

Comparison of Antibiotic Resistance Rate of Medically Important Microorganisms between Japan and Korea

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Background: A surveillance system for antibiotic resistance is well organized in both Japan and Korea; however, a comparative analysis by microorganism has not previously been conducted.

Methods: We compared the latest antibiotic resistance rates of medically important pathogens, such as *Staphylococcus aureus*, enterococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, between Japan and Korea. Data were collected by JANIS (Japan Nosocomial Infections Surveillance) and KARMS (Korean Antimicrobial Resistance Monitoring System) from 2007-2012.

Results: In 2012, the proportions of oxacillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus faecium* (VRE), cefotaxime-resistant *E. coli*, ceftazidime-resistant *K. pneumoniae*, imipenem-resistant *P. aeruginosa*,

and imipenem-resistant *A. baumannii* were 53%, 0.4%, 16.6%, 2.9%, 18.5%, and 2% in Japan and 67%, 32%, 29%, 40%, 28%, and 70% in Korea, respectively.

Conclusion: There were large differences in the frequencies of VRE, ceftazidime-resistant *K. pneumoniae*, and imipenem-resistant *A. baumannii* between Japan and Korea. A collaborative study to probe the differences in the antibiotic resistance rates between the two countries should be performed. (Ann Clin Microbiol 2015;18:111-118)

Key Words: *Acinetobacter baumannii*, Carbapenem, Resistance, Methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant enterococci

INTRODUCTION

The occurrence of multiple drug resistant microorganisms and increases in antibiotic resistance are hurdles in the management of bacterial infections. Surveillance of antibiotic resistance rates is important to monitor trends and establish policy to combat resistance and provide data for empirical therapy. Regional or national antibiotic resistance data should be provided periodically to clinicians. In addition, efforts to delay or decrease antibiotic resistance should be established. The education of medical personnel on the optimal usage of antibiotics, public antibiotic awareness campaigns, microbiological culture-based management, antibiotic stewardship by infectious disease specialists, prevention of nosocomial infections, and disinfection and clean-

ing of the hospital environment should be implemented together to reduce antibiotic resistance [1].

Although Japan and Korea are very close geographically, we found that the antibiotic resistance rates of some medically important pathogens vary between these countries. These data will help to determine the current state of antibiotic resistance in these two countries as well as understand why these differences exist. Although there were innumerable bacteria isolated from patients, we included the most common bacteria for this comparison, including *Staphylococcus aureus* and enterococci among Gram-positive cocci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* among Gram-negative bacilli.

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MATERIALS AND METHODS

Data on antibiotic resistance rates were collected by JANIS (Japan Nosocomial Infections Surveillance), which is operated by the National Institute of Infectious Diseases in Japan. JANIS is the national surveillance program organized by the Ministry of Health, Labour, and Welfare. JANIS is designed to provide national data on the incidence and prevalence of nosocomial infections and antimicrobial resistant bacteria in hospitals [2]. JANIS also helps each participating hospital map out strategies for infection control. Participation is not mandatory, but voluntary. Approximately 1,300 hospitals with more than 200 beds participate and submit antimicrobial resistance data each month. Microbiologists in the laboratories of the participating hospitals extract data on bacterial isolates from an automated analyzer, convert them to the JANIS format and submit the data to the JANIS website. A feedback report is created within 48 h of data submission. This report shows the inter-hospital comparison of antibiotic resistance or potential outbreaks. Repeat culture data from the same patient within one month is not included in the data. The resistance rate is calculated by the sum of all of the isolates submitted from each hospital.

Data on the antibiotic resistance rates in Korea were retrieved from the annual report produced by KARMS (Korean Antimicrobial Resistance Monitoring System), which is run by the National Institute of Health in Korea [3]. Approximately 30 university-affiliated hospitals or general hospitals (>100 beds) participate in this program and submit antibiotic resistance data once per year. Although KARMS also receives data from small hospitals (<100 beds), we excluded these data for the comparison because the Japanese data were only collected from large hospitals. KARMS also has data on the resistance rates of diarrhea-causing pathogens, *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae*. This organization has also collected nationwide surveillance on vancomycin-resistant *S. aureus* (VRSA) and carbapenemase-producing *Enterobacteriaceae* (CPE). The antibiotic resistance rate is calculated as the arithmetic mean of each hospital's data to reduce bias from larger hospitals. In addition, KARMS excludes data from institutions with less than 20 isolates of an organism. Only the data from the first isolate of each patient are included to remove bias caused by repeated collection. A feedback report is not created for the participating hospitals.

