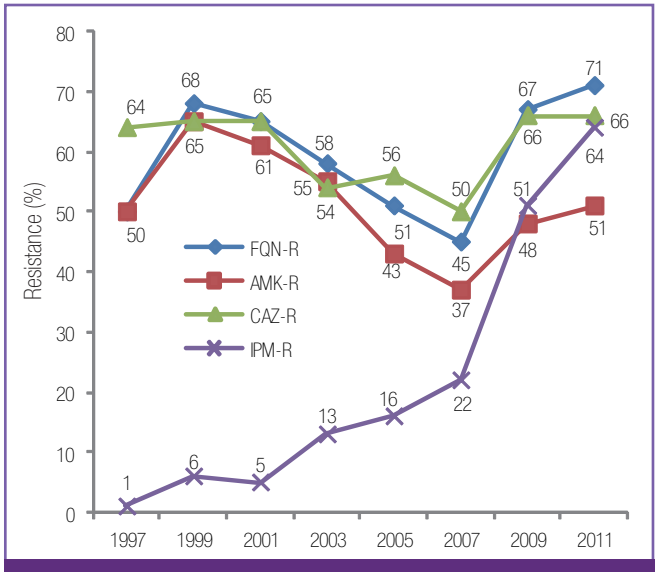

Figure 5. Trends in resistance of *Acinetobacter* spp. isolated from 1997 to 2011 from KONSAR-participating hospitals.
FQN-R, fluoroquinolone resistance; AMK-R, amikacin resistance; CAZ-R, ceftazidime resistance; IPM-R, imipenem resistance.

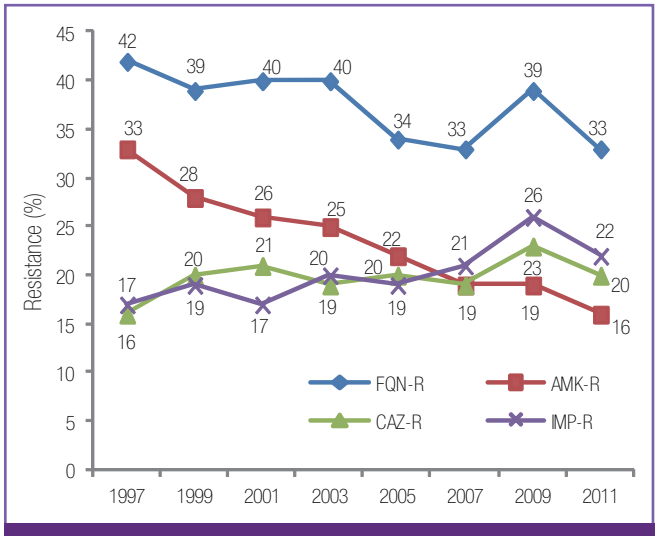

Figure 6. Trends in resistance of *P. aeruginosa* samples isolated from 1997 to 2011 from KONSAR-participating hospitals.
FQN-R, fluoroquinolone resistance; AMK-R, amikacin resistance; CAZ-R, ceftazidime resistance; IPM-R, imipenem resistance.

gradually increased from 20% in 2005 to 29% in 2009, but decreased to 23% in 2011.

Of the Gram-negative bacilli, *K. pneumoniae* resistance to ceftazidime decreased from 32% in 2005 to 24% in 2011, resistance to cefoxitin decreased from 24% in 2005 to 14% in 2011 (Fig. 4), and resistance to amikacin decreased from 24% in 2005 to 8% in 2011.

From 2005 to 2011, resistance rates of *Acinetobacter* spp. to fluoroquinolone increased from 51% to 71%, to amikacin increased from 43% to 51%, and to ceftazidime increased from 56% to 66% (Fig. 5). The proportion of imipenem-resistant isolates steadily increased from 16% in 2005 to 22% in 2007, and to 64% in 2011.

