

## Bacterial Resistance to Antimicrobial Agents: An Overview from Korea

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*Antimicrobial resistance of bacteria has become a worldwide problem. Available data suggest that the resistance problem is comparatively more serious in Korea. In large hospitals, the proportion of methicillin-resistant Staphylococcus aureus (MRSA) has been reported at over 70%, and of penicillin-nonsusceptible Streptococcus pneumoniae at around 70%. Infection or colonization of vancomycin-resistant enterococci has started to increase. Extended-spectrum  $\beta$ -lactamase producing Escherichia coli and Klebsiella pneumoniae has become widespread and even carbapenem-resistant Pseudomonas aeruginosa has been increasing. Community-acquired pathogens such as Salmonella, Shigella and Neisseria gonorrhoeae are often resistant to various antimicrobial agents. The prevalence of resistant bacteria can lead to erroneous empirical selection of either noneffective or expensive drugs, prolonging hospitalization and higher mortality. The emergence and spread of resistant bacteria are unavoidable unless antimicrobial agents are not used at all. The high prevalence of resistant bacteria in Korea seems to be related to antibiotic usage: 1) easy availability without prescription at drug stores, 2) injudicious use in hospitals, and 3) uncontrolled use in agriculture, animal husbandry, and fisheries. Nosocomial infection is an important factor in the spread of resistant bacteria. Antimicrobial resistance problems should be regarded as the major public health concern in Korea. It is urgently required to ban the sale of antibiotics without prescription, to use antibiotics more judiciously in hospitals by intensive teaching of the principles of the use of antibiotics, and to establish better control measures of nosocomial infections. Regulation of antimicrobials for other than human use should also be required. These issues are not easy to address and require the collective action of governments, the pharmaceutical industry, health care providers, and consumers.*

**Key Words:** Antimicrobial resistance, nosocomial pathogen, medical practice, antimicrobial agent

The introduction of penicillin 50 years ago was followed by an extraordinary period of discovery, exuberant use, and predictable obsolescence. The discovery of antibiotics was followed by the emergence of resistant bacteria, either through the

mutation of genes or the acquisition of novel resistance determinants. All species of pathogens found in hospitals, apart from staphylococci, pneumococci, enterococci, species of *Enterobacteriaceae* and mycobacteria, are resistant now at least to some antimicrobial agents. Indeed, now infections with antibiotic-resistant staphylococci and enterococci that cannot be treated by previously successful regimens have made frequent headline news. The therapeutic crisis due to antimicrobial resistance has especially compromised the chemotherapy of hospitalized patients with serious infections.

The level of antibiotic resistance in Korea may be among the highest in the world. We have observed

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an unusually high occurrence of multiple-resistant bacterial infections in Korea. Especially, methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) began to pose serious clinical problems in the 1980s. The resistance rates of certain gram-negative bacilli, e.g., *Escherichia coli*, *Enterobacter*, *Klebsiella* and *Pseudomonas aeruginosa* have also been increasing rapidly.

Clinicians in Korea are now confronted with the difficult problem of treating multiple-resistant nosocomial infections. Patients die more often in spite of treatment with broad-spectrum antibiotics. We have insufficient data for in vitro antimicrobial susceptibility. First, most reports have come from large university hospitals and rarely from local clinics. Second, NCCLS disk diffusion method and automated systems, may have failed to detect resistance with certain mechanisms. Third, it is possible that some hospitals have failed to use current breakpoints of susceptibility. Despite these limitations, it is apparent that resistant bacteria are very prevalent in Korea and in medical practice we should remember that we are confronting bacteria which are mostly armed with various resistant mechanisms.

### Staphylococcal infection

Early in the antibiotic era, *S. aureus* was already recognized as capable of developing resistance to penicillin. By the end of the 1940s,  $\beta$ -lactamase-producing strains became prevalent and by the end of the next decade, many clinical isolates were resistant to virtually all available systemic antibiotics, including tetracyclines and erythromycin. In the early 1960s, the introduction of semisynthetic penicillinase-resistant penicillins, such as methicillin and first-generation cephalosporins increased the therapeutic choice. Methicillin is stable and cephalosporins are relatively stable to the activity of staphylococcal  $\beta$ -lactamases. Even before the widespread clinical use of methicillin, however, methicillin resistance was described (Jevons, 1961; Knox, 1961). At first, such strains were isolated only sporadically and were resistant mostly to  $\beta$ -lactams. In the latter part of the 1970s, *S. aureus* strains resistant not only to  $\beta$ -lactams, but also to many other

antibiotics including aminoglycosides, appeared and spread worldwide (Brumfitt *et al.* 1989).

