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In Vitro Activities of Eight Antibiotics Against Methicillin-Resistant *S. aureus* and *S. epidermidis* Strains Isolated in Korea

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Staphylococcus aureus and Staphylococcus epidermidis strains isolated at eight large medical centers in Korea were examined for methicilin resistance and resistance to eight other antibiotics; cefazolin, cefamandole, cefuroxime, cefoxitin, cefotaxime, moxalactam, penicillin G and vancomycin. Methicillin resistance was found in 296 of 1225 strains (24.2%) of S. aureus and 126 of 348 strains (36.2%) of S. epidermidis. Methicillinresistant strains were isolated from all sources with the frequency of isolation ranging from 11% to 60%. From pleural effusion, throat swab and blood, methicillin-resistant strains of S. aureus were more frequently isolated with statistical significance (Chi-squared test, 95% confidence). Almost all of Methicillin-resistant S. aureus (MRSA) and S. epidermidis (MRSE) strains were multiply resistant to one or more tested eight antibiotics. However only 7(2.4%) of 296 MRSA strains and 2(1.6%) of 126 MRSE strains were resistant to vancomycin. Vancomycin was the most effective antibiotic against staphylococcal isolates as well as MRSA and MRSE.

Key Words: *In vitro activities of antibiotics, Methicillin-resistant S.aureus, methicillin-resistant S.epidermidis*

INTRODUCTION

Staphylococcus aureus is still an important causative agent of hospital-acquired infection, account for 15-20% of all nosocomial infection (Crossley et al., 1979; Wenzel, 1982). Because of the prevalence of staphylococci resistant to one or more antimicrobial agents, particularly in hospital population, it is essential to determine the drug susceptibility of infecting organisms (Boyce, 1981).

Penicillinase-producing strains are usually susceptible to semisynthetic penicillins; hence patients are treated with methicillin, oxacillin or a cephalosporin until the drug sensitivity is known.

However such penicillinase-resistant penicillins or cephalosporins may not be effective in treatment of staphylococcal infection because of high incidence of methicillin-resistant *S.aureus* (Chong and Lee, 1983; Collins et al., 1983; Richmond et al., 1977; Watanakunakorn et al., 1982). Epidemics of MRSA continue to be reported in many countries including Korea (Chong, 1986; Haley et al., 1982; Kayer, 1975; Klimek, 1976; Myers and Linnemann, 1982; O'Toole et al.,

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1970; Saravolatz et al., 1982; Thompson et al., 1982; Thompson and Wenzel, 1982; Weinstein and Kabins, 1981).

MRSA strains isolated in Korea are usually resistant to many antimicrobial agents including penicillin and cephalosporin (Chong, 1986; Chong and Lee, 1983), while vancomycin is considered to be one of uniformly active agent against MRSA (Chokkavelu et al., 1984; Craven et al., 1983; Foldes et al., 1983; Locksley et al., 1982; Traub et al., 1982; Weinstein and Kabins, 1981; Wenzel, 1982; Williams, 1982).

This investigation was designed to determine the incidence of MRSA and MRSE in Korea, and to determine their susceptibility patterns to penicillin G, cephalosporins and vancomycin.

MATERIALS AND METHODS

S.auresu and *S.epidermidis* strains were isolated from clinical samples during 1986 at Seoul National University Hospital, Catholic Medical College Hospital, Kyunghee University Hospital, Yonsei University Hospital, and Hanyang University Hospital in Seoul; Cheonnam National university Hospital in Kwangju; Kyungbuk National university Hospital in Taegu; Paik Hospital, Pusan, Korea. Each isolates were identified by using API STAPH®, API System S.A., Montalieu Vercieu, France and stored at −70°C until testing.

Moxalactam diammonium (SI-526-4C), penicillin G potassium buffered (SI-526-5D), cefazolin sodum (SI-766-5L), cefamandole lithium (SI-88-4L), vancomycin hydrochloride (SI-657-5N), cefuroxime sodium (SI-150-5A), cefotaxime sodium and methicillin sodium were obtained from Eli Lilly, Indianapolis, Indiana, U.S.A. and cefoxitin sodium (Fill No.: 18817) was obtained from Merk Sharp and Dohme, West Point, N. J., U.S.A.

Standard discs of antimicrobial agents were obtained from BBL (Sensi-Disc®), Becton Dickinson and Co., Cockeysville, M.D., U.S.A. The stock solution of each antimicrobial agent was prepared and diluted according to the manufacturer's instructions and stored at −70°C until use. Antibiotic solution were thawed only once before use.

