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Original Article

Korean Nationwide Surveillance of Antimicrobial Resistance in 2000 with Special Reference to Vancomycin Resistance in Enterococci, and Expanded-Spectrum Cephalosporin and Imipenem Resistance in Gram-Negative Bacilli

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Antimicrobial resistance surveillance is necessary to determine the size of the problem and to guide empirical selection of antimicrobial agents for treating infected patients. The aim of this study was to analyze the results of susceptibility tests performed by hospitals participating in the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) program. The rates of oxacillin-resistant staphylococci, penicillin-non-susceptible pneumococci, and ampicillin-resistant *E. faecium* were over 70%. Ampicillin-resistant *H. influenzae* increased to 68%. Expanded-spectrum cephalosporin-resistant *K. pneumoniae*, fluoroquinolone-resistant *E. coli*, and imipenem-resistant *P. aeruginosa* remained at 16% through 27%, depending on the species. The proportions of vancomycin- resistant *E. faecium* and imipenem-resistant *P. aeruginosa* were 18 - 24% and 19-21%, respectively, indicating the seriousness of antimicrobial resistance. In conclusion, the increasing prevalence of resistant bacteria indicates that more concerted effort is required to conserve the usefulness of precious new antimicrobial agents.

Key Words: Antimicrobial resistance, Korean resistance surveillance, pathogenic bacteria

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INTRODUCTION

Increasing antimicrobial resistance of bacteria is a worldwide problem. The effects of antimicrobial resistance range from the failure of an individual patient to respond to therapy and changes needed in empirical therapy to increases in prescription costs, hospital stay, and the social costs of morbidity and mortality from infection.[1] Antimicrobial resistance surveillance became more important with an increase of resistant bacteria. The major reasons for surveillance are to determine the size of the problem, to see whether resistance is increasing, to detect any previously unknown types of resistance, and to determine whether any particular type of resistance is spreading or associated with an outbreak.[1]

Some resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin G-non-susceptible pneumococci, and extended-spectrum β-lactamase-producing gram-negative bacilli, have been relatively more prevalent in Korea.[2-4] Recent studies in a Korean hospital revealed a rapid rise in vancomycin-resistant enterococci[5] and presence of metallo-β-lactamase-producing gram-negative bacilli.[6,7]

Previous surveillances in Korea showed high prevalence of expanded-spectrum (3rd generation) cephalosporin resistance in *Klebsiella pneumoniae*, and fluoroquinolone resistance in *Escherichia coli*, *Acinetobacter* spp., and *Pseudomonas aeruginosa*.[8-10]

Increase of vancomycin-resistant *Enterococcus faecium* and imipenem-resistant *P. aeruginosa*[10] were new trends observed in nearly all participating hospitals. Longitudinal investigation of resistance trends was most beneficial in detecting subtle changes in resistance.[11]

In this study, routine susceptibility test data for 2000 in Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) program participating hospitals with different sizes and locations were analyzed to determine the persistence of some of the serious resistances and identify the trend of new resistances.

MATERIALS AND METHODS

Participating hospitals

The susceptibility test data for five and eight important species or groups of gram-positive cocci and gram-negative bacilli, respectively, were collected from 33 of 68 KONSAR hospitals in 2000. The KONSAR hospital laboratories have been voluntarily participating in a WHO/CDC-organized quality control program to improve performance. After excluding data from hospitals with unacceptable quality control performance, data from 23 hospitals were analyzed. When a hospital tested less than 20 isolates of a species, the data were also excluded from the analysis.

Susceptibility testing and analysis

For susceptibility testing, the laboratories used either the NCCLS disk diffusion method[12] or commercial broth microdilution systems, i.e., Vitek (bioMerieux, Marcy l'Etoile, France) or MicroScan (Dade MicroScan Inc., West Sacramento, CA, U.S.A.). The resistance rates did not include those in the intermediate category. Penicillin G-non-susceptible pneumococci were mostly screened by using oxacillin disks.[12] The hospitals were divided into three groups according to size and location, i.e., hospitals with ≥1000 beds, those with <1000 beds in Seoul, and those with <1000 beds in non-Seoul region. The mean resistance rates in each group were calculated from the resistance rates in each hospital to minimize the influence of large numbers of isolates in some hospitals.

