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Increasing Prevalence of Vancomycin-Resistant *Enterococcus faecium*, Expanded-Spectrum Cephalosporin-Resistant *Klebsiella pneumoniae*, and Imipenem-Resistant *Pseudomonas aeruginosa* in Korea: KONSAR Study in 2001

The 5th year KONSAR surveillance in 2001 was based on routine test data at 30 participating hospitals. It was of particular interest to find a trend in the resistances of enterococci to vancomycin, of Enterobacteriaceae to the 3rd generation cephalosporin and fluoroquinolone, and of *Pseudomonas aeruginosa* and acinetobacters to carbapenem. Resistance rates of Gram-positive cocci were: 70% of *Staphylococcus aureus* to oxacillin; 88% and 16% of *Enterococcus faecium* to ampicillin and vancomycin, respectively. Seventy-two percent of pneumococci were nonsusceptible to penicillin. The resistance rates of Enterobacteriaceae were: *Escherichia coli*, 28% to fluoroquinolone; *Klebsiella pneumoniae*, 27% to ceftazidime, and 20% to cefoxitin; and *Enterobacter cloacae*, $\geq$40% to cefotaxime and ceftazidime. The resistance rates of *P. aeruginosa* were 21% to ceftazidime, 17% to imipenem, and those of the acinetobacters were $\geq$61% to ceftazidime, aminoglycosides, fluoroquinolone and cotrimoxazole. Thirty-five percent of non-typhoidal salmonellae were ampicillin resistant, and 66% of *Haemophilus influenzae* were β-lactamase producers. Notable changes over the 1997-2001 period were: increases in vancomycin-resistant *E. faecium*, and amikacin- and fluoroquinolone-resistant acinetobacters. With the increasing prevalence of resistant bacteria, nationwide surveillance has become more important for optimal patient management, for the control of nosocomial infection, and for the conservation of the newer antimicrobial agents.

Key Words : *Drug Resistance, Microbial; Korea; Vancomycin Resistance; Enterococcus faecium; ESBL; Pseudomonas aeruginosa*

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INTRODUCTION

Infections due to antimicrobial resistant bacteria are difficult to cure (1). Antimicrobial resistance can also lead to a delay in the administration of appropriate drugs, and the drugs required to treat resistant pathogens can be toxic (2). Antimicrobial resistance has become a worldwide problem with the exception of a few countries in northern Europe (3). However, even in Sweden, where resistant bacteria are rare, increases of ciprofloxacin-resistant *Escherichia coli* and imipenem-resistant *Pseudomonas aeruginosa* have been reported (4).

The prevalence of resistant bacteria varies significantly in different countries as it is influenced by the amount of antimicrobial agents used. The major reasons for performing surveillance are to determine the size of the problem, to see whether resistance is increasing or not, to detect any previously unknown types of resistance, and to determine whether any particular type of resistance is spreading or is associated with an outbreak (1).

Antimicrobial resistance surveillance became increasingly important given the wide spread dissemination of resistant bacteria. Analysis of routine susceptibility data has some limitations, which include its inaccuracy, but it does not require much resource. Longitudinal studies of resistance trends are considered most beneficial for the detection of subtle changes in resistance (5). A previous nationwide surveillance in Korea showed increasing resistance rates of *Enterococcus faecium* to vancomycin, Enterobacteriaceae to fluoroquinolones, the 3rd generation cephalosporins, cephamycins and fluoroquinolones, and *P. aeruginosa* and acinetobacters to carbapenems (6). It is hoped that the Korean National Health Insurance Program, which in 2001 abolished over-the-counter sales of antimicrobial agents and started to scrutinize proper use of antimicrobial agents at hospitals, has had some impact upon reducing resistant bacteria.

The aim of the surveillance in 2001was: to determine any

changing trends in the above-mentioned serious resistances in particular, besides the common resistances at Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) hospitals in different locations, and to determine possible emergence of new resistances.

MATERIALS AND METHODS

Data Collection

Routine susceptibility test data for major aerobic pathogenic bacteria in 2001 were collected from 31 hospitals located in 8 cities/provinces in Korea. However, the data obtained from 30 hospitals were analyzed, excluding one hospital with poor performance versus the WHO/CDC quality control program. As did in the previous study (6), less than 20 isolates of a species from a hospital was excluded from the analysis.