In general, the number of microorganisms analyzed were 5–10 times greater in Japan than in Korea. The number ranged from

25,000 to 200,000 in Japan and 5,000 to 15,000 in Korea, depending on the microorganism. We described only the data on antibiotics tested in both countries at the same time. In the case of *S. aureus*, JANIS reported data separately according to methicillin resistance: methicillin-resistant *S. aureus* (MRSA), and methicillin-susceptible *S. aureus*, whereas KARMS did not separate the data by methicillin resistance. Therefore, we could compare only the oxacillin resistance rate for *S. aureus*. Antibiotic resistance data were compared from 2007 to 2012. Both of JANIS and KARMS used interpretive criteria which was published by Clinical and Laboratory Standards Institute (CLSI). Most of interpretive criteria was identical in both countries except breakpoint for extended-spectrum cephalosporins and carbapenems in *Enterobacteriaceae*. Both breakpoints were changed during 2010–2011, and adopted by KARMS since 2011. However, JANIS did not use new breakpoint and continued to use old breakpoint for consistency of data.

RESULTS

1. Resistance of Gram-positive cocci

1) *Staphylococcus aureus*

Oxacillin-resistant *S. aureus* steadily decreased both in Japan (60.0% in 2008 vs. 53.0% in 2012) and Korea (75% in 2008 vs. 67% in 2012) (Fig. 1A). There is an approximate 15% difference in the oxacillin resistance rate between the two countries. As the resistance rates of other antibiotics were separately presented according to oxacillin resistance in Japan, data on the other antibiotics could not be compared.

2) Enterococci

The resistance rates of *Enterococcus faecalis* to levofloxacin (18–26%) and vancomycin (0%) in Japan were similar to those (levofloxacin 25–34% and vancomycin 1–2%) in Korea, while the resistance rates to ampicillin (0.4–1% in Japan vs. 1–16% in Korea) were very different. The ampicillin resistance rates have gradually increased in Korea.

The resistance rate of *Enterococcus faecium* to ampicillin and levofloxacin in Japan (85–87% and 81–83.4%, respectively) was similarly high (90–94% and 86–93%, respectively) to the rate in Korea, and linezolid resistance was similarly low (0–0.1% in Japan vs. 0.6–1% in Korea). However, the vancomycin resistance rates were remarkably different (0–2% in Japan vs. 26–43% in Korea) (Fig. 1B).

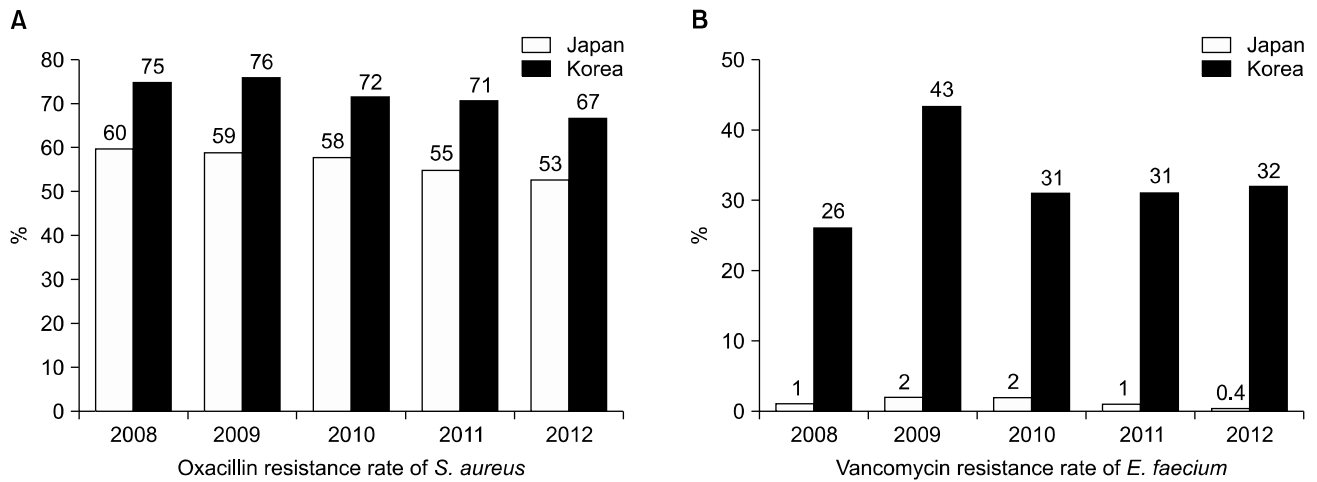


Fig. 1. (A) Oxacillin resistance rate of *Staphylococcus aureus*. (B) Vancomycin resistance rate of *Enterococcus faecium*.

