Asian Epidemiology of Pneumococcal Resistance : Data from the ANSORP

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INTRODUCTION

S. pneumoniae has long been one of the most important bacterial pathogens causing pneumonia, meningitis, otitis media, and septicemia [1,2]. It remains the single most common defined pathogen in hospitalized patients with community-acquired pneumonia [3,4]. For many years, pneumococci were uniformly susceptible to penicillin until the first report of penicillin-resistance from a clinical specimen in 1967 [5]. The extensive use of large numbers of antimicrobial agents, however, has fueled the crisis in antibiotic resistance in the era of modern chemotherapy [6].

GLOBAL EPIDEMIOLOGY OF PNEUMOCOCCAL RESISTANCE

During the recent three decades, the resistance of *S. pneumoniae* to penicillin has been rapidly increasing in many parts of the world [7-10]. Data on the prevalence of pneumococcal resistance to penicillin from Hungary, South Africa, and Spain were alarmingly high, with 59%, 45%, and 44% of all pneumococcal isolates, respectively [11-13]. Even in the United States, resistance rate to penicillin among pneumococcal isolates steeply rose up to 25 % in some area [14]. Dr. Appelbaum presented the update epidemiology of pneumococal resistance all over the world in the symposium.

ASIAN EPIDEMIOLOGY OF PNEUMOCOCCAL RESISTANCE

1. Previous data from Asian countries

There have been scanty data regarding pneumococcal resistance in Asian region. If we focus on the Asian epidemiology of pneumococcal resistance, we can easily find out that more thorough epidemiologic investigation is warranted in this area. According to the data based on the MEDLINE search for epidemiologic reports on pneumococcal resistance during recent 10 years, over half of total publications were from Euopean countries and the United States. There were 19 publications from Asian countries. Japan has 9 published data, but 7 of them appeared in local Japanese journals. Korea, Japan, Hong Kong, Taiwan, Philippines, Thailand and Singapore reported the pneumococcal resistance of each country in international journals. This is obviously incomplete and these data lacked controlled design to compare the antimicrobial resistance with each other.

In Japan, penicillin resistance rate ranged from 16 to 42 % according to investigators. Taiwan seems to have a different problem in terms of resistance

pattern. Penicillin resistance in Taiwan is not so high, but multidrug-resistance (MDR) to three or more classes of antibiotics was over 30 %. Hong Kong has 29 % of penicillin resistance in one report in 1995.

Table 1. Reported incidence of pneumococcal resistance from Asian countries until 1996 before the ANSORP study (excluding Korea)

country	Author	Year	Resistance rate	
			Penicillin(HLR))	MDR
Japan	Komori	1996	28(6)	
	Yoshida	1995	16	
	Konno	1994	42	
Taiwan	Hsueh	1996	7(0)	33
	Hsueh	1996	12	41
Hong Kong	Kam	1995	29	

2. Korean epidemiology of pneumococcal resistance

Recent reports from Korea showed that the prevalence of penicillin-resistance ranged from 70 % to 77 % [15-17], which certainly underlined the importance of more thorough and continous epidemiologic investigation of antibiotic resistance in *S. pneumoniae* in this area.

When I analyze the antibiotic resistance of invasive pathogens from 1989 to 1995 in two tertiary care hospitals in Seoul, Korea, penicillin resistance was 68 % with 56 % of high-level resistance (Table 2). Thirty-four percent of total isolates possessed MDR. It means one out of three pneumococcal isolates which cause actual diseases had MDR in Korea.

Table 2. Antibiotic resistance of invasive isolates of pneumococci in Korea (1989-1995)

Antibiotic	Resistance rate(%)(n=104)		
	S	I	R
Penicillin	32.7	10.6	56.7
Cefotaxime	40.4	30.8	28.8
Imipenem	4.24	55.8	0
Erythromycin	43.3	18.3	38.5
Multidrug-resistance		34.6	

In general, β-lactam agents have been the most commonly used antimicrobials in our country in the treatment of infectious diseases. Obviously, the selective pressure from injudicious use of β-lactam antimicrobial agents is certainly the main factor responsible for the development of resistance[18]. Interestingly, over half of the total isolates or almost all isolates with penicillin-resistance were also intermediately susceptible to imipenem according to the current breakpoint from the NCCLS. This figure is consistent with previous data from Korea [15] but is clearly higher than those from other countries [19]. Clinical significance of intermediate susceptibility to

imipenem, however, should be further evaluated. Serogroup distribution could be another contributing factor to high incidence of penicillin-resistance. Serotypes 19F, 23F, 6B, 14, and 1, which most isolates in this study belonged to, are more commonly associated with penicillin resistance.