The resistance rates of *P. aeruginosa* to fluoroquinolone and ceftazidime were 33-39% and 19-23% in 2005-2011 (Fig. 6). However, the rate of amikacin resistance decreased from 22% in 2005 to 16% in 2011 and the rate of imipenem resistance slightly increased from 19% in 2005 to 26% in 2009 and then decreased to 22% in 2011 among *P. aeruginosa* isolates.

Discussion

The prevalence of antibiotic-resistant bacteria varies significantly by time, country, and patient population. Antimicrobial resistance surveillance studies are important for monitoring the levels of endemic or emerging resistance. This KONSAR study report showed that the majority of hospital laboratories used commercial broth microdilution methods for *E. coli* (Gram-negative) and *S. aureus* (Gram positive) susceptibility testing.

In terms of laboratory analysis of susceptibility data, the CLSI [10] recommends including only the first isolate in cases of multiple isolates from a single patient, in order to effectively guide clinicians in the empirical selection of appropriate antimicrobial agents. In this study, we excluded duplicate isolates. However, excluding duplicate isolates may have the effect of underestimating the resistance rates of some organisms to certain antimicrobial agents, especially when this analysis is conducted only once a year. To detect the development of resistance during antimicrobial therapy, the CLSI [3] recommends susceptibility testing to third-generation cephalosporins in *Enterobacter*, *Citrobacter*, and *Serratia* spp. isolates obtained three to four days after initial isolation. *P. aeruginosa* should be tested for susceptibility to all antimicrobial agents; and staphylococci should be tested for susceptibility to fluoroquinolones.

Although the commercial laboratory isolates included bacterial strains originating from hospitals, we tried to separate and compare the hospital and commercial laboratory isolates in order to follow up trends in each MDR microorganisms to make comparisons with previous KONSAR studies. In 2011, *E. coli*, *S. aureus*, CNS, *K. pneumoniae*, and *P. aeruginosa* were the five most prevalent organisms isolated by hospitals (Table 1). Compared with 2009 data, the relative prevalences of *K.*

pneumoniae and *P. aeruginosa* changed. In 2009, *K. pneumoniae* was the fifth most prevalent and *P. aeruginosa* the fourth most prevalent bacterial species isolated. Among the commercial laboratory isolates, *E. coli*, *P. aeruginosa*, *S. aureus, K. pneumoniae* and CNS (in order of decreasing prevalence) were the most commonly isolated. *E. faecalis* was the seventh most common in 2011 but fifth in 2009. Among ICU isolates, *S. aureus*, *Acinetobacter* spp., CNS, *P. aeruginosa*, and *K. pneumoniae* were the five most commonly isolated microorganisms. EARSS/EARS-Net data from 2011 (www.ecdc.europa.eu) showed that *E. coli* was the most prevalent species, accounting for 73% (344,700 of 471,596) of bacterial isolates, followed by *K. pneumoniae* (16%, 74,985 isolates) and *P. aeruginosa* (11%, 51,911 isolates). These data are similar to our results.

Antimicrobial pressure is much higher on ICUs than on general wards [11, 12]. Analysis of ICU data from 20 hospitals in this study showed that extended-spectrum cephalosporin-resistant *E. coli* and *K. pneumoniae*, imipenem-resistant *Acinetobacter* spp. and *P. aeruginosa*, oxacillin/cefoxitin-resistant *S. aureus*, and VR-EFM were more prevalent among ICU isolates than non-ICU isolates (Fig. 1). A comparison of resistance in ICU isolates analyzed in this study with data from an international study showed that rates of MRSA and piperacillin-resistant *P. aeruginosa* were similar to rates from regions outside the United States: 84% and 84.1% for MRSA, and 84% and 78% for piperacillin-resistant *P. aeruginosa* [13].