Table 1. Antibiotic resistance rate of *Escherichia coli* in Japan and Korea*

Antibiotics	Years											
	2007		2008		2009		2010		2011		2012	
	J	K	J	K	J	K	J	K	J	K	J	K
Ampicillin	43	67	45	67	44	69	46	70	48	69	49	70
Amikacin	0	3	0	1	0	2	0	2	0.2	4	0.2	1
Levofloxacin	24	28	27	32	27	32	30	36	31	40	34	40
Cefotaxime	7	13	9	21	10	22	13	23	15	26	17	29
Ceftazidime	3	11	3	19	3	20	4	21	5	24	5	27
Aztreonam	5	9	6	20	6	21	7	22	9	25	9	27
Imipenem	0	0	0	0.1	0	<0.1	0	0.3	0.1	0.1	0.1	0.2

*In Korea, revised breakpoint for extended-spectrum cephalosporins and carbapenems were adopted since 2011.

Abbreviations: J, Japan; K, Korea.

2. Resistance of Gram-negative rods

1) *E. coli*

The resistance rate to levofloxacin was similar between the two countries, with 24-34.3% in Japan and 28-40% in Korea (Table 1). The resistance rate of *E. coli* to cefotaxime ranged from 7 to 16.6% in Japan to 13 to 29% in Korea. The ceftazidime resistance rates were 3-5.2% in Japan and 11-27% in Korea. Similarly, resistance to aztreonam was 5-9.4% in Japan and 9-27% in Korea. The resistance rates to amikacin and imipenem were as low as 0-0.2% and 0-0.1% in Japan to 1-4% and 0-0.2% in Korea, respectively.

2) *K. pneumoniae*

The resistance rates to amikacin ranged from 0 to 0.3% in Japan; however, the resistance rates were as high as 11-20% in

Korea (Table 2). The resistance rate to levofloxacin was also very different (2-2.7% in Japan vs. 16-32% in Korea). The *K. pneumoniae* cefotaxime resistance rates were 3-5.4% in Japan and 33-44% in Korea. The ceftazidime resistance rates were 2.9-3.4% in Japan and 36-47% in Korea. Similarly resistance rates to aztreonam were 3.7-5% in Japan and 28-48% in Korea. Resistance to imipenem was as low as 0-0.2% in Japan and 0.2-1% in Korea.

3) *P. aeruginosa*

The resistance rate to amikacin in *P. aeruginosa* was very low (2.6-4%) in Japan, whereas it was as high as 15-26% in Korea (Table 3). Similarly, there was a discrepancy in the gentamicin resistance rate between Japan (6.1-10%) and Korea (22-35%). This pattern was similar for piperacillin (11-12.1% in Japan vs. 30-39% in Korea). Resistance to levofloxacin was

Table 2. Antibiotic resistance rate of *Klebsiella pneumoniae* in Japan and Korea*

Antibiotics	Years											
	2007		2008		2009		2010		2011		2012	
	J	K	J	K	J	K	J	K	J	K	J	K
Amikacin	0	18	0	20	0	20	0	15	0.3	11	0.2	11
Levofloxacin	2	16	2	26	2	32	2	27	3	28	2	30
Cefotaxime	3	33	5	36	4	44	5	37	5	38	5	41
Ceftazidime	3	36	3	39	3	47	3	37	3	39	3	40
Aztreonam	4	28	5	40	5	48	4	37	4	40	4	41
Imipenem	0	0.2	0	0.5	0.8	4	0	0.5	0.2	0.6	0.2	1

*In Korea, revised breakpoint for extended-spectrum cephalosporins and carbapenems were adopted since 2011.

Abbreviations: J, Japan; K, Korea.