The resistance rates were compared to those of previous years and among hospital groups to identify important trends. We did not determine the statistical significance of the difference in resistance rates, as it changes depending on the statistical method used,[13] and as clustering is a phenomenon of infectious processes.[14]

RESULTS

The surveillance showed that among the 122,244 isolates of bacteria tested, the following were relatively more prevalent, and thus having more clinical impact: *S. aureus* (22.1%), coagulase-negative staphylococci (10.7%), enterococci (8.9%), *E. coli* (17.4%), *K. pneumoniae* (9.0%), *P. aeruginosa* (14.1%), and *Acinetobacter* spp. (8.0%). Among the enterococci, the proportions of *E. faecalis* and *E. faecium* were 63.9% and 36.1%, respectively.

The resistance rate of gram-positive cocci are shown in Table 1. The methicillin resistance rates, determined by using oxacillin disks, were 70% for both *S. aureus* and coagulase-negative staphylococci. The resistance rate of *S. aureus* to cotrimoxazole was 6%, but the rates to all other antimicrobial agents were high, except to vancomycin. The rate of penicillin-non-susceptible pneumococci was 76%. The resistance rates of *E. faecalis* and *E. faecium* were 2% and 87% to ampicillin, and 0.9% and 20% to vancomycin, respectively.

The resistance rates of gram-negative bacilli are shown in Table 2. Among the *E. coli* isolates, 73% were resistant to ampicillin. The resistance rates to cephalothin and piperacillin were 39% to 57%, but those to cefepime were 3% to 10%, depending on the species in the family *Enterobacteriaceae*. The resistance rates of *E. coli* and *K. pneumoniae* were 6% and 25% to ceftazidime, and 5% and 16% to cefoxitin, respectively. The resistance rates of *E. cloacae* to ceftazidime and cefotaxime were 43% and 35%, respectively, and those of *S. marcescens* were 17% and 27%, respectively. The resistance rates to other antimicrobial agents were highly variable depending on the species: 29% to 41% to gentamicin, 5% to 21% to amikacin, 41% to 49%

Table 1. Antimicrobial Resistance of *Staphylococcus, S. pneumoniae* and *Enterococcus* Isolated in 2000

Antimicrobial agents	Resistance rate (%)				
	S. aureus (26,987)	C-N Staphylococci[a] (13,050)	*S. pneumoniae* (2,285)	*E. faecalis* (6,914)	*E. faecium* (3,912)
Oxacillin	70	70	76	-	-
Ampicillin	-[b]	-	-	2	87
Erythromycin	74	59	78	84	96
Cotrimoxazole	6	45	-	-	-
Tetracycline	66	49	-	82	35
Gentamicin	73	66	-	-	-
Ciprofloxacin	64	32	-	43	86
Vancomycin	0	0.04	-	0.9	20

[a]C-N, coagulase-negative.
[b]-, not tested.

Table 2. Antimicrobial Resistance of Gram-Negative Bacilli Isolated in 2000

Antimicrobial agents	Resistance rate (%)					
	E. coli (21,268)	*K. pneumoniae* (11,051)	*E. cloacae* (4,536)	*S. marcescens* (3,839)	*Acinetobacter* spp. (9,836)	*P. aeruginosa* (17,204)
Ampicillin	73	-[b]	-	-	-	-
Ampicillin-sulbactam	33	33	-	-	30	-
Cephalothin	39	42	-	-	-	-
Cefotaxime	7	15	35	27	68	-
Ceftazidime	6	25	43	17	68	19
Cefepime	3	7	2	10	58	18
Cefoxitin	9	16	-	-	-	-
Piperacillin	57	42	53	39	73	39
Piperacillin-tazobactam	4	12	23	21	57	28
Imipenem	0	0	0.5	1.3	5	20
Amikacin	5	9	12	21	59	32
Gentamicin	29	29	37	41	70	44
Fluoroquinolone[a]	27	9	10	18	70	42
Cotrimoxazole	49	41	42	43	67	-
Tetracycline	64	28	43	89	70	-

[a]Ciprofloxacin, ofloxacin or levofloxacin was used for the test.
[b]-, not tested.

to cotrimoxazole, and 28% to 89% to tetracycline. Fluoroquinolone resistance rate was relatively high for *E. coli*, 27%, but the rates were between 9 and 18% for other species in the family *Enterobacteriaceae*, 42% for *P. aeruginosa*, and 70% for *Acinetobacter* spp.

The resistance rate of non-typhoidal *Salmonella* to ampicillin was 25% (data not shown). The susceptibility of *H. influenzae*, which were tested by some of the hospitals, showed that ampicillin resistance rate was 68%; most of them were due to β-lactamase production (data not shown).

The resistance rates of *Acinetobacter* spp. to imipenem and ampicillin-sulbactam were 5% and

30%, respectively, and those to other drugs were between 57 and 73%. The resistance rates of *P. aeruginosa* were 18% to cefepime, 19% to ceftazidime, and 20% to imipenem (Table 2).

Comparison of the resistance rates in this study to previous years showed that the resistance rates of *S. aureus* to oxacillin (MRSA) and erythromycin, and that of pneumococci to penicillin remained ≥ 70% (Fig. 1). We observed a steady rise in the resistance rate of *E. faecium* to ampicillin: from 70% in 1997 to 87% in 2000. In addition, *E. faecium* resistance to vancomycin rose from 4% in 1997 to 20% in 2000.

The resistance rates of *E. coli* to fluoroquinolone, *K. pneumoniae* to ceftazidime and cefoxitin, and *Acinetobacter* spp. to imipenem remained similar (Fig. 2). The resistance rate of *H. influenzae* to ampicillin steadily rose from 58% in 1997 to 68% in 2000.

The vancomycin resistance rate of *E. faecium* was slightly lower in large hospitals in 1997, but was higher in non-Seoul medium hospitals in 2000 (Fig. 3). The resistance rates of *P. aeruginosa* to ceftazidime and imipenem remained similar during the last four years, and the rates did not differ significantly in the three groups of hospitals (Fig. 4).

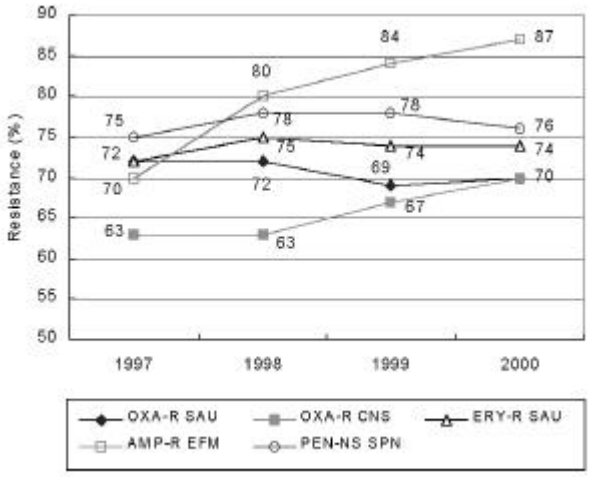

Fig. 1. Trend of antimicrobial resistance of gram-positive cocci during 1997 to 2000. OXA-R SAU, oxacillin-resistant *S. aureus*; OXA-R CNS, oxacillin-resistant coagulase- negative staphylococci; ERY-R SAU, erythromycin-resistant *S. aureus*; AMP-R EFM, ampicillin-resistant *E. faecium*; PEN-NS SPN, penicillin-nonsusceptible *S. pneumoniae*.

DISCUSSION

Surveillance for resistance has been stressed as an important part of modern clinical microbiology,[11] although the limited number of studies linking surveillance to reduction in antibiotic resistance, most of which relate to effective antibiotic policy implementation, questions its clinical and financial benefits.

It was reported that surveillance methods are often inappropriate.[1] Surveillance by collecting data from each laboratory has many problems due

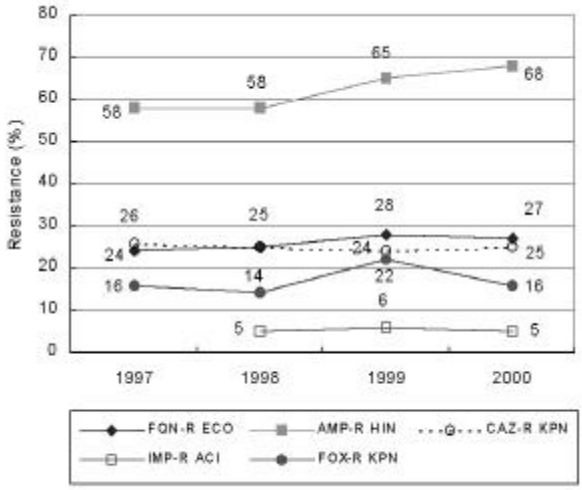

Fig. 2. Trend of antimicrobial resistance of gram-negative bacilli during 1997 to 2000. FQN-R ECO, fluoroquinolone-resistant *E. coli*; AMP-R HIN, ampicillin-resistant *H. influenzae*; CAZ-R KPN, ceftazidime-resistant *K. pneumoniae*; IMP-R ACI, imipenem-resistant *Acinetobacter* spp.; FOX-R KPN, cefoxitin-resistant *K. pneumoniae*.

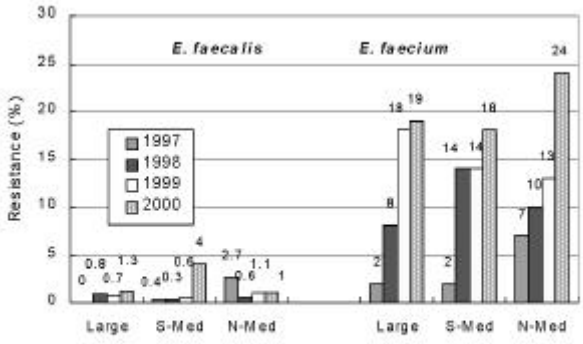

Fig. 3. Rates of vancomycin resistance of enterococci in different groups of hospitals. S-Med, Seoul medium hospitals; N-Med, non-Seoul medium hospitals.

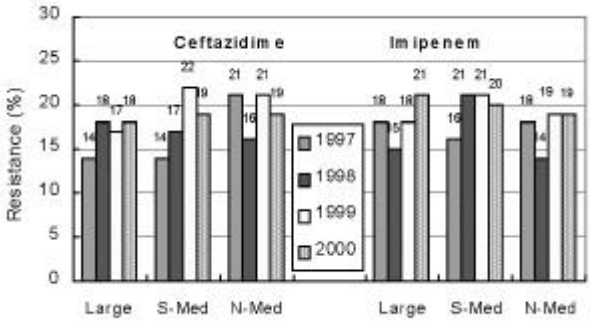

Fig. 4. Rates of ceftazidime and imipenem resistance of *P. aeruginosa* in different groups of hospitals. Abbreviations: see Fig. 3.

to the use of different methods of species identification and of susceptibility testing. Although this surveillance method has inherent limitations, it is the easiest and less costly method.

More accurate results can be obtained when isolates are collected and tested at a central laboratory.[11] However, this method is very expensive. The current KONSAR program consists of two different studies: an analysis of routine susceptibility test data determined by individual participating hospital laboratories, and confirmation of the species and susceptibility of isolates collected from the hospitals.

The need to improve current surveillance methods has been a topic of discussion.[1] Aside from problems in the accuracy of identifying species and testing susceptibility, analytical methods, such as separating community acquired and nosocomial infections, can also change the resistance rate significantly. The inclusion of multiple isolates from the same patient can also detect resistance, which was developed during treatment, but increases the resistance rate.

Resistance surveillance can provide essential information for the empirical selection of antimicrobial agents.[15] *In vitro* resistance undoubtedly increases morbidity, mortality, and costs.[16] Mosdell, et al.[17] showed that the incidence of complications increased approximately 2-fold if empirical therapy for intra-abdominal sepsis failed to cover all the pathogens subsequently isolated. Similar results were also reported in blood stream infections.[18]

Antimicrobial selection for treating infections usually begins with empirical selection. Therefore, surveillance is needed to determine current resistance with which empirical selection of optimal antimicrobial agents is possible. The WHO recommends empirical use of drugs, which are active against at least 80% of the local *Shigella* isolates.[19] This guideline cannot be applied to all infections because the clinical effectiveness of an antimicrobial agent depends not only on the susceptibility of a pathogen, but also on many host factors. It was reported that, in the therapy of blood stream infections, the susceptibility data had less impact on the interventions than gram staining results,[20] indicating the necessity of rapid laboratory reports.

Antimicrobial resistance is a worldwide problem except in a few countries in Northern Europe.[21] Fridkin, et al.[13] reported that antimicrobial resistance was increasing in nearly all healthcare associated pathogens, even in the United States where they have much improved measures to control nosocomial infections. We have been hoping that the National Health Insurance Program, which abolished over-the-counter sales of antimicribial agents and increased scrutiny on the proper use of antimicrobial agents at hospitals, could reduce resistance.

The high proportion of *S. aureus* (22.1%) among all the isolates tested in this study reflects the prevalence of the infection. MRSA is one of the typical nosocomial pathogens.[22] The resistance rate of *S. aureus* to oxacillin has been high for many years in Korea,[2] as is the case in some other Asian countries such as Japan.[23] In this study, the proportions of MRSA were only slightly lower in non-Seoul medium hospitals than in large hospitals (65% vs. 72%), indicating a wide dissemination of the resistance throughout the country. The resistance rate of coagulase-negative staphylococci was slightly lower than that of *S. aureus* until 1998, probably due to inappropriate NCCLS breakpoint subsequently revised in 1999.[12] It is also a concern that resistance rates of coagulase-negative staphylococci to oxacillin is similar to that of *S. aureus*, as this opportunistic pathogen is a major cause of hospital-acquired bacteremia.[24] The more active drug against MRSA was cotrimoxazole, except for vancomycin, but the clinical utility of this drug is not apparent.

Pneumococci are a major cause of community-

acquired lower respiratory infections.[25] The penicillin-non-susceptible rate of pneumococci was only slightly lower in the medium-size hospitals (74%) than large hospitals (81%), indicating that penicillin-non-susceptible isolates are widespread in the community. Penicillin-non-susceptible pneumococcal pneumonia responds to treatment with β-lactams. However, meningitis caused by such isolates is refractory to β-lactam therapy.[25]

The proportion of ampicillin-resistant *E. faecalis* was 2%, which was higher than 0% observed at the coordinating laboratory of the KONSAR program. Differentiation of enterococcal species is not always easy. It was considered that ampicillin-resistant *E. faecalis* was probably due to misidentification of the species.[1]

Other important reasons for surveillance include controlling the spread of resistance.[15] We experienced with MRSA and penicillin-nonsusceptible pneumococci, that once resistant organisms became highly prevalent, it was impossible to control them. Once resistance genes accumulated in the environment, it is considered to be impossible to eliminate them.[26] Moreover, selective pressure can result from other than antimicrobial use in humans and animals. A possible accumulation and dissemination of *vanA* gene was reported through disposal of waste derived from production of vancomycin.[27] Vancomycin-resistant *E. faecium* has significantly increased since 1998 (Fig. 3). Contrary to the common notion that vancomycin-resistant enterococcal infection is prevalent among severely ill patients in large hospitals, the vancomycin-resistance rate of *E. faecium* in 2000 was higher in non-Seoul medium hospitals than in large tertiary-care hospitals, indicating wide dissemination of the resistance in all types of Korean hospitals. The increasing resistance of *E. faecium* to vancomycin, despite heightened efforts to control infection, is a cause of concern.[5]

Ampicillin has been a commonly used antimicrobial agent to treat various infections due to certain species of *Enterobacteriaceae*. The high resistance rate of *E. coli* to this drug, however, indicates empirical selection is now more difficult. *H. influenzae* and pneumococci are frequent causes of bacterial meningitis.[28] The resistance rate of *H. influenzae* to ampicillin rose even higher, to 68%, in 2000. Considering the prevalence of penicillin-non-susceptible pneumococci and ampicillin-resistant *H. influenzae*, ampicillin is no more useful for the empirical treatment of bacterial meningitis. The resistance rate of non-typhoidal *Salmonella* to ampicillin was 25%, while that to cotrimoxazole was 4.7% and to ciprofloxacin was 0% (data not shown). The antimicrobial treatment of gastroenteritis due to non-typhoidal *Salmonella* is not always indicated,[29] but when empirical antimicrobial treatment is required, cotrimoxazole or ciprofloxacin should be considered the appropriate first-line drugs.

Fluoroquinolones are one of the three major broad-spectrum classes of antimicrobial agents, with increasing use for an ever broadening number of indications.[30] Fluoroquinolone resistance rate of *E. coli*, 27% in 2000, was similar to 24% in 1997, but the rate of *Acinetobacter* spp., 70% (Table 2), was much higher than 56% in 1997.[8]

Expanded-spectrum cephalosporins are ineffective for treating infections due to ESBL-producing isolates of *E. coli* and *K. pneumoniae*, although some of them are inhibited by low concentrations of these drugs.[31] Therefore, the ceftazidime resistance rates may not accurately reflect the rate of ESBL producers and clinical efficacy. A high prevalence of ESBL-producing and plasmid-mediated AmpC β-lactamase-producing isolates were reported in Korea.[4,32] In this study, the rates of ceftazidime and cefoxitin resistance were much higher for *K. pneumoniae* than for *E. coli*, suggesting more prevalence of ESBL- or plasmid-mediated AmpC β-lactamase-producing strains in this species (Table 2). *K. pneumoniae* was considered to have an ability to capture resistance genes more easily than other species. Cephamycins, such as cefoxitin, are active against ESBL-producing isolates, but plasmid-mediated AmpC β-lactamase-producing isolates are resistant not only to third-generation cephalosporins but also to cephamycins.[32]

Carbapenems are very useful drugs as they are stable to hydrolysis even to ESBL and AmpC β-lactamases.[33] Therefore, the increase in imipenem-resistant gram-negative bacilli is cause for concern. The resistance rates of *P. aeruginosa* to ceftazidime and imipenem were similar in this study (Fig. 4). In a study, 8.7% of the imipenem-resis-

tant *P. aeruginosa* were due to the production of acquired metallo-β-lactamase, VIM, genes of which were transferable.[6]

P. aeruginosa and *Acinetobacter* spp. are typical nosocomial pathogens with multi-drug resistance. This study showed that imipenem-resistant *P. aeruginosa* has spread to all hospitals regardless of size and location (Fig. 4).

Imipenem-resistant isolates of species in the family *Enterobacteriaceae* were extremely rare, and the rate of *Acinetobacter* spp. remained low at 5% in this study (Table 2). However, the imipenem resistance rate of *Acinetobacter* spp. at the coordinating laboratory rose to 13% in 2002, and a previous study showed that 50% of the imipenem-resistant isolates had the VIM-2 or IMP-1 metallo-β-lactamase gene.[7] Continued monitoring of the *Acinetobacter* spp. resistance to imipenem in other KONSAR hospitals is necessary.

In conclusion, the continued prevalence of methicillin-resistant staphylococci, penicillin-non-susceptible pneumococci, ampicillin-resistant *E. faecium* and *H. influenzae*, expanded-spectrum cephalosporin-resistant gram-negative bacilli, together with recent increases in vancomycin-resistant *E. faecium*, fluoroquinolone-resistant gram-negative bacilli, and imipenem-resistant *P. aeruginosa* in all groups of hospitals indicate the seriousness of antimicrobial resistance. Clinicians must depend on more laboratory guidance, while laboratories must provide susceptibility test results for optimal patient management more rapidly. Concerted effort is required to conserve the usefulness of precious new antimicrobial agents.

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