Correlation between antibiotic use and antibiotic resistance: A multicenter study using the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system in Hokkaido, Japan

Keisuke Kagami, Ph.D. [a, b, *], Nobuhisa Ishiguro, M.D., Ph.D. [b], Sumio Iwasaki, B.S. [b, c], Takayuki Usami, B.S. [b, c], Tatsuya Fukumoto, Ph.D. [b, c], Kasumi Hayasaka [b, c], Reiko Oyamada [b], Tsubasa Watanabe [b], Sho Nakakubo, M.D., Ph.D. [b, d], Yusuke Niinuma, B.S. [a, b], Takashi Hagino, B.S. [e], Yoshifumi Abe, M.S. [e], Ikuya Fujimoto, M.S. [f], Hideki Maekawa, B.S. [g], Ryo Fujibayashi, B.S. [g], Satoshi Fuke, M.D., Ph.D [h, i], Kuniko Asahi [i, j], Shuichi Ota, M.D., Ph.D. [k, l], Tatsuya Nagakura, B.S. [l], Toshinari Okubo, M.S. [m], Hideomi Asanuma, M.D., Ph.D. [n], Toshihiro Ito, M.D. [o], Sho Okano, B.S. [p], Erika Komatsu, B.S. [q], Kota Sasaki, B.S. [r], Kei Hashimoto, B.S. [s], Kazutoshi Washiya, B.S. [s], Yumiko Kato [t], Katsunori Kusumi [u], Yasufumi Asai, M.D., Ph.D [v], Yuichi Saito, B.S. [w], Yoshiyuki Sakai, M.D., Ph.D. [x], Minoru Sakurada, B.S. [y], Yuji Sakimoto, B.S. [z, aa], Yukari Ichikawa, M.S. [ab], Takahiro Kinebuchi, B.S. [ac], Dai Kondo, B.S. [ad], Syuhei Kanno, B.S. [ae, af], Minoru Kobayashi [af], Kagami Hirabayashi, M.D., Ph.D. [ag, ah], Shinako Saitou [ah, ai], Katsuhiko Saito, Ph.D. [aj], Yuuki Ebina, B.S. [ak], Yuusuke Koshizaki [al], Makoto Chiba, M.S. [am], Atsushi Yasuda [an], Toshiya Sato, M.D., Ph.D. [ao, ap], Atsuo Togashi, M.D., Ph.D. [ao, ap], Takashi Abe [aq], Takahiro Fujita, M.D., Ph.D, M.P.H. [ar], Kengo Umehara, M.S. [as], Masaru Amishima, M.D., Ph.D. [at], Nobuo Murakami, M.D., Ph.D. [au, av], Tetsuya Yagi, M.D., Ph.D. [aw], Shuhei Fujimoto, M.D., Ph.D. [ax], Taichi Tajima, M.P.H. [ay], Mitsuru Sugawara, Ph.D. [a, az], Yoh Takekuma, Ph.D. [a], and the Hokkaido Infection Control Group (HICG)

[a] Department of Pharmacy, Hokkaido University Hospital; Kita-14-jo, Nishi-5-chome, Kita-ku, Sapporo 060-8648, Japan

[b] Department of Infection Control and Prevention, Hokkaido University Hospital; Kita-14-jo, Nishi-5-chome, Kita-ku, Sapporo 060-8648, Japan

[c] Division of Laboratory and Transfusion Medicine, Hokkaido University Hospital; Kita-14-jo, Nishi-5-chome, Kita-ku, Sapporo 060-8648, Japan

[d] Department of Respiratory Medicine, Faculty of Medicine, Hokkaido University; Kita-15-jo, Nishi-7-chome, Kita-ku, Sapporo 060-8648, Japan

[e] Infection Control Room, NTT Medical Center Sapporo; Minami-1-jo, Nishi-15-chome, Chuo-ku, Sapporo 060-0061, Japan