Minimal inhibitory concentrations (MICS) were determined by agar dilution method according to the method described by Washington II (Washington II, 1985). Interpretation of disc diffusion method was performed according to the method of Barry (Barry and Thornsberry, 1985).

Table 1. Susceptibility of 1225 strains of *S.aureus* and 348 strains of *S.epidermidis* to nine antibiotics

Antibiotics	Number (%) of resistant strains	
	S.aureus	*S.epidermidis*
Methicillin	296 (24.2%)	126 (36.2%)
Cefazolin	253 (20.7%)	52 (14.9%)
Cefamandole	81 (6.6%)	12 (3.4%)
Cefuroxime	267 (21.8%)	56 (16.1%)
Cefoxitin	240 (19.6%)	72 (20.7%)
Moxalactam	265 (21.6%)	140 (40.2%)
Cefotaxime	249 (20.3%)	55 (15.8%)
Penicillin G	1135 (92.7%)	303 (87.1%)
Vancomycin	8 (0.7%)	5 (1.4%)

RESULTS

One thousand two hundred twenty five strains of *S.aureus* and three hundred forty eight strains of *S.epidermidis* were examined for in vitro susceptibility against nine antibiotics (Table 1). Almost one quarter of *S.aureus* strains and more than one third of *S.epidermidis* strains were resistant to methicillin. Vancomycin was the most effective antibiotic followed by cefamandole. Resistance to other antibiotics ranged from 19.6% for cefoxitin to 92.7% for penicillin G in

Table 2. The frequency of isolation of MRSA and MRSE from various clinical samples

Source	*S.aureus*		*S.epidermidis*	
	Total No. of isolates	No. (%) of MRSA strain	Total No. of isolates	No. (%) of MRSE strain
Pus	736	150 (22.4%)	100	35 (35.0%)
Throat swab	145	62 (20.0%)	10	6 (60.0%)
Urine	95	25 (26.3%)	85	36 (42.4%)
Blood	76	22 (28.9%)	88	30 (34.1%)
Pleural effusion	25	10 (40.0%)	6	2 (33.3%)
Peritoneal effusion	8	1 (11.1%)	15	3 (20.0%)
Others	77	11 (14.3%)	44	14 (31.8%)

S.aureus and from 14.9% for cefazolin to 87.1% for penicillin G in *S.epidermidis*.

The frequency of isolation MRSA and MRSE strains from various sources is shown in Table 2. Methicllin-resistant strains were isolated from all sources with the frequency of isolation ranging from 11% to 60%. From pleural effusion, throat swab and blood, methicillin-resistant strains of *S.aureus* were more frequently isolated with statistical significance (Chi-squared test, 95% confidence). And compared with *S.aureus*, methicillin-resistant strains *S.epidermidis* were more frequently isolated from pus, throat swab and urine with statistical significance (Chi-squared test, 95% confidence).

The cumulative percent inhibition of MRSA and MRSE strains by nine antibiotics are shown in Fig. 1 and Fig. 2. Vancomycin was the most active antibiotic against MRSA with MIC50 and MIC90 of 0.8ug/ml and 1.5ug/ml, respectively. Cefamandole with MIC50 and MIC90 of 9.1ug/ml and 30.2ug/ml respectively, was the second most active antibiotic. Vancomycin was also the most active antibiotic against MRSE, followed by cefamandole. For the rest of antibiotics, less than 50% of MRSA strains were inhibited at 8ug/ml. MRSE were generally more susceptible compared to MRSA; more than 50% of MRSE were susceptible to vancomycin, cefamandole and cefazolin at the concentration of 8ug/ml.

Ninety nine percent of *S.aureus* and ninety eight percent of *S.epidermidis* strains were shown multiple drug-resistance, and more than 85% of MRSA and 40% of MRSE strains showed resistant to four or more antibiotics. Almost all of strains, except eight strains of MRSA and two strains of MRSE, were resistant to penicillin G.

However, only 7(2.4%) MRSA and 2(1.6%) of MRSE strains were resistant to vancomycin.