Table 3. Antibiotic resistance rate of *Pseudomonas aeruginosa* in Japan and Korea

Antibiotics	Years											
	2007		2008		2009		2010		2011		2012	
	J	K	J	K	J	K	J	K	J	K	J	K
Amikacin	4	21	4	26	3	25	3	22	3	16	3	15
Gentamicin	10	30	8	35	7	31	7	31	7	23	6	22
Levofloxacin	19	34	19	39	18	39	18	42	17	36	16	41
Piperacillin	11	30	12	38	11	39	12	36	12	32	12	31
Ceftazidime	12	21	12	28	12	28	12	26	11	22	11	23
Cefepime	11	21	11	30	10	27	10	27	10	20	9	22
Aztreonam	18	27	19	27	18	29	17	26	16	24	17	28
Imipenem	22	23	22	29	20	32	21	29	20	25	19	28
Meropenem	14	19	15	24	14	25	13	22	12	33	12	24

Abbreviations: J, Japan; K, Korea.

twice as high as in Korea (16–19% vs. 36–41%). The resistance rates were slightly higher for aztreonam (16.3–19% vs. 24–28%), ceftazidime (10.9–12% vs. 22–28%), and cefepime (8.9–11% vs. 20–30%) in Korea. Resistance to imipenem was slightly higher (18.5–22% vs. 23–32%), and resistance to meropenem was moderately higher (11.8–15% vs. 22–33%) in Korea.

4) *A. baumannii*

The resistance rates of *A. baumannii* were markedly different between the two countries. Although the resistance rates to ampicillin-sulbactam (4–7.2%), amikacin (3–5%), imipenem (2–2.2%), and meropenem (2–2.9%) were less than 10% in Japan, those to amikacin (36–53%), ampicillin-sulbactam (40–70%), imipenem (27–72%), and meropenem (40–68%) were much higher in Korea (Table 4). In particular, the resistance rates to imipenem and meropenem steadily increased in Korea each year. The resistance rates to gentamicin (9.6–11%), levofloxacin (7–11%), pi-

peracillin (9–16%), ceftazidime (7–10.5%), and cefepime (10–12%) were approximately 10% in Japan, while they were 58–78% for gentamicin, 58–73% for levofloxacin, 58–80% for piperacillin, 57–78% for ceftazidime, and 55–76% for cefepime in Korea.

DISCUSSION

Antibiotic resistance has been closely monitored in both Japan and Korea. However, the numbers of participating hospitals are quite different, accordingly so are the numbers of bacteria analyzed. The JANIS system is more interactive and current because JANIS provides a feedback report within 48 hrs and each laboratory submits data every month. This feedback report might be very helpful for monitoring the outbreak of certain organisms or detecting quality control problems in the laboratory. KARMS receives data annually from a restricted

Table 4. Antibiotic resistance rate of *Acinetobacter baumannii* in Japan and Korea

Antibiotics	Years											
	2007		2008		2009		2010		2011		2012	
	J	K	J	K	J	K	J	K	J	K	J	K
Ampicillin-sulbactam	4	40	6	51	9	53	6	70	4	59	7	53
Amikacin	5	52	4	49	3	48	4	53	5	48	5	36
Gentamicin	11	58	10	64	11	69	10	78	10	68	10	66
Levofloxacin	7	NA	9	58	10	66	11	73	10	69	10	71
Piperacillin	9	62	11	58	14	68	16	80	13	73	13	73
Ceftazidime	7	57	8	63	9	72	10	78	10	70	11	69
Cefepime	10	55	10	58	11	71	12	76	10	70	11	69
Imipenem	2	27	2	45	2	52	2	72	2	67	2	70
Meropenem	2	40	2	52	2	57	2	53	3	NA	2	68

Abbreviations: J, Japan; K, Korea; NA, not available.

numbers of hospitals. To provide more credible nationwide data, the number of participating hospitals should be extended. In addition, more frequent data submissions and feedback reports should be designed in the future. The calculation of the mean resistance rate is different between JANIS and KARMS. JANIS used the sum of all of the data, whereas KARMS calculated the arithmetic mean. Each method has an advantage, but the calculation method should be discussed between the two institutions in the future.