[f] Department of Pharmacy, Kitasapporo Hospital; Shinkotoni 9 Jo 1-1-1, Kita-ku, Sapporo 001-0909, Japan

[g] Department of Pharmacy, Hokkaido Gastroenterology Hospital; Honcho-1-jo, 1-chome, Higashi-ku, Sapporo 065-0041, Japan

[h] Department of Respiratory Medicine, KKR Sapporo Medical Center; Hiragishi 1-jo, 6-chome, Toyohira-ku, Sapporo 062-0931, Japan

[i] Department of Infection Control and Prevention, KKR Sapporo Medical Center; Hiragishi 1-jo, 6-chome, Toyohira-ku, Sapporo 062-0931, Japan

[j] Department of Laboratory Medicine, KKR Sapporo Medical Center; Hiragishi 1-jo, 6-chome, Toyohira-ku, Sapporo 062-0931, Japan

[k] Department of Hematology, Sapporo Hokuyu Hospital; Higashi-Sapporo 6-6, Shiroishi-ku, Sapporo 003-0006, Japan

[l] Department of Infection Control and Prevention, Sapporo Hokuyu Hospital; Higashi-Sapporo 6-6, Shiroishi-ku, Sapporo 003-0006, Japan

[m] Department of Pharmacy, IMS Sapporo Internal Medicine Rehabilitation Hospital; 124 Teinekayayama, Teine-ku, Sapporo 006-0049, Japan

[n] Department of Neonatology, Hokkaido Medical Center for Child Health and Rehabilitation;

Kanayama 1-jo, 1-chome, Teine-ku, Sapporo 006-0041, Japan

[o] Department of Cardiology, Sapporo Teishinkai Hospital; Kita-33-jo, Higashi-1-chome 3-1, Higashi-ku, Sapporo 065-0033, Japan

[p] Department of Pharmacy, Sapporo Teishinkai Hospital; Kita-33-jo, Higashi-1-chome 3-1, Higashi-ku, Sapporo 065-0033, Japan

[q] Department of Pharmacy, Ebetsu City Hospital; Wakakusacho-6, Ebetsu 067-8585, Japan

[r] Department of Clinical Laboratory, Ebetsu City Hospital; Wakakusacho-6, Ebetsu 067-8585, Japan

[s] Department of Pharmacy, Hakodate Goryoukaku Hospital; 38-3, Goryoukaku-cho, Hakodate 040-8611, Japan

[t] Department of Infection Control and Prevention, Hakodate Central General Hospital; 33-2, Honcho, Hakodate, Hokkaido 040-8585, Japan

[u] Department of Pharmacy, Hakodate Central General Hospital; 33-2, Honcho, Hakodate, Hokkaido 040-8585, Japan

[v] Department of Cardiology, Hakodate Shintoshi Hospital; 331-1 Ishikawa-cho, Hakodate, Hokkaido 041-0802, Japan

[w] Department of Pharmacy, Hakodate Shintoshi Hospital; 331-1 Ishikawa-cho, Hakodate, Hokkaido 041-0802, Japan

[x] Department of Pediatrics, Hakodate Municipal Hospital; 1-10-1, Minato-cho, Hakodate-shi, Hokkaido 041-8680, Japan

[y] Department of Pharmacy, Hakodate Municipal Hospital; 1-10-1, Minato-cho, Hakodate-shi, Hokkaido 041-8680, Japan

[z] Department of Pharmacy, Yakumo General Hospital; 50 Shinonome-cho, Yakumo Town, Futami-gun 049-3197, Japan

[aa] Infection Control Room, Yakumo General Hospital; 50 Shinonome-cho, Yakumo Town,

Futami-gun 049-3197, Japan

[ab] Infection Control Management, Asahikawa Red Cross Hospital; 1-1-1-1, Akebono, Asahikawa 070-8530, Japan

[ac] Department of Laboratory Medicine, Social Welfare Corporation Hokkaido Social Work Association Furano Hospital; 1-30, Sumiyoshi-cho, Furano-shi, Hokkaido 076-8765, Japan