DISCUSSION

For the past 30 years the difficulties of preventing, controlling and treating staphylococcal sepsis have

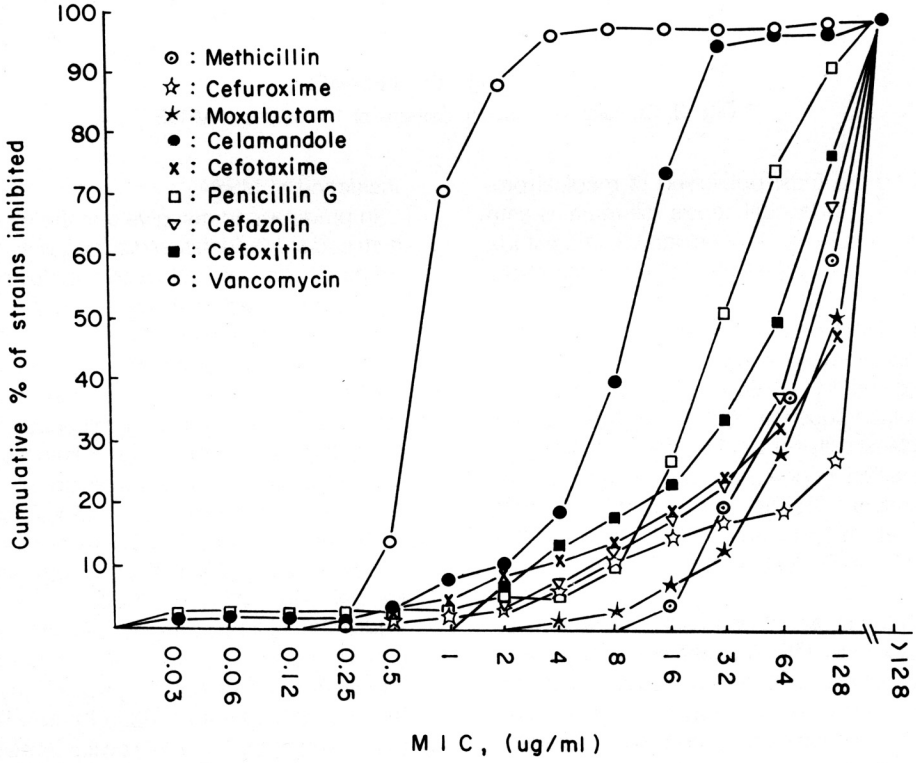

Fig. 1. Cumulative sensitivity patterns of 296 strains of MRSA.

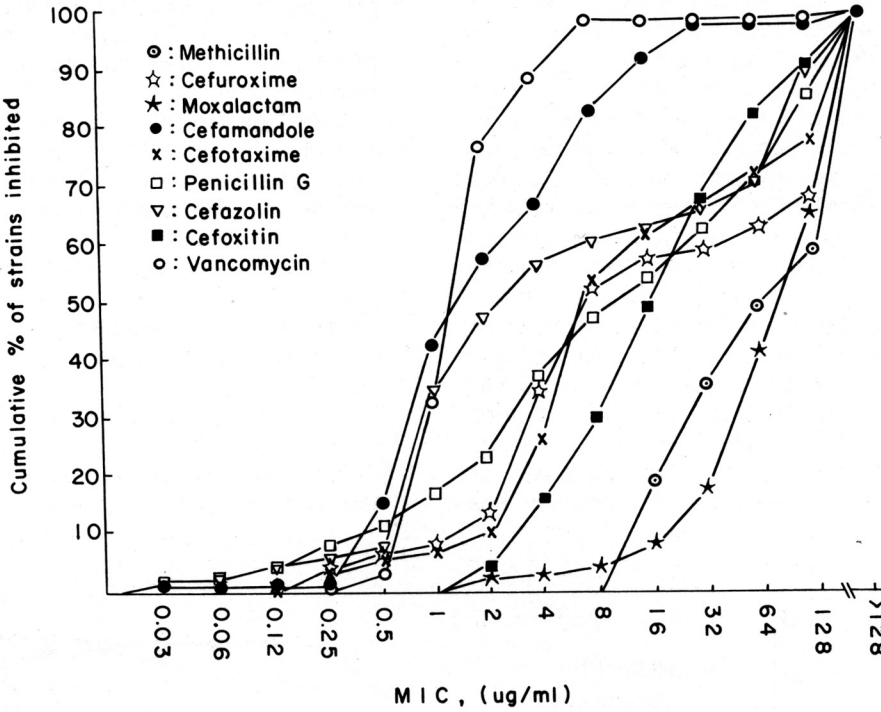

Fig. 2. Cumulative sensitivity patterns of 126 strains of MRSE.

been among the most publicised of medical problems. Yet staphylococcal sepsis still remains as a therapeutic problems of considerable magnitude (Boyce, 1981; Crossley et al., 1979; Dunkle et al., 1981; Williams, 1982).