The *S. aureus* oxacillin resistance rate was very high in the late 2000s; however, it has decreased slightly recently. MRSA was approximately 15% lower in Japan compared to Korea. A molecular epidemiological study demonstrated that community genotypes had already emerged as a result of intensive care unit (ICU)-acquired MRSA infection [4]. Therefore, it is important to control both community-acquired and hospital-acquired MRSA infections [4,5]. Cohorting MRSA patients or carriers might reduce transmission to nearby inpatients. Accurate diagnosis, strict regulation of antibiotic usage, improved hand hygiene or antibiotic stewardship by infectious disease specialists might be necessary to reduce MRSA infections [1]. A survey was performed on the infection control of multidrug-resistant microorganisms in Korea's general hospitals in 2005 [6]. Approximately two-thirds of these hospitals had antibiotic control programs, and 96% had control programs for multidrug-resistant microorganisms. Surveillance cultures for MRSA and VRE (vancomycin-resistant *E. faecium*) were taken in 26.7% and 21.6%, respectively, at that time. According to a recent report by KONSAR (Korean Nationwide Surveillance of Antibiotic Resistance program) in 2011, the rate of MRSA was 66% and

the rate of VRE was 23%. The KONSAR program has operated since 1988 and was initiated with support from WHO (World Health Organization) [7]. Many hospitals have participated voluntarily in submitting antibiotic resistance rates to KONSAR annually.

Although vancomycin resistance in *E. faecalis* was very rare in both countries, there was a large difference in *E. faecium*. The resistance rate of *E. faecium* to vancomycin occurred at a rate of less than 2% in Japan, whereas the rate was more than 40% in Korea in 2012. The antibiotics used for the treatment of MRSA infections or oral vancomycin usage for treatment of *Clostridium difficile*-associated diseases might have caused this huge difference in VRE. There was a successful control of a VRE outbreak in the ICU by the implementation of aggressive, multifaceted interventions, such as cohorting, active rectal surveillance cultures, daily extensive cleaning of environmental surfaces and environmental cultures, antibiotic restriction, and education of the hospital staff [8]. Some people argue that antibiotic overuse for livestock, especially chickens, might be the major contributing factor to the VRE surge. Although the use of avoparcin, a glycopeptide antibiotic, was banned for livestock farms starting in 1999, 2.9% of chickens were VRE positive [5]. Strict regulation of antibiotic use was implemented in Korea in 2011 [5]. However, there was no genetic correlation found between VRE isolated from humans and chickens in 2005 in Korea [9]. Therefore, further investigation is required to determine the impact on humans from antibiotic used on livestock. The current very low VRE rate in Japan seems quite curious, considering that VRE is rather common in Western countries and Korea [5]. The reason of the low VRE rate in Japan should

be studied further to provide insight into ameliorating the VRE issue in Korea.

Extended-spectrum β -lactamase (ESBL) producing *E. coli* were 2-3 times more common, whereas the incidence of ESBL-producing *K. pneumoniae* was almost 10 times more common in Korea. Compared to *E. coli*, the resistance rates to amikacin and levofloxacin also exhibited large differences in *K. pneumoniae*. According to a previous report by KONSAR, increases in ceftazidime- and fluoroquinolone-resistant *K. pneumoniae* were noted from 2005 to 2007 [10]. The rate of cefotaxime-resistant *E. coli* was 17% and cefotaxime-resistant *K. pneumoniae* was 24% in the KONSAR 2011 study [11]. There is a discrepancy in the data between KONSAR and KARMS because the participating hospitals are different. The data may have also been affected by the types of susceptibility tests used in the participating hospitals, such as disk diffusion or commercial broth microdilution, and the breakpoint of CLSI. A 13-year study at a single university-affiliated hospital demonstrated an increase in the *E. coli* resistance rate to cefotaxime and ciprofloxacin, but not in *K. pneumoniae* [12]. CTX-M-producing ST131 *E. coli* have emerged as a significant cause of both community-onset and hospital-acquired infections in Japan and Korea as well as in the other Asian countries [13]. There was a correlation between monthly ciprofloxacin use and the monthly rate of ciprofloxacin-resistant *E. coli* [14], suggesting that restricting antibiotic use might decrease antibiotic resistance rates under certain conditions. Carbapenem-producing *Enterobacteriaceae* do not seem to be a serious problem in either country.