[ad] Department of Pharmacy, Social Welfare Corporation Hokkaido Social Work Association Furano Hospital; 1-30, Sumiyoshi-cho, Furano-shi, Hokkaido 076-8765, Japan

[ae] Department of Pharmacy, Oji General Hospital; 3-4-8, Wakakusacho, Tomakomai, Hokkaido 053-0021, Japan

[af] Infection Control Room, Oji General Hospital; 3-4-8, Wakakusacho, Tomakomai, Hokkaido 053-0021, Japan

[ag] Department of Cardiologists, Tomakomai City Hospital; 5-20, Simizu-1-chome, Tomakomai 053-8567, Japan

[ah] Department of Infection Control and Prevention, Tomakomai City Hospital; 5-20, Simizu-1-chome, Tomakomai 053-8567, Japan

[ai] Department of Infection Prevention and Control Certified Nurse, Tomakomai City Hospital; 5-20, Simizu-1-chome, Tomakomai 053-8567, Japan

[aj] Department of Pharmacy, Nemuro City Hospital; 1-2, Ariiso-cho, Nemuro, Hokkaido 087-8686, Japan

[ak] Department of Pharmacy, Obihiro Kosei General Hospital; 10-chome, 1-banchi, Nishi14-jominami, Obihiro 080-0024, Japan

[al] Department of Clinical Laboratory Technology, Obihiro Kosei General Hospital; 10-chome, 1-banchi, Nishi14-jominami, Obihiro 080-0024, Japan

[am] Department of Pharmacy, Kitami Red Cross Hospital; Kita-6-jo, Higashi-2-chome, Kitami 090-8666, Japan

[an] Department of Clinical Laboratory, Kitami Red Cross Hospital; Kita-6-jo, Higashi-2-chome, Kitami 090-8666, Japan

[ao] Department of Pediatrics, Iwamizawa Municipal General Hospital; 9-jo, Nishi-7-chome, 2-banchi, Iwamiziawa 068-8555, Japan

[ap] Department of Infection Prevention Office, Iwamizawa Municipal General Hospital; 9-jo, Nishi-7-chome, 2-banchi, Iwamiziawa 068-8555, Japan

[aq] Department of Laboratory Medicine, Takikawa Municipal Hospital; Ohmachi 2-2-34, Takikawa, Hokkaido 073-0022, Japan

[ar] Department of Infectious Diseases, National Hospital Organization Hokkaido Cancer Center; 4-2-3-54-Kikusui, Shiroishi-ku, Sapporo 003-0804, Japan

[as] Department of Pharmacy, National Hospital Organization Hokkaido Cancer Center; 4-2-3-54-Kikusui, Shiroishi-ku, Sapporo 003-0804, Japan

[at] Office for Infection Control and Prevention, NHO Hokkaido Medical Center; Yamanote 5-7-1-1, Nishi-ku, Sapporo 063-0005, Japan

[au] Center for Regional Medicine, Gifu University School of Medicine; 1-1, Yanagido, Gifu 501-1194, Japan

[av] Gifu General Healthcheckup Centre; 4-47, Hikie, Gifu 501-6133, Japan

[aw] Department of Infectious Diseases, Nagoya University Hospital; 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan

[ax] Department of Bacteriology and Bacterial Infection, Division of Host Defense Mechanism, Tokai University School of Medicine; 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan

[ay] AMR Clinical Reference Center, National Center for Global Health and Medicine; 1-21-1, Toyama, Shinjuku, Tokyo 162-8655, Japan.

[az] Laboratory of Pharmacokinetics, Faculty of Pharmaceutical Sciences, Hokkaido University; Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan

*Corresponding Author

Keisuke Kagami, Ph.D.