In Korea, hospital-associated MRSA is a serious problem. In this study, the prevalence of MRSA was 66% in both hospital- and commercial laboratory-tested isolates (Table 2, Fig. 2). Of the invasive *S. aureus* isolates reported in the 2011 EARS-Net data, 54.6% of 1,307 *S. aureus* isolates from Portugal, 20.1% of 4,716 isolates from France, and 13.6% of 3,408 isolates from the United Kingdom were non-susceptible to oxacillin (www.ecdc.europa.eu).

Vancomycin-resistant enterococci are also important Gram-positive nosocomial pathogens (Table 2). In this study, vancomycin resistance was 1.2% for hospital-isolated *E. faecalis* and 23% for hospital-isolated *E. faecium*. In 2011, the resistance rates of vancomycin in Denmark, Finland, and France were found to be ≤ 1%, while the rates in Germany and Greece were 11% and 23%, respectively (www.ecdc.europa.eu). The European report also showed that resistance rates varied by hospital, even within countries.

Commercial laboratory-tested *E. faecium* isolates showed slightly higher resistance rates to teicoplanin and vancomycin than isolates tested in hospital laboratories (Table 2, Fig. 1). These data suggest that the prevalence of nosocomial VR-EFM infection was common in participating secondary care hospitals and primary care clinics.

Interestingly, the resistance rates of *E. coli* and *K. pneumoniae* to cephalothin/cefazolin, piperacillin-tazobactam, amikacin, and ciprofloxacin/levofloxacin were lower among hospital isolates than among commercial laboratory isolates (Table 3). In 2011, the CLSI [3] lowered the resistance breakpoints of cefotaxime to ≥ 4 μg/mL, ceftazidime to ≥ 16 μg/mL, and aztreonam to ≥ 16 μg/mL. The CLSI also eliminated the requirement for ESBL testing of *E. coli*, *K. pneumoniae* spp., and *P. mirabilis*. In this study, only five hospitals followed these guidelines, with the remaining hospitals testing for ESBL production. The rates of ESBL-positivity were slightly lower for hospital-isolated *E. coli* and *K. pneumoniae* than for commercial laboratory-tested isolates (Table 3, Fig. 2). The resistance rates of hospital-isolated *E. cloacae* and *S. marcescens* to cefotaxime, ceftazidime, and piperacillin-tazobactam were higher compared to those of isolates tested in commercial laboratories.

Currently, resistance to carbapenems is the most worrying type of antimicrobial resistance. Carbapenem resistance among *Acinetobacter* spp. was higher than that among *P. aeruginosa* (Table 3, Fig. 5, Fig. 6). Resistance to imipenem was higher in hospital-tested *Acinetobacter* spp. isolates than in commercial laboratory-tested isolates (Table 3, Fig. 2). In this study, 22% of hospital-isolated *P. aeruginosa* were resistant to imipenem. This is much higher than the 5.5% observed in Denmark and 4.6% in the Netherlands, but lower than the 66.7% found in Romania (www.ecdc.europa.eu). The imipenem resistance rate of *P. aeruginosa* isolates tested in hospital laboratories was lower than for isolates tested in commercial laboratories.

Ampicillin resistance among hospital-isolated non-typhoidal *Salmonella* spp. substantially increased from 20% in 2009 [14] to 36% in 2011 (data not shown). Resistance rates differed significantly depending on the hospital, ranging from 3% to 83%. These data indicate the presence of local outbreaks in some settings. In this study, 53% of hospital isolates and 48% of commercial laboratory isolates of *H. influenzae* were resistant to ampicillin, suggesting stability, since previous data were 58.5% in 2005 and 2006 [15].

The prevalence of imipenem-resistant *P. aeruginosa* decreased slightly between 2009 and 2011, while imipenem resistance in *Acinetobacter* spp. increased (Fig. 5 and 6). According to previous KONSAR studies, imipenem resistance rates among *P. aeruginosa* isolates were 19% in 2005, 26% in

2009, and 22% in 2011. Among *Acinetobacter* spp., resistance rates were 16% in 2005, 51% in 2009, and 64% in 2011. The drastic increase in the prevalence of imipenem-resistant *Acinetobacter* spp. is mostly due to OXA-type carbapenemase production. Almost all carbapenem-resistant *A. baumannii* carried $bla_{\text{OXA-23}}$-like or IS*Aba1*-activated $bla_{\text{OXA-51}}$-like genes, while most non-*baumannii Acinetobacter* carried metallo-β-lactamase genes [16].