With regards to the source of penicillin-resistant strains in this study, community-acquired infection (62.5 %) was more common than nosocomial infection, whereas proportion of resistant strains among total strains was similar regardless of mode of acquisition. These data suggest that penicillin-resistance is widely prevalent in the community in Korea and the unusually high rate of resistance in this study was not affected by the nosocomial spread of resistance. The most common type of infection was pneumonia with or without bacteremia regardless of resistance status.

3. Spread of pneumococcal resistance : evidence of clonal origin

One recent data from Korea documented the rapid increase of resistance rate from 29 % in 1988 to 77 % in 1993 [16]. This is about three-fold increase during 5 years. Besides the injudicious use of antimicrobial agents and specific serotypes, spread of resistance could be an another reason for rapidly increasing resistance rate in Korea.

Pulsed-field gel electrophoresis (PFGE) and PBP profile analysis were carried out to document the spread of resistant organisms in Korea, which could amplify the resistance rate. Penicillin-resistance from the remodeling of PBP genes mediated by interspecies recombinational events can spread either by the dissemination of resistant PBP genes (horizontal spread) or by the dissemination of resistant organisms in certain geographical area (clonal spread) [20]. There have been several reports which demonstrated the spread of resistance between different countries or within a certain region since 1991, when the first report documented the intercontinental spread of a multiresistant clone of serotype 23 F *S. pneumoniae* between Spain and Cleveland, USA [21-25]. Our data documented the genetic relationship between Korean MDR strains by PFGE typing, which can provide a high degree of discriminatory power in evaluating the epidemiological relatedness of bacterial pathogens. Over 80 % of MDR strains from Korea showed almost identical DNA restriction patterns on PFGE, which strongly supports the genetic relatedness of resistant pneumococci isolated in our country. Data from PFGE could also document the possible spread of resistant pneumococci between Korea, Spain, and the United States (Fig. 1).

PBP profiles of these strains also confirmed the epidemiological relatedness of resistant pneumococci from Korea and other countries. MDR strains from Korea and other countries in this study showed extensive alterations of PBPs 1a, 2x, and 2b. Most resistant strains, however, shared a common changing pattern of PBP profiles, which represented a PBP family of common clonal origin. The results of PBP patterns were consistent with those of PFGE.

By using PFGE and PBP profiles, we could demonstrate the spread of resistant pneumococci in Korea, which could partly explain the recent increase and the unusually high rate of resistance to penicillin or cephalosporins as well as intercontinental spread of resistant pneumococci between Korea, Spain, and the United States [17].

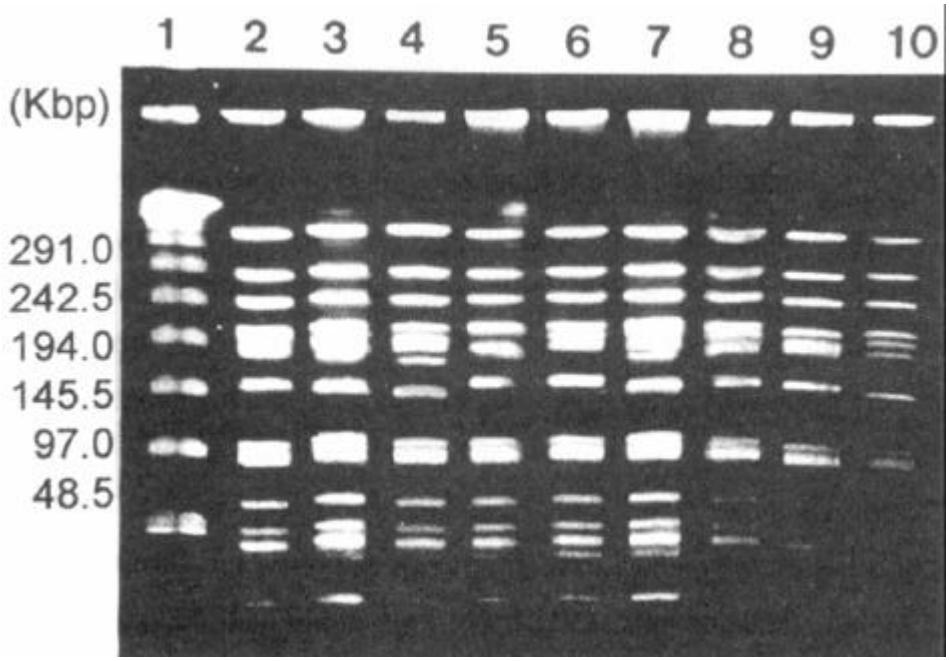

Figure 1. PFGE patterns (type A pattern) of chromosomal DNA restriction fragments of multidrug resistant pneumococcal isolates from different contries digested with Sma I. Lane 1, lambda DNA marker ; lanes 2 to 4, 9 and 10, MDR strains from Korea ; lanes 5 to 7, strains from united states ; lane 8, strain from Spain. Serogroups of strains were 23 (lanes 2,3,5,6,7), 19 (lane 4), and 14 (lane 8). Strains in lanes 9 and 10 were not serotyped.