A rapid increase of MRSA was reported from the mid-1980s in large university hospitals in Korea. The proportion increased from 24.2% in 1988 to 74.2% in 1995 (Chang *et al.* 1988; Ryu *et al.* 1995). In the early 1990s, the proportion rose over 50% in most large hospitals. Most hospitals failed to control the spread of MRSA within their hospitals. A lack of effective infection control programs together with an inappropriate use of broad-spectrum antibiotics may have enhanced the rapid increase. Nowadays, MRSA is one of the most commonly isolated endemic nosocomial pathogens in many hospitals.

The methicillin resistance of most clinical isolates is attributed to the presence in the bacterial membrane of a novel penicillin-binding protein 2a (PBP 2a) with a low affinity for  $\beta$ -lactam antibiotics (Malouin *et al.* 1986). Therefore, MRSA with PBP 2a can synthesize the cell wall in spite of the presence of all  $\beta$ -lactams, including cephalosporins. Infections caused by MRSA are serious medical problems because only a few effective therapeutic agents are available.

Currently, the treatment of choice for MRSA infection is glycopeptide antibiotics, vancomycin or teicoplanin. However, in the debilitated or immunocompromised patient, we have often failed to eradicate MRSA by glycopeptide treatment. Along with the wide use of fluoroquinolones, the resistance in MRSA rapidly increased; only a year after introduction of quinolones in our hospital, the resistance rate increased from 0% in 1990 to 66.7% in 1991 (Choi *et al.* 1993). The usefulness of quinolones in the treatment of MRSA infections is likely to be seriously compromised in the near future.

MRSA infection was traditionally thought to be hospital-acquired, but occasionally the infection was recognized in the community (Kim *et al.* 1993). Unfortunately, any clinico-epidemiologic study to elucidate the factors which are involved in MRSA infection in the community has been lacking.

There have been no reports of vancomycin-resistant *S. aureus* (VRSA) in Korea, but in view of the high prevalence of MRSA, there is a possibility of the emergence of VRSA in the future.

Infections due to coagulase-negative staphylococci (CNS) seldom occur in healthy individuals. Host

factors that pose the greatest risk of infection by these organisms include defects in mucosal membranes or skin, immunosuppression and, most importantly, the presence of a foreign body, especially indwelling intravenous catheters, peritoneal dialysis catheters, cerebrospinal fluid shunts, hemodialysis shunts, vascular grafts, and prosthetic valves. Methicillin-resistant strains of CNS were first reported in 1960 (Elek, 1960). CNS isolated from bacteremia patients at a Korean university hospital from 1986 to 1989 showed a methicillin-resistance rate of 63.2% (Lee *et al.* 1990). Recent reports revealed that more than 71% of CNS isolates in large hospitals were resistant to methicillin.

### Pneumococcal infection

*S. pneumoniae* continues to be a common cause of serious and life-threatening infections, such as pneumonia, bacteremia and meningitis. It is also a frequent cause of otitis media and sinusitis (Istre, 1987). Pneumococci were very susceptible organisms to penicillin G with minimum inhibitory concentrations (MICs) of  $<0.06 \mu\text{g/mL}$ , requiring no susceptibility test. However, pneumococci with various degrees of penicillin resistance have been isolated throughout the world (Ward, 1981). In the late 1970s and the 1980s, rates of penicillin-resistant *S. pneumoniae* (PRSP) increased to 50% in some Western countries, particularly in Spain, and multiple resistance also increased (Klugman *et al.* 1990; Lister *et al.* 1995; Schreiber *et al.* 1995). A recent American study showed that 25% of invasive *S. pneumoniae* isolates were penicillin-resistant (Hofmann *et al.* 1995). Resistance rates were usually higher in the isolates of children, and variable depending on the region and population groups.

In Korea, PRSP increased from 29% in 1988 to 71% in 1992 (Lee *et al.* 1993). In another study, 37% of the strains isolated in the period 1991–1993 were intermediate and 33% were resistant to penicillin G (Park *et al.* 1994). Eighty-three percent of the isolates from children and 59% of those from normally sterile body fluids were nonsusceptible to penicillin. A significantly higher rate of penicillin resistance was associated with hospitalization, an age of under 15 years, or ongoing antimicrobial therapy.