Strains of *Staphylococcus aureus* that are resistant to penicillinase-resistant penicillin including methicillin were recognized first in 1960 and are being isolated with increasing frequency. Furthermore MRSA strains are characteristically resistant to other antibiotics, including penicillin, cephalosporins, erythromycin and aminoglycosides (Benner and Morthland, 1967; Crossley et al., 1979; Guenthner and Wenzel, 1984; Kayser, 1975; Peacock et al., 1981; Thompson et al., 1982).

Although the selection of an antibiotic to treat infections caused by MRSA poses several problems of pharmacokinetics and clinical feature, it is essential to determine the in vitro drug sensitivity of infecting strain. It is unclear whether penicillinase-resistant penicillins or cephalosporins are effective for the treatment of staphylococcal infection because of a high incidence of MRSA.

In pragmatic terms, give that the infecting bacterium under consideration display suitable sensitivities, a combination of flucloxacillin or fusidic acid with each other or with erythromycin or rifampicin should cover most eventualities (Dixson et al., 1985; Foldes et al., 1983; Markowitz et al., 1983).

Although vancomycin is highly bactericidal to staphylococci in vitro, it may produce febrile reactions, thrombophlebitis and deafness, and often showed failure in treatment. Therefore its extreme toxicity precludes routine use, it should be used only in the pace of apparent failure of other treatment (Gopal et al., 1976; Weinstein and Kabins, 1981; Wenzel, 1982; Willaims, 1982).

MRSA have been responsible for many nosocomial epidemics in Korea as in other countries. It had been reported that all of 1154 strains of *S.aureus* isolated from 1964 to 1968 in Korea were sensitive to methicillin. Since 1974, several invesigators have been reported that isolation frequencies of MRSA in Korea ranged from 3% to 33% And it had been also

reported that MRSA was more frequently isolated from clinical samples of inpatient that from those of outpatient (Chong, 1986; Chong and Lee, 1983).

In this study, we determined the isolation frequency of MRSA and MRSE isolated from nationwide clinical samples and analyzed in vitro antibiotic sensitivity of eight antibiotics against MRSA and MRSE strains. Tested antibiotics were penicillin-G, vancomycin, first generation cephalosporin (cephazolin), three second generation cephalosporins (cefuroxime, cefoxitin, cefamandole) and two third generation of cephalosporins (cefotaxime, moxalactam).

The results of our study confirm the finidings of other investigators, and the patterns of in vitro antibiotic sensitivity of MRSA and MRSE strains isolated in Korea were similar to that of MRSA and MRSE strains isolated in other countries (Collins et al., 1983; Laverdiere et al., 1978; Markowitz et al., 1983; Richmond et al., 1977).

The data obtained in this study summerized into several comments. First, frequency of resistant strains of *S.aureus* to methicillin in Korea was 24.2% and that of *S.epidermidis* was 36.2%. And against vancomycin, only 0.7% of *S.aureus* and 1.4% of *S.epidermidis* strains were resistant. Penicillin G was no more effective drug against staphylococcus in Korea. 10-20% of *S.aureus* and *S.epidermidis* strains resistant to tested cephalosporins except cefamandole. Among tested cephalosporins, cefamandole was the most effective antibiotic to isolates of staphylococci in Korea. The reason of that may be due to recently introducing cephalosporin in Korea.

Second, almost all of MRSA and MRSE strains isolated in Korea were proved as multiply drug-resistant strains (99.9% among MRSA and 97.6% among MRSE strains). Multiply drug-resistant strains of MRSA were more frequently isolated than other countries (Collins et al., 1983; Laverdirere et al., 1978; Markowitz et al., 1983; Richmond et al., 1977).

Third, vancomycin was very active antibiotic to both MRSA and MRSE strains isolated in Korea. And 70-80% of MRSA strains were resistant against tested cephalosporin except cefamandole. Therefore, at present, cephalosporins may be not suituable antibiotic to treating infection due to these strains in Korea.

In conclusion, most of MRSA and MRSE strains isolated in Korea were multiply drug-resistant strains and vancomycin was most active antibiotic among tested eight antibiotics in Korea.

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