Colistin-resistant *A. baumannii* isolates have previously been detected in Korea [17]. While colistin-resistance rates in *Acinetobacter* spp. isolated in Korea vary substantially between studies [18], colistin susceptibility must be included in surveillance studies because colistin is the last resort for treatment of MDR *Acinetobacter* spp. infections [19]. In this study, the colistin resistance rate in hospital-isolated *Acinetobacter* spp. was less than 2%, which was significantly lower than previous reports of 30.6% [17] and 9.1% [20].

The emergence of antibiotic resistance is inevitable and therefore efforts to decrease the impact of resistance and prolong the effectiveness of available agents are required. For this reason, surveillance of antimicrobial resistance must continue, in order to determine trends in emerging resistant organisms in Korea such as OXA-48 and OXA-232-producing Gram-negative bacilli [21, 22].

In conclusion, this KONSAR study of data collected in 2011 showed that among bacteria isolated in hospital laboratories, the prevalence of ciprofloxacin/levofloxacin resistance and amikacin resistance in *Acinetobacter* spp. increased; imipenem resistance also increased substantially in this microorganism. The prevalence of carbapenem-resistant, amikacin-resistant, ceftazidime-resistant, and ciprofloxacin/levofloxacin-resistant *P. aeruginosa*, and ceftazidime-resistant, ciprofloxacin/levofloxacin-resistant, amikacin-resistant, and cefoxitin-resistant *K. pneumoniae* decreased compared with data from 2009. MDR organisms were much more common among isolates taken from ICUs.

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References

1. Chong Y, Lee K, Park YJ, Jeon DS, Lee MH, Kim MY, Chang CH, Kim EC, Lee NY, Kim HS, Kang ES, Cho HC, Paik IK, Lee HS, Jang SJ, Park AJ, Cha YJ, Kang SH, Lee MH, Song W, Shin JH. Korean nationwide surveillance of antimicrobial resistance of bacteria in 1997. Yonsei Med J 1998;39:569-77.
2. Clinical and Laboratory Standards Institute.. Performance standards for antimicrobial susceptibility testing; nineteenth informational supplement M100-S19. Wayne, PA: CLSI; 2009.
3. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-first informational supplement. CLSI document M100-S21. Wayne, PA: CLSI; 2011.
4. O'Brien TF, Stelling JM. WHONET: removing obstacles to the full use of information about antimicrobial resistance. Diagn Microbiol Infect Dis 1996;25:162-8.
5. Lee K, Lee MA, Lee CH, Lee J, Roh KH, Kim S, Kim JJ, Koh E, Yong D, Chong Y ; KONSAR Group. Increase of ceftazidime- and fluoroquinolone-resistant *Klebsiella pneumoniae* and imipenem-resistant *Acinetobacter* spp. in Korea: analysis of KONSAR study data from 2005 and 2007. Yonsei Med J 2010;51:901-11.
6. Fridkin SK, Hill HA, Volkova NV, Edwards JR, Lawton RM,