For *P. aeruginosa*, the resistance rates to amikacin, gentamicin, piperacillin, ceftazidime, and cefepime were 2-3 times higher in Korea. Resistance to imipenem or meropenem was moderately higher in Korea. An alarming rise in imipenem-resistant *P. aeruginosa* (3% in 1998 to 27.8% in 2010) and *A. baumannii* (5% in 1998 to 68.9% in 2010) was observed in the 13-year study [12]. The rate of imipenem-resistant *P. aeruginosa* was 22%, and imipenem-resistant *A. baumannii* was 64% in the KONSAR 2011 study [11]. In case of *A. baumannii*, the resistance rates to amikacin, ampicillin-sulbactam, imipenem and meropenem were almost 10 times higher in Korea. This large gap in multidrug-resistant (MDR) *A. baumannii* should be well studied in both countries. Carbapenem-resistant *A. baumannii* is also highly prevalent in China, Taiwan, and Hong Kong [13]. A previous KONSAR study noted a gradual increase in imipenem-resistant *Acinetobacter* spp. (22% in 2007) [10]. Carbapenem resistance was mostly due to OXA type carbapenemase pro-

duction in *A. baumannii* [7]. It is difficult to prevent *Acinetobacter* spp. infections in hospitalized patients because these organisms are ubiquitous in the hospital environment [7]. Multiple interventions, including cohorting, promotion of hand hygiene, active surveillance in ICU, and environmental cleaning, might have controlled the carbapenem-resistant *A. baumannii* outbreak in a tertiary care hospital in Korea [15]. In addition, increased usage of alcohol-based hand gel and a decrease in carbapenem consumption in the hospital might have reduced the incidence of carbapenem-resistant *A. baumannii* [15].

We suggested a cooperative study regarding VRE and MDR *A. baumannii* between the two countries because there is a large difference in the observed resistance rates. There were many presentations in the Japan-Korea joint symposium about the microorganisms listed in this article. However, further steps should be made to understand why some bacteria exhibited similar antibiotic resistance patterns and others, especially VRE and MDR *A. baumannii*, are so different.

In conclusion, the authors compared the nationwide antibiotic resistance report systems in Japan and Korea. JANIS collected data from more than 1,000 hospitals and seems to be rather interactive and current because of the monthly data submission. The feedback report is helpful in monitoring outbreaks of multidrug resistant pathogens. JANIS has a plan to open the system to the smaller hospitals as well as to the foreign countries. The KARMS system is less rigorous than JANIS. KARMS recruited data from only 32 hospitals with more than 100 beds, although it did also include data from commercial laboratories, which primarily handle specimens from small hospitals or clinics. Annual data submission and no feedback report may limit the utilization of KARMS' data. However, KARMS has collected data from smaller hospitals and includes additional data points, such as the resistance rates of *M. tuberculosis* and *N. gonorrhoeae*, and VRSA surveillance. Additional investments should be made by the government to establish an interactive system, such as JANIS, and more laboratories should participate to make representative nationwide data. Additionally, the quality control of antibiotic susceptibility tests or harmonization of reports using the same minimal inhibitory concentration breakpoint criteria should be considered by JSCM (Japanese Society for Clinical Microbiology) and KSCM (Korean Society for Clinical Microbiology) in the future. More active and cooperative activities should be carried out between these two organizations to solve problems related to antibiotic resistance.

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=국문초록=

한국과 일본의 주요 병원균 항균제 내성률 비교

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배경: 한국과 일본에서 항균제 내성률 조사는 잘 이루어지고 있지만, 직접 균종별로 비교한 연구는 많지 않다.

방법: 저자들은 임상적으로 중요한 황색포도알균, 장알균, 대장균, 폐렴간균, 녹농균 및 *Acinetobacter baumannii*에 대하여 한국과 일본의 항생제 내성률을 비교하였다. 2007년부터 2012년까지 한국 KARMS (Korean Antimicrobial Resistance Monitoring System)와 일본 JANIS (Japan Nosocomial Infections Surveillance) 자료를 참조하였다.

결과: 2012년 메티실린내성 황색포도알균, 반코마이신내성 장알균, 세프트락심내성 대장균, 세프트리지담내성 폐렴간균, 이미페넴내성 녹농균 및 이미페넴내성 *A. baumannii* 비율은, 한국에서는 각각 67%, 32%, 29%, 40%, 28%와 70%인 반면, 일본에서는 각각 53%, 0.4%, 16.6%, 2.9%, 18.5% 및 2%를 보였다.

결론: 한국에서의 내성률이 일본에 비해서 높았지만, 특히 반코마이신내성 장알균, 세프트리지담내성 폐렴간균 및 이미페넴내성 *A. baumannii* 비율이 매우 큰 차이를 보이고 있어, 이에 대한 추후 한일공동연구가 필요하다. [Ann Clin Microbiol 2015;18:111-118]

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