PRSP was often resistant to other antimicrobial agents, including those which can be used for the treatment of less serious infections; the resistance rates were 89% to cefaclor, 82% to cefotaxime, 65% to chloramphenicol, 52% to erythromycin and 15% to ciprofloxacin. None were resistant to teicoplanin or vancomycin. It was reported that one-third of invasive strains of pneumococci were multidrug resistant (Song *et al.* 1997) and were mostly serotypes 6, 14, 19F, and 23F. Song *et al.* suggested that the geographic spread of resistant clones may have contributed to the rapid increase of penicillin- and multidrug-resistant pneumococci in Korea.

The increasing prevalence of resistant pneumococci highlights the need for routine susceptibility testing of pneumococci. Without susceptibility testing, penicillin G cannot be recommended as the drug of choice anymore in Korea. In most laboratories, the screening is done by the NCCLS oxacillin disk method. For isolates from serious infection, MIC determination is required. For serious infections due to intermediate penicillin-resistant strain (MICs 0.1–1.0  $\mu\text{g/mL}$ ), a third-generation cephalosporin may be used. Vancomycin may be useful for infection with a resistant strain (MIC  $\geq 2.0 \mu\text{g/mL}$ ). Possible alternatives for nonserious infections include erythromycin and clindamycin when the strains are susceptible.

### Enterococcal infection

Possibly due to the widespread use of cephalosporins, enterococci have assumed increasing clinical importance as nosocomial pathogens. Some enterococcal infections are a therapeutic challenge because of their intrinsic resistance to many antibiotics and the compromised state of patients. Almost all clinical isolates are tolerant to  $\beta$ -lactams and glycopeptides. For the treatment of serious infections, a synergistic effect can be obtained with the combination of a  $\beta$ -lactam and an aminoglycoside when the strain is susceptible to a high level of the latter. In 1992, high level resistance rates of enterococci were 67% to gentamicin and 49% to streptomycin (Choi *et al.* 1993). Lee *et al.* (1992) reported that 20% of *E. faecalis* and 59% of *E. faecium* were resistant to high-level gentamicin. If the isolate is high-level resistant to both amino-

glycosides, a synergistic effect cannot be expected and the only alternative is to administer 12 g/day of ampicillin for at least 6 weeks.

Vancomycin-resistant *Enterococcus* (VRE), first reported from clinical sources in 1986 in France, has become relatively common in many U.S. hospitals. In 1992, the first vancomycin-resistant *E. durans* of VanA phenotype was isolated from a patient with acute leukemia in Korea (Park *et al.* 1992). Thereafter, patients with VRE infection or colonization were reported in some university hospitals. Jeong *et al.* (1996) even reported two isolates of VanB type VRE which were imported from the U.S. The interhospital or intercountry spread of VRE is a worrisome phenomenon. Cheong *et al.* (1998) reported that the prevalence rate of VRE was 1% (2/202) among clinical enterococcal isolates in 1996, but Peck *et al.* (1996) reported that the rectal VRE colonization rate among hospitalized patients in the medical ward was 8.1%. The risk factors for VRE colonization/infection were acute leukemia and other hematologic malignancies, hospitalized patients in the intensive care units, and previous use of 3rd-generation cephalosporins and vancomycin. VRE was reported from Korean hospitals located in Seoul, Pusan, Kwangju and Suwon (Jeong *et al.* 1998; Kim *et al.* 1998). Most VRE infections in Korea were hospital-acquired, as was the case in the U.S.

Although VRE is still believed to be uncommon in Korea, a gradual increase is apparent and routine testing for vancomycin susceptibility has become necessary, not only for treated patients but also to establish a national surveillance and control system. There are no established therapies for infections due to enterococci resistant to both vancomycin and  $\beta$ -lactams. Regimens that have been tried with some success in individual cases or experimentally include ciprofloxacin plus rifampin plus gentamicin, ampicillin plus vancomycin if in vitro testing shows synergistic activity, and chloramphenicol or tetracycline if the strain is susceptible to them.