Department of Pharmacy, Hokkaido University Hospital; Kita-14-jo, Nishi-5-chome, Kita-ku, Sapporo 060-8648, Japan

Tel: +81-11-706-5685; Fax: +81-11-706-7616; E-mail: kkagami@huhp.hokudai.ac.jp

Conflict of Interest

All authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Correlation between antibiotic use and antibiotic resistance: A multicenter study using the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system in Hokkaido, Japan

Highlights

- The J-SIPHE system enabled multicenter analysis of antibiotic use and resistance.
- Carbapenem use correlated with carbapenem-resistant *Pseudomonas aeruginosa* occurrence.
- Quinolone use correlated with fluoroquinolone-resistant *Escherichia coli* occurrence.

Correlation between antibiotic use and antibiotic resistance: A multicenter study using the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system in Hokkaido, Japan

Abstract

Background: The Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system aggregates information related to antimicrobial resistance (AMR) measures in participating medical institutions nationwide and is intended to be used for promotion of AMR measures in participating facilities and their communities. This multicenter study aimed to determine the usefulness of the J-SIPHE system for evaluating the correlation between antibiotic use and antibiotic resistance in Hokkaido, Japan.

Methods: Data on antibiotic use and detection rate of major resistant Gram-negative bacteria at 19 hospitals in 2020 were collected from the J-SIPHE system, and data correlations were analyzed using JMP Pro.

Results: The detection rate of carbapenem-resistant *Pseudomonas aeruginosa* was significantly positively correlated with carbapenem use (Spearman's $\rho = 0.551$; $P = 0.015$). There were significant positive correlations between the detection rate of fluoroquinolone-resistant *Escherichia coli* and the use of piperacillin/tazobactam, carbapenems, and quinolones [$\rho = 0.518$ ($P = 0.023$), $\rho = 0.76$ ($P < 0.001$), and $\rho = 0.502$ ($P = 0.029$), respectively].

Conclusion: This is the first multicenter study to investigate the correlation between antibiotic use and antibiotic resistance using the J-SIPHE system. The results suggest that using this system may be beneficial for promoting AMR measures.

Keywords: J-SIPHE; multicenter study; surveillance; antibiotic use; antimicrobial resistance

Correlation between antibiotic use and antibiotic resistance: A multicenter study using the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system in Hokkaido, Japan

Introduction

In recent years, the increase in antimicrobial resistance (AMR) has become a global issue, threatening public health.[1-3] Resistant bacteria make it difficult to treat infections, extending hospital stay, increasing medical costs, and increasing the mortality rate.[1-3] Various factors are involved in the increase in AMR, with the rise in antibiotic use being one factor.[4-12] However, the evidence for the correlation between antibiotic use and antibiotic resistance is controversial.[4-12] Furthermore, many studies investigating this correlation involved a single facility.[4-12] Therefore, a multicenter study is required to clarify this correlation.

The Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system[13] is a national surveillance system for AMR measures. It was developed by the National Center for Global Health and Medicine, the AMR Clinical Reference Center, commissioned by the Japanese government in 2019, in response to adoption of the Global Action Plan on AMR issued by the World Health Organization (WHO).[14,15] The J-SIPHE system aims to aggregate information related to AMR measures in medical institutions nationwide and is intended to be utilized for promotion of AMR measures in participating facilities and their communities (Figure 1).[13] The aggregated information includes the status of antibiotic use, the emergence of major bacteria and antimicrobial-resistant bacteria, hand rub usage, and the incidence of healthcare-associated and bloodstream infections. Data are uploaded by medical institutions on the website of the J-SIPHE system and aggregated in the J-SIPHE server. The registered information can be visualized as a graph on the website and downloaded at any time. Each medical institution, such as local communities and related facilities, can use the data when

introducing AMR measures in each facility and regional cooperation. In addition, aggregated data are provided by the AMR Clinical Reference Center to medical institutions as annual reports, playing the role of a national database.