Gaynes RP, McGowan JE Jr; Intensive Care Antimicrobial Resistance Epidemiology Project Hospitals. Temporal changes in prevalence of antimicrobial resistance in 23 US hospitals. Emerg Infect Dis 2002;8:697-701.
7. Van Beneden CA, Lexau C, Baughman W, Barnes B, Bennett N, Cassidy PM, Pass M, Gelling L, Barrett NL, Zell ER, Whitney CG. Aggregated antibiograms and monitoring of drug-resistant *Streptococcus pneumoniae*. Emerg Infect Dis 2003;9:1089-95.
8. Sahm DF, Marsilio MK, Piazza G. Antimicrobial resistance in key bloodstream bacterial isolates: electronic surveillance with the Surveillance Network Database--USA. Clin Infect Dis 1999;29:259-63.
9. Felmingham D, Grüneberg RN. The Alexander Project 1996-1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. J Antimicrob Chemother 2000;45:191-203.
10. Clinical and Laboratory Standards Institute. Analysis and presentation of cumulative antimicrobial susceptibility test data; approved guideline-Third Edition, M39-A3. Wayne, PA: CLSI; 2008.
11. Zhanel GG, DeCorby M, Laing N, Weshnoweski B, Vashisht R, Tailor F, Nichol KA, Wierzbowski A, Baudry PJ, Karlowsky JA, Lagacé-Wiens P, Walkty A, McCracken M, Mulvey MR, Johnson J, Canadian Antimicrobial Resistance Alliance (CARA), Hoban DJ. Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005-2006. Antimicrob Agents Chemother 2008;52:1430-7.
12. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003;289:885-8.
13. Rosenthal VD, Maki DG, Jamulitrat S, Medeiros EA, Todi SK, Gomez DY, Leblebicioglu H, Abu Khader I, Miranda Novales MG, Berba R, Ramírez Wong FM, Barkat A, Pino OR, Dueñas L, Mitrev Z, Bijie H, Gurskis V, Kanj SS, Mapp T, Hidalgo RF, Ben Jaballah N, Raka L, Gikas A, Ahmed A, Thu le TA, Guzmán Siritt ME; INICC Members. International Nosocomial Infection Control Consortium (INICC) report, data summary for 2003-2008, issued June 2009. Am J Infect Control 2010;38:95-104, e2.
14. Lee K, Kim MN, Kim JS, Hong HL, Kang JO, Shin JH, Park YJ, Yong D, Jeong SH, Chong Y; KONSAR Group. Further increases in carbapenem-, amikacin-, and fluoroquinolone-resistant isolates of *Acinetobacter* spp. and *P. aeruginosa* in Korea: KONSAR study 2009. Yonsei Med J 2011;52:793-802.
15. Bae S, Lee J, Lee J, Kim E, Lee S, Yu J, Kang Y. Antimicrobial resistance in *Haemophilus influenzae* respiratory tract isolates in Korea: results of a nationwide acute respiratory infections surveillance. Antimicrob Agents Chemother 2010;54:65-71.
16. Lee K, Kim MN, Choi TY, Cho SE, Lee S, Whang DH, Yong D, Chong Y, Woodford N, Livermore DM. Wide dissemination of OXA-type carbapenemases in clinical *Acinetobacter* spp. isolates from South Korea. Int J Antimicrob Agents 2009;33:520-4.
17. Ko KS, Suh JY, Kwon KT, Jung SI, Park KH, Kang CI, Chung DR, Peck KR, Song JH. High rates of resistance to colistin and polymyxin B in subgroups of *Acinetobacter baumannii* isolates from Korea. J Antimicrob Chemother 2007;60:1163-7.
18. Lee K, Yong D, Jeong SH, Chong Y. Multidrug-resistant *Acinetobacter* spp.: increasingly problematic nosocomial pathogens. Yonsei Med J 2011;52:879-91.
19. Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of Acinetobacter baumannii: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 2012;67:1607-15.
20. Sung H, Choi SJ, Yoo S, Kim MN. *In vitro* antimicrobial synergy against imipenem-resistant *Acinetobacter baumannii*. Korean J Lab Med 2007;27:111-7.
21. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. J Antimicrob Chemother 2012;67:1597-606.
22. Potron A, Rondinaud E, Poirel L, Belmonte O, Boyer S, Camiade S, Nordmann P. Genetic and biochemical characterisation of OXA-232, a carbapenem-hydrolysing class D β-lactamase from Enterobacteriaceae. Int J Antimicrob Agents 2013;41:325-9.