Main methods of susceptibility testing used were, the NCCLS disk diffusion test (7) by 21 hospitals and commercial broth microdilution systems, i.e., Vitek (bioMerieux, Marcy l'Etoile, France) or MicroScan (Dade MicroScan Inc., West Sacramento, CA, U.S.A.) by 9 hospitals. Methicillin-resistant staphylococci were tested using oxacillin, and penicillin G-nonsusceptible pneumococci were screened mainly by the oxacillin-disk method (7).

Data analysis

Hospitals were divided into three groups according to location and bed capacity (≥1,000 beds countrywide, <1,000 beds in Seoul, and <1,000 beds in non-Seoul). Resistance rates did not include intermediates. The mean resistance rate in each hospital group was calculated from the mean resistance rates at each hospital, to minimize the influence of a large number of isolates at some hospitals (8).

The resistance rates of some important organisms to certain antimicrobial agents were compared to those of previous years. However, the statistical significances of changes in resistance were not determined, because this depends on the statistical method used (8), and because the purpose of surveillance includes the detection of outbreaks of resistant infections (9).

RESULTS

The susceptibility data analyzed were of 169,032 isolates, which consisted of 79,167 (46.8%) isolates of Gram-positive cocci, and 89,865 (53.2%) isolates of Gram-negative bacilli. Proportions of the organisms were: *Staphylococcus aureus* 24.1%, coagulase-negative staphylococci 11.1%, *Enterococcus faecalis* 6.0%, *E. faecium* 3.8%, pneumococci 1.8%, *E. coli* 12.0%, *Klebsiella pneumoniae* 7.0%, *Enterobacter cloacae* 3.8%, *Serratia marcescens* 3.4%, non-typhoidal salmonellae 0.6%, acinetobacters 9.4%, *P. aeruginosa* 16.5%, and *Haemophilus influenzae* 0.4%.

The resistance rates of Gram-positive cocci are shown in Table 1. Those of *S. aureus* to oxacillin, erythromycin, and gentamicin were ≥70%, but the rates of coagulase-negative staphylococci to these antimicrobial agents were somewhat lower. The resistance rates of *S. aureus* to cotrimoxazole were lower than that of coagulase-negative staphylococci (12% vs. 42%), but were higher to ciprofloxacin (64% vs. 34%) and to tetracycline (63% vs. 43%). Vancomycin-intermediate or -resistant staphylococci were not present.

The rate of penicillin-nonsusceptible pneumococci was 72%, and that of ciprofloxacin-resistance was 6%. The resistance rates of *E. faecium* were much higher than those of *E. faecalis* to ampicillin (88% vs. 2%), and to ciprofloxacin (88% vs. 43%), but lower to tetracycline (23% vs. 81%). The vancomycin resistance rates of *E. faecium* and *E. faecalis* were 16% and 1%, respectively.

The resistance rates of Gram-negative bacilli are shown in Table 2. Resistance rate of *E. coli* to ampicillin was 75%, and to both piperacillin and cotrimoxazole ≥50%. Resistance rates to other antimicrobial agents were: 9% to ceftazidime, 11% to cefoxitin, 30% to gentamicin, and 28% to fluoroquinolone. Twenty-seven per cent and 20% of *K. pneumoniae* were resistant to ceftazidime and cefoxitin, respectively, and 12% were

Table 1. Antimicrobial resistance rates of *Staphylococcu* species, *S. pneumoniae* and *Enterococcus* species

Antimicrobial agents	Resistance rate (%)				
	S. aureus (n=40,824)	Coagulase-negative staphylococci (n=18,779)	*S. pneumoniae* (n=3,071)	*E. faecalis* (n=10,076)	*E. faecium* (n=6,417)
Oxacillin	70	69	72	–*	–
Ampicillin/penicillin	97	92	–	2	88
Erythromycin	74	58	79	–	–
Cotrimoxazole	12	42	–	–	–
Tetracycline	63	43	–	81	23
Gentamicin	70	57	–	–	–
Ciprofloxacin	64	34	6	43	88
Vancomycin	0	0	–	1	16

*Not tested.

Table 2. Antimicrobial resistance rates of Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp.