The J-SIPHE system can aggregate data on antibiotic use and the detection rate of resistant bacteria. However, no studies have investigated these correlations using data from the J-SIPHE system. In the present study, we collected individual data on antibiotic use and the detection rate of resistant bacteria from the J-SIPHE system. We statistically analyzed these correlations via a multicenter study in Hokkaido, Japan. In this study, we evaluated the correlation between broad-spectrum antibiotics and five Gram-negative resistant bacteria (carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacteriaceae*, fluoroquinolone-resistant *Escherichia coli*, third-generation cephalosporin-resistant *E. coli*, and third-generation cephalosporin-resistant *Klebsiella pneumoniae*). These bacteria have been of concern due to their increasing resistance rate and are targeted in the AMR countermeasure plan of the Japanese government.[15]

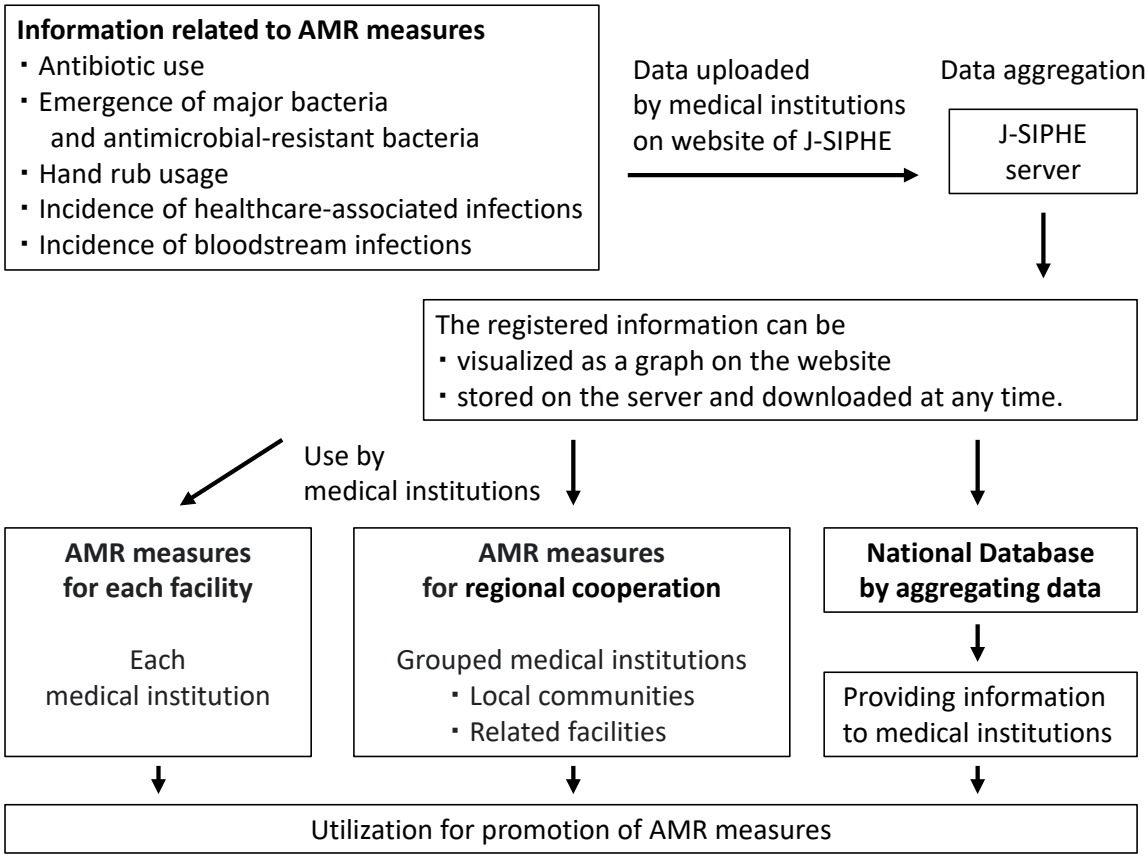

Figure 1

Figure 1. Overview of the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) system. Abbreviations: AMR, antimicrobial resistance.