4. Asian Network for Surveillance of Resistant Pneumococci (ANSORP)

1) Background and history of the ANSORP

ANSORP was first initiated by Dr. Jae-Hoon Song (Samsung Medical Center, Seoul, Korea) in 1996 to carry out more organized surveillance of pneumococcal resistance in Asian region, where epidemiology was not well investigated. As noted in the molecular epidemiologic studies, resistance can spread bewteen different countries and continents. It can be easier for countries, which are geographically close such as Asian countries. ANSORP was organized to serve not only for obtaining the update epidemiology but for the future strategies for control programs of pneumococcal resistance in Asian region. Currently, 17 distinguished investigators from 15 centers in 12 countries in Asia are participating in the ANSORP study. The followings are the current roster of the ANSORP as of April 1997 :

2) ANSORP study

ANSORP study consists of 2 steps ; step 1 is a basic epidemiology using disk diffusion test and Etest, which can document the current status of pneumcoccal resistance in this region. Step 2 is molecular epidemiologic study using PFGE, PCR fingerprinting of PBPs, and ribotyping with resistant strains from Asian countries to

investigate the spread of resistance between countries.

For disk diffusion test, 6 antimicrobial agents were selected according to the recommendation of the National Committee for Clinical Laboratory Standards (NCCLS). Penicillin resistance is screened by 1 μg oxacillin disk. Erythromycin, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin were tested. All in vitro tests were performed according to the unified protocol, which was distributed by me. It was based on the NCCLS manual. Interpretation criteria of the disk diffusion tests were also based on the 1995 NCCLS guideline.

E test was performed for resistant strains which were screened by oxacillin disk diffuion test. For resistant strains, MICs of penicillin, amoxycillin/clavulanate, cefuroxime, cefotaxime, and imipenem were determined by Etest according to the unified study protocol. MIC interpretive standards for *S. pneumoniae* by Etest were based on the 1995 NCCLS guideline [26].

Based on the interim data as of March 1997, ANSORP study showed that Korea has the highest prevalence rate of penicillin-resistance among Asian countries.

Country	ANSORP center code	Investigators	ANSORP center
Korea	1	Jae-Hoon Song, Nam Yong Lee	Samsung Medical Center
Korea	2	Chik Hyun Pai	Asan Medical Center
Japan	3	Satoshi Ichiyama	Nagoya University
Japan	4	Ryoji Yoshida	Nagasaki Univeristy
China	5	Wang Fu	Shanghai Medical Univ.
Hong Kong	6	Seto Wing Hong	Queen Mary Hospital
Thailand	7	Anan Chongthaleong	Saint Louis Hospital
Thailand	8	Nalinee Aswapokee	Mahidol University
Taiwan	9	Cheng-Hsun Chiu	Chang Gung Children's Hospital
India	10	M.K. Lalitha Kurien Thomas	Christian Medical College
Sri Lanka	11	Jennifer Perera	University of Colombo
Singapore	12	Ti Teow Yee	National University Hospital
Malaysia	13	Farida Jamal	Univ. Kebangsaan Malaysia
Indonesia	14	Usman Chatib Warsa	University of Indonesia
Vietnam	15	Bui Xuan Vinh	Nhi Dong 2 Children's Hopital

Japan is next to Korea in terms of penicillin-resistance, where percentage of susceptible strains is lower than that of Korea. Comparing with the previous data from Asian countries, ANSORP study revealed the actual status of resistance in many countries, where antibiotic resistance was not investigated previously, as well as the increasing rate of resistance in Japan, Thailand, Hong Kong, Singapore, and Korea (see figures at the end of the text).

ANSORP study is still ongoing at this moment. Some ANSORP centers already completed their study by disk diffusion test and E test, but others do not yet. The study will be extended until adequate number of strains are tested in each ANSORP centers. Interim data in the text are data which were collected until the end of March, 1997.

Molecular epidemiologic study of the ANSORP is at the beginning stage. Multiresistant strains from Singapore and Taiwan showed that PFGE patterns of some strains were identical with that of Korean strains. These data suggest that there might be spread of resistance between Korea and these countries.

CONCLUSION

Increasing problem of pneumococcal resistance should be the subject of common concern in many countries not only because of high incidences but because of the spread of resistance to geographically distant areas which could amplify the resistance problem. Through the international collaboration study such as the ANSORP study, we can look into the current problem of antimicrobial resistance which is the key to the future strategies for a global crisis.

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