Antimicrobial agents	Resistance rate (%)					
	E. coli (n=20,332)	*K. pneumoniae* (n=11,856)	*E. cloacae* (n=6,447)	*S. marcescens* (n=5,701)	*P. aeruginosa* (n=27,940)	*Acinetobacter* spp. (n=15,900)
Ampicillin	75	–*	–	–	–	–
Ampicillin-sulbactam	32	33	–	–	–	45
Cephalothin	39	36	–	–	–	–
Cefotaxime	9	18	40	36	57	73
Ceftazidime	9	27	44	26	21	65
Cefepime	5	9	7	11	20	52
Aztreonam	7	24	35	25	22	76
Cefoperazone-sulbactam	3	7	9	15	28	18
Cefoxitin	11	20	–	–	–	–
Cefotetan	3	7	–	–	–	–
Piperacillin	60	42	58	45	33	66
Piperacillin-tazobactam	5	12	24	22	24	48
Imipenem	0	0	0.4	0.6	17	6
Amikacin	6	12	12	22	26	61
Gentamicin	30	26	37	42	40	70
Tobramycin	25	30	40	23	37	69
Fluoroquinolone†	28	10	10	19	40	65
Cotrimoxazole	50	22	35	34	–	62
Tetracycline	59	30	30	86	–	74

*Not tested. †Mostly tested by using ciprofloxacin, but some hospitals used ofloxacin or levofloxacin.

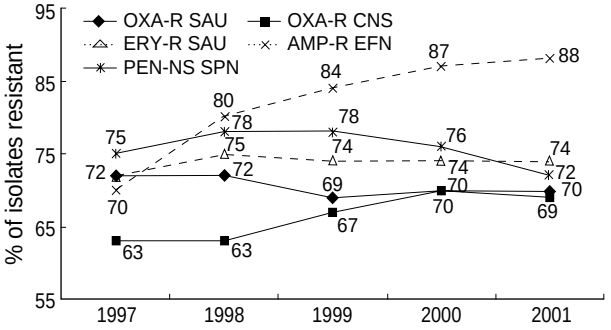

Fig. 1. The trend of resistance of *Staphylococcus* isolates to oxacillin and erythromycin, and *Enterococcus* to ampicillin, and of penicillin G-nonsusceptible *S. pneumoniae*. OXA, oxacillin; ERY, erythromycin; AMP, ampicillin; PEN, penicillin G; R, resistant; NS, nonsusceptible; SAU, *S. aureus*; CNS, coagulase-negative *Staphylococcus*; EFM, *E. faecium*; SPN, *S. pneumoniae*.

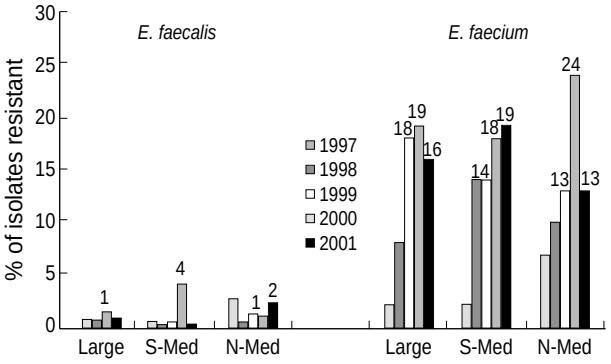

Fig. 2. The trend of resistance of *Enterococcus* isolates to vancomycin at large (≥1,000 beds), and medium (<1,000 beds) hospitals. S, Seoul; NS, non-Seoul; Med, medium.

resistant to amikacin. Of the *E. cloacae* isolates, ≥40% were resistant to cefotaxime and ceftazidime, and 40% were to tobramycin. Imipenem resistance rates of *E. cloacae* and *S. marcescens* were 0.4% and 0.6%, respectively. The resistance rates of *S. marcescens* to cefoperazone-sulbactam and amikacin, at 15% and 22%, respectively, were the highest among Enterobacteriaceae species analyzed. The resistance rates of *P. aeruginosa* to ceftazidime and cefotaxime were 21% and 57%, respectively. The resistance rates to imipenem and amikacin 17% and 26%, respectively. Of the acinetobacters, ≥65% were resistant to piperacillin, cefotaxime, ceftazidime, and aztreonam. Cefepime resistance rate of 52% was the highest among Gram-negative bacilli. Also, ≥61% of the isolates were resistant to aminoglycosides, fluoroquinolone and cotrimoxazole. The imipenem resistance rate of all isolates was 6%.