Methods

Study design

This cross-sectional study was conducted in Japan's Hokkaido Infection Control Group (HICG). The participating hospitals were NTT Medical Center Sapporo, Kitasapporo Hospital, Hokkaido Gastroenterology Hospital, KKR Sapporo Medical Center, Sapporo Hokuyu Hospital, IMS Sapporo Internal Medicine Rehabilitation Hospital, Hokkaido Medical Center for Child Health and Rehabilitation, Sapporo Teishinkai Hospital, Ebetsu City Hospital, Hakodate Goryoukaku Hospital, Hakodate Central General Hospital, Hakodate Shintoshi Hospital, Hakodate Municipal Hospital, Yakumo General Hospital, Asahikawa Red Cross Hospital, Social Welfare Corporation Hokkaido Social Work Association Furano Hospital, Oji General Hospital, Tomakomai City Hospital, Nemuro City Hospital, Obihiro Kosei General Hospital, Kitami Red Cross Hospital, Iwamizawa Municipal General Hospital, Takikawa Municipal Hospital, Hokkaido University Hospital, National Hospital Organization Hokkaido Cancer Center, and NHO Hokkaido Medical Center. Each participating hospital registered data related to AMR measures in the J-SIPHE system. On the website of the J-SIPHE system, the amount of antibiotic use and the number of detected resistant bacteria per hospitalized patient were automatically calculated. In this study involving 26 hospitals, the data of 19 hospitals that registered both antibiotic use and resistant bacteria information in 2020 were collected from the website, and their correlations were analyzed.

This study analyzed national surveillance data that did not include individual patient data; hence, the requirement for ethics committee approval and informed consent was waived.

Antibiotic use

The amount of antibiotics used was obtained from the J-SIPHE system; the study analyzed

the broad-spectrum antibiotic use (piperacillin/tazobactam, third-generation cephalosporins, fourth-generation cephalosporins, carbapenems, aminoglycosides, and quinolones, including both intravenous and oral antibiotics). Antibiotic use was evaluated based on the antibiotic use density (AUD). AUD was calculated as antibiotic use (in grams)/defined daily dose (DDD) per 100 patient-days on the website of the J-SIPHE system. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, as assigned by the World Health Organization (WHO).[16]

Antibiotic resistance

Susceptibility testing was performed via the broth microdilution method with the turbidity standard technique using a MicroScan WalkAway plus System (Beckman Coulter, Tokyo, Japan). Susceptibility was determined following the Clinical Laboratory Standards Institute (CLSI) guideline.[17]

The number of detected resistant bacteria per 1,000 patient-days was obtained from the J-SIPHE system and included carbapenem-resistant *P. aeruginosa*, carbapenem-resistant *Enterobacteriaceae*, fluoroquinolone-resistant *E. coli*, third-generation cephalosporin-resistant *E. coli*, and third-generation cephalosporin-resistant *K. pneumoniae*. If the same bacteria were detected multiple times in the same patients within one month, it was counted as a one-time detection.

Correlations between antibiotic use and antibiotic resistance and between use of each antibiotic

We analyzed the correlation between the amount of antibiotic use and the detection rate of resistant bacteria. In addition, we also analyzed the correlation between each antibiotic use in order to consider confounding factors. For example, if some antibiotic uses are correlate with

the detection rate of resistant bacteria, it is unclear whether all of them are directly associated with the resistant bacteria, or only one antibiotic is directly associated with the resistant bacteria and other antibiotics are confounding factors caused by the status of antibiotic use in hospitals.

Analysis by ward

For hospitals where ward information on antibiotic use and/or resistant bacteria was registered in the J-SIPHE system, we also analyzed antibiotic use and resistance by ward characteristics. The wards were divided into intensive care unit (ICU), medical, and surgical wards for analysis.

Analysis by the presence or absence of certified nurses in infection control

We analyzed antibiotic use and the detection rate of resistant bacteria in hospitals with and without certified nurses in infection control, who receive certification from the Japanese Nursing Association and most of them work as full-time infection preventionists.