### Gram-negative bacterial infection

Increased use of "3rd-generation" cephalosporins has been followed by a rising prevalence of extended-spectrum  $\beta$ -lactam-resistant gram-negative bacteria in hospitals. A study showed that among the

gram-negative bacteria isolated in 72 hospitals during 1994–1995, strains resistant to 3rd-generation cephalosporins, fluoroquinolones or imipenem were not rare (Chong *et al.* 1996). Among the *E. coli* isolates, 80% were resistant to ampicillin, and 40% to both gentamicin and tobramycin. An outbreak of quinolone-resistant *E. coli* infection was reported recently in neutropenic patients with leukemia (Yoo *et al.* 1997). Nosocomial pathogens such as *Klebsiella*, *Enterobacter*, and *Serratia* species showed an increasing resistance to 3rd-generation cephalosporins and aminoglycosides. Cefotaxime-resistance rates increased from 1% to 11% in *E. coli* and from 6% to 30% in *K. pneumoniae* respectively from 1986 to 1993, mostly due to extended-spectrum  $\beta$ -lactamase (ESBL)-production (Lee *et al.* 1994). More frequent isolation of ESBL-producing strains from patients in ICU than from those in general wards or outpatient clinics (Lee *et al.* 1994), and an outbreak of infections in a neonatal intensive care unit (Lee *et al.* 1997) documented their importance as a nosocomial pathogens. Pai *et al.* (1997) reported 12.5%–22% of *K. pneumoniae* found in university hospitals were ESBL producers. These facts suggest that 3rd-generation cephalosporins became much less useful for the treatment of hospital-acquired *E. coli* and *K. pneumoniae* infections.

The resistance rates of *P. aeruginosa* isolates were over 30% to carbenicillin, piperacillin, ticarcillin, gentamicin, tobramycin, and fluoroquinolones. Resistant strains were not rare even to amikacin (26%), aztreonam (17%), ceftazidime (12%) and imipenem (11%) (Chong *et al.* 1996). A higher imipenem resistance rate of 14%–19% in medium-sized hospitals compared to 3% in tertiary hospitals was considered to be due to uncontrolled use of the drug. One of the most powerful  $\beta$ -lactams against gram-negative bacilli is beginning to lose its usefulness.

Enteric infections are mostly acquired in the community. *Salmonella typhi* remained susceptible to ampicillin and chloramphenicol, except those strains acquired in foreign countries. However, the resistance rate of other serovars isolated in 1990 were 33% to ampicillin, 31% to chloramphenicol, and 35% to trimethoprim/sulfamethoxazole (Chong, 1991). Even ESBL-producing strains have been recently reported. The resistance of *Shigella* has

been well known. Most (62.5–95.8%) of *Shigella flexneri* have also shown to be resistant to ampicillin (Park *et al.* 1993). These results have clearly shown that ampicillin or trimethoprim/sulfamethoxazole can not be selected empirically without prior susceptibility testing for the treatment of infections due to nontyphoidal *Salmonella* and *Shigella*.

Among the *Haemophilus influenzae* isolated from clinical specimens in 1991, 30.6% were  $\beta$ -lactamase producers (Chong *et al.* 1992). Although 90% of *Moraxella catarrhalis* strains isolated mainly from respiratory tracts were  $\beta$ -lactamase positive, more than 90% were susceptible to cephalothin, chloramphenicol, tetracycline, erythromycin, cotrimoxazole and pefloxacin (Park *et al.* 1996).

The proportion of penicillinase-producing *N. gonorrhoeae* (PPNG) in Korea increased from 21.9% in 1981 to 64.9% in 1994 (Kim *et al.* 1996). The effect of penicillins cannot be expected when they are used without  $\beta$ -lactamase testing. The rapid increase of a fluoroquinolone-nonsusceptible strain from 9% to 54% from 1992 to 1996 is a very troubling development. Studies are required to determine the clinical significance of the reduced susceptibility to fluoroquinolone. It was reported that none of the strains were resistant to ceftriaxone or spectinomycin (Lee *et al.* 1998).

In conclusion, the frequent misuse and uncontrolled use of antibacterial agents in clinical practice are considered to be the major factors responsible for the increase of resistant bacteria in Korea. Resistant bacteria may be widespread due to nosocomial infections. In the community, the use of antimicrobial agents for even nonbacterial infections in humans and their extensive use in the nonmedical field may be aggravating the resistance problem. The problem of therapeutic failure and the increased medical cost is becoming more serious in Korea as antimicrobial-resistant bacteria become more prevalent, particularly in hospital settings. The prevalence of resistant bacteria makes empirical selection of antimicrobial agents increasingly difficult, requiring accurate *in vitro* susceptibility testing. Further investigation is urgently needed on the status of antimicrobial resistance in the community and on of overall misuse. It may be possible to reduce resistant bacteria by using antimicrobial agents prudently, by banning their sale without prescription at drug

stores, and by controlling the nosocomial spread of infection. Control of the nonmedical use of antimicrobial agents may also help to reduce resistant bacteria. These issues are not easily addressed and will require the collective action of governments, the pharmaceutical industry, health care providers, and consumers.

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