Among the 990 isolates of non-typhoidal salmonellae, 35% were resistant to ampicillin, and 4% to cotrimoxazole, but none were resistant to fluoroquinolone. In the case of *H. influenzae*, some hospitals tested ampicillin susceptibility, while others tested β-lactamase production, and still others tested both. Among the 699 isolates of *H. influenzae*, 64% were ampicillin resistant and 66% were β-lactamase producers.

During the period 1997-2001, the resistance rates of *S. aureus* to oxacillin and erythromycin remained similar (Fig. 1). Penicillin-nonsusceptible pneumococci declined slightly from 75% to 72%, whereas ampicillin-resistant *E. faecium* increased steadi-

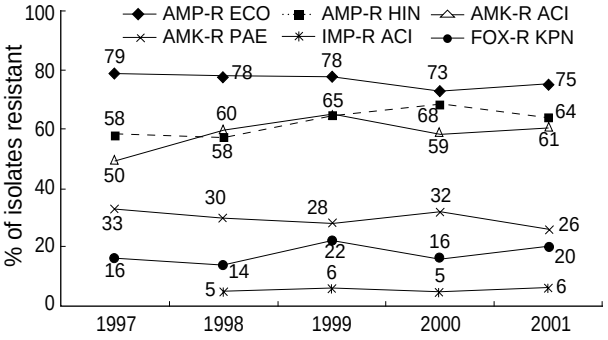

Fig. 3. Trend of resistance of *E. coli* and *H. influenzae* isolates to ampicillin, *K. pneumoniae* to cefoxitin, *P. aeruginosa* to amikacin, and *Acinetobacter* spp. to amikacin and imipenem. AMP, ampicillin; AMK, amikacin; FOX, cefoxitin; IMP, imipenem; ECO, *E. coli*; KPN, *K. pneumoniae*; ACI, *Acinetobacter* spp.; PAE, *P. aeruginosa*; HIN, *H. influenzae*.

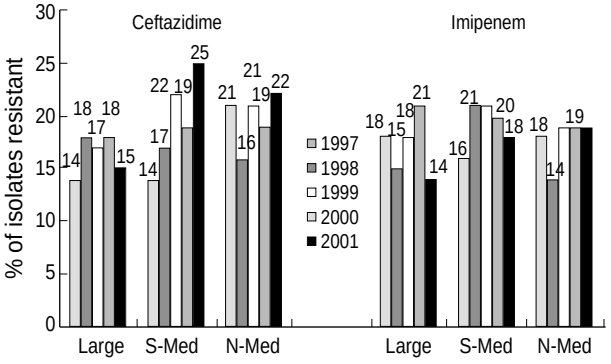

Fig. 5. Trend of resistance of *P. aeruginosa* and *Acinetobacter* isolates to ceftazidime and imipenem at large and medium hospitals. S, Seoul; NS, non-Seoul; Med, medium.

ly from 70% to 88%. Vancomycin-resistant *E. faecium* isolates increased at all hospital groups: from 2% to 16% at large hospital group, from 2% to 19% at the Seoul medium hospital group, and from 7% to 13% at the non-Seoul medium hospital group (Fig. 2).

During the 1997-2001 period, cefoxitin-resistant *K. pneumoniae* increased from 16% to 20%, and ampicillin-resistant *H. influenzae* from 58% to 64% (Fig. 3). The amikacin resistance rate of *P. aeruginosa* declined slightly from 33% to 26%, while that of acinetobacters gradually increased from 50% to 61%. The resistance rates of acinetobacters to fluoroquinolone rose from 56% to 65% (Fig. 4), while the rates to imipenem remained to be 5% to 6% (Fig. 3). Ceftazidime- and imipenem-resistant *P. aeruginosa* were present in all hospital groups (Fig. 5).

DISCUSSION

The surveillance of resistance is an important part of modern clinical microbiology (5), but surveillance methods are

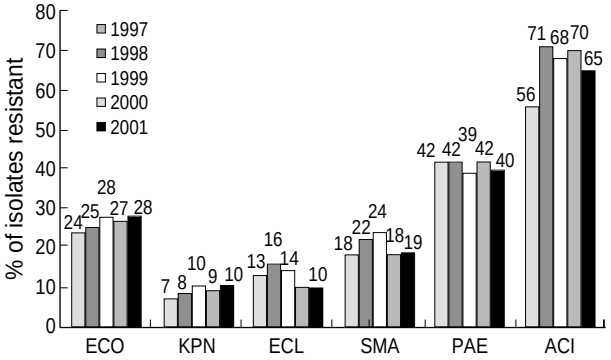

Fig. 4. Trend of resistance of Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* isolates to fluoroquinolone. ECO, *E. coli*; KPN, *K. pneumoniae*; ECL, *E. cloacae*; SMA, *S. marcescens*; PAE, *P. aeruginosa*; ACI, *Acinetobacter* spp.

considered often inappropriate (1). The surveillance, which is based on collecting data from each laboratory has many problems due to the different methods used for species identification and for susceptibility testing. More accurate results can be obtained if isolates are collected and tested at a central laboratory (5), but this method is very expensive.

Current KONSAR program consists of two different forms of surveillance: one is the analysis of routine susceptibility test data, which were determined by individual participating hospitals, i.e., this study, and the other is the determination of the prevalence of certain resistances in isolates collected from participants, e.g., the study on metallo-β-lactamase-producing strains (10).

Both the necessity and the limitations of surveillance were discussed in a previous study (6). It is difficult to distinguish between community- and nosocomially-acquired pathogens, although their resistance rates differ markedly. However, some organisms, such as methicillin-resistant staphylococci, vancomycin-resistant enterococci, *P. aeruginosa* and acinetobacters are typical nosocomial pathogens, while non-typhoidal salmonellae are mostly community-acquired pathogens.

The high proportion of *S. aureus* (24.1%) among the isolates tested in the present study indicates its continued importance. Methicillin-resistant *S. aureus* (MRSA) is one of the typical nosocomial pathogens (11). The proportion of MRSA and methicillin-resistant coagulase-negative staphylococci, 70% and 69%, respectively, were similar to those reported for 1999 and 2000 (Fig. 1). MRSA is also prevalent in Japan. Surveillance in 1998-2000 in Kinki, Japan, showed the proportion of MRSA was approximately 60% (12).

The more active drug against MRSA remained to be cotrimoxazole except for vancomycin, but the rate of 12% was much higher one than the 1% found in Japan. Two isolates of true vancomycin-resistant *S. aureus* were reported in the United States in 2002 (13, 14). No vancomycin-resistant *S. aureus* were recognized in the present study.

The penicillin-nonsusceptible rate of pneumococci decreased

slightly from 78% in 1999 to 72% in 2001. A reduction in penicillin-nonsusceptible isolates may be the result of the abolition of over-the-counter sales of common antimicrobial agents in 2001. It will be interesting to observe whether this declining trend continues. In Japan, the proportion of penicillin-nonsusceptible pneumococci, by the broth microdilution method, was 65% in 1998 and 81% in 2000 (12). We should know that the proportions were based on breakpoint for the treatment of meningitis (7). Therefore, pneumonia caused by penicillin-intermediate isolates may respond to penicillin therapy (15). Pneumococci cause community-acquired lower respiratory tract infections more frequently than meningitis.

The ampicillin-resistant rate of *E. faecalis*, 1%, was slightly lower than the 2% found in 2000, though still higher than the <1% found at the coordinating laboratory of the KONSAR program. It was considered that ampicillin-resistant *E. faecalis* was due to misidentification of the species (1). These indicate the need to retest the species when an *E. faecalis* isolate shows resistance to ampicillin.

Vancomycin resistance rate of *E. faecium* in 2001 remained similar to those in 2000 at large- and medium-hospital groups in Seoul. Although the rate at the non-Seoul medium-hospital group declined from 24% in 2000 to 13% in 2001 (Fig. 2), vancomycin-resistant *E. faecium* seemed to be established in all hospital groups, as was at the coordinating hospital (16). It is a concern that once a resistance gene has became accumulated to an environment, it is impossible to eliminate them (17).

The ampicillin resistance rate of *E. coli* did increase further and that of *H. influenzae* increased only slightly. Ampicillin had been a commonly used drug because it was available without prescription, but currently no antimicrobial agent can be bought without a prescription since 2001. It is interesting to see the future surveillance could show a downward trend again. In the present study, 64% of the *H. influenzae* isolates were resistant to ampicillin and the proportion of β-lactamase producers was similar. The proportion of β-lactamase-producing isolates in the United States was 36%, while that was only 3% in Japan. In a European study (18), the prevalence of β-lactamase producers varied from 8.1% to 34.8% depending on countries. It is interesting that in Japan 39.6% of the isolates were β-lactamase-negative ampicillin-resistant (BLNAR) strains (19).

The resistance rates of non-typhoidal salmonellae, i.e., 35% to ampicillin, 4% to cotrimoxazole and none to ciprofloxacin, were similar to those reported in 2000 (6). When empirical antimicrobial treatment of non-typhoidal salmonellae infection is required (20), cotrimoxazole or ciprofloxacin should be appropriate first-line drugs in Korea. In the present study, 0.4% of non-typhoidal salmonellae were resistant to the 3rd generation cephalosporin. Further study is required to determine whether extended-spectrum β-lactamase (ESBL)-producing isolates are present. In a Korean hospital, ESBL-producing non-typhoidal salmonellae were detected as early as 1995 (21).

Fluoroquinolones are increasingly used, as they are one of the three major broad-spectrum classes of antimicrobial agents (22). Fluoroquinolone resistance rate of *E. coli* gradually rose from 24% in 1997 to 28% in 2001. The rate of acinetobacters, 65% was only slightly lower than that of the 70% in 2000 (6).

Expanded-spectrum cephalosporins are ineffective for the treatment of infections caused by ESBL-producing isolates of *E. coli* and *K. pneumoniae*, although they may be inhibited by low concentrations of these drugs (23). It was reported that bacteremic patients with ESBL-producing *K. pneumoniae* had higher initial treatment failure rates than those with non-ESBL-producing isolates (24). Also, the cefoxitin resistance rate 20% of *K. pneumoniae* suggests plasmid-mediated AmpC β-lactamase production (25). Therefore, ceftazidime resistance rates cannot reflect the proportion of ESBL producers, although high prevalence of ESBL-producing *K. pneumoniae* has been reported in Korea (26). Cephamycins, such as cefoxitin, are active against ESBL-producing isolates, but plasmid-mediated AmpC β-lactamase-producing isolates are resistant not only to all cephalosporins but also to cephamycins.

Carbapenems are very useful drugs as they are stable to hydrolysis even to ESBL- and AmpC β-lactamases (27). Although VIM-2 metallo-β-lactamase-producing *S. marcescens* and *E. cloacae* have been reported (28, 29), the imipenem resistance rates of *E. cloacae* and *S. marcescens* were low (0.4% and 0.6%, respectively), suggesting that carbapenem-resistant Enterobacteriaceae are rare. The imipenem resistance rates of *P. aeruginosa* to ceftazidime and imipenem remained similar in all hospital groups (Fig. 5). In another study about 9% of imipenem-resistant *P. aeruginosa* were due to the production of acquired metallo-β-lactamases (30). Acinetobacters are often multidrug resistant. At a hospital in India, 29% of acinetobacters isolated in 1996-1998 were resistant to imipenem, though the hospital did not use imipenem at that time (31). In our present study, the imipenem resistance rate of acinetobacters remained similar (Fig. 3). However, the imipenem resistance rate rose to 13% in 2002 at the coordinating laboratory. Another study showed that approximately 11.4% and 14.2% of imipenem-nonsusceptible isolates possessed the VIM-2 or the IMP-1 metallo-β-lactamase gene (10). We consider that close observation of this trend is necessary.

Given the increase in the prevalence of resistant bacteria, the empirical selection of antimicrobial agents becomes increasingly difficult and rapid microbiological testing increasingly crucial. As was found in the previous study, some laboratories tested susceptibility to too few antimicrobial classes (data not shown). Diagnostic bacteriology results cannot be obtained immediately, but clinical microbiologists should remember that early results only can aid the appropriate management of patients, and consequently reduce emergence and the spread of resistance. It was reported that early preliminary microbiology results of blood stream infection had a greater impact on antimicrobial management than susceptibility data (32).

In conclusion, methicillin-resistant staphylococci, penicillin-nonsusceptible pneumococci, ampicillin-resistant *E. faecium* and *H. influenzae*, and expanded-spectrum cephalosporin-resistant Gram-negative bacilli remain prevalent. Vancomycin-resistant *E. faecium*, fluoroquinolone-resistant Gram-negative bacilli, and imipenem-resistant *P. aeruginosa* are increasing at all groups of hospitals. Given this increasing resistance, not only rapid and accurate routine susceptibility testing, but also the nationwide resistance surveillance become even more important for optimal patient management, the control of nosocomial infection, and eventually to conserve newer antimicrobial agents.

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