Statistical analysis

Correlations between antibiotic use and antibiotic resistance and correlations between each antibiotic use were analyzed using Spearman's rank correlation coefficient. Antibiotic use and antibiotic resistance by ward were analyzed using the Steel-Dwass test. Antibiotic use and antibiotic resistance in hospitals with or without certified nurses in infection control were analyzed using the Wilcoxon rank-sum test. For all comparisons, P values < 0.05 were considered statistically significant. All calculations were performed using JMP Pro version 14 (SAS Institute Inc., Japan).

Results

Participating hospitals

In this study, 19 hospitals were evaluated; 3 hospitals had < 200 beds, 14 hospitals had 200–500 beds, and 2 hospitals had ≥ 500 beds (Table 1). The median number of beds was 327 (interquartile range [IQR], 255–480). The characteristics of the wards in the 19 hospitals are shown in Table 1.

Table 1. Characteristics of wards in 19 hospitals in the Hokkaido Infection Control Group (HICG)

Hospital	Total (bed number)	Ward		
		ICU	Medical	Surgical
A	924	38	426	460
B	532	50	229	253
C	492	34	314	144
D	484	10	288	186
E	480	–	316	164
F	472	49	155	268
G	440	8	169	263
H	438	46	237	155
I	380	6	205	169
J	327	–	252	75
K	281	8	185	88
L	272	30	90	152
M	270	4	167	99
N	270	–	133	137
O	255	–	131	124
P	244	28	61	155
Q	177	8	119	50
R	135	–	135	–
S	95	–	95	–

Abbreviations: ICU, intensive care unit.

Antibiotic use

The data on broad-spectrum antibiotic use in the 19 hospitals is shown in Table 2. Quinolones were used most often [median AUD (IQR), 3.24 (1.56–3.94)] followed by third-generation cephalosporins [median AUD (IQR), 3.01 (2.23–5.01)]. The median AUD of carbapenems was 1.13 (IQR, 0.59–1.81).

Antibiotic resistance

The number of detected resistant bacteria per 1,000 patient-days in the 19 hospitals is shown in Table 2. Fluoroquinolone-resistant *E. coli* was detected most frequently [median (IQR), 0.68 (0.54–0.8)] followed by third-generation cephalosporin-resistant *E. coli* [median (IQR), 0.41 (0.31–0.58)].

Table 2. Antibiotic use and detection rate of resistant bacteria in 19 hospitals in the Hokkaido Infection Control Group (HICG)

Antibiotic agent/resistant bacteria	Median (interquartile ranges)	
Antibiotic use		
(AUD: DDDs/100 patient-days)		
Piperacillin/tazobactam	1.92	(1.37–2.89)
Third-generation cephalosporins	3.01	(2.23–5.01)
Fourth-generation cephalosporins	0.45	(0.17–1.18)
Carbapenems	1.13	(0.59–1.81)
Aminoglycosides	0.1	(0.03–0.27)
Quinolones	3.24	(1.56–3.94)
The resistant bacteria detection rate		
(Number of detected resistant bacteria/1,000 patient-days)		
Carbapenem-resistant *Pseudomonas aeruginosa*	0.08	(0.05–0.19)
Carbapenem-resistant *Enterobacteriaceae*	0.01	(0–0.04)
Fluoroquinolone-resistant *Escherichia coli*	0.68	(0.54–0.8)
Third-generation cephalosporin-resistant *Escherichia coli*	0.41	(0.31–0.58)
Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	0.05	(0.02–0.08)

Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses.

Correlation between antibiotic use and resistant bacteria

The correlation between the amount of antibiotic use and the detection rate of resistant bacteria is shown in Table 3 and Figure 2. In carbapenem-resistant *P. aeruginosa*, the detection rate was significantly positively correlated with carbapenem use (Spearman's $\rho = 0.551$; $P = 0.015$) and negatively correlated with third-generation cephalosporin use (Spearman's $\rho = -0.467$; $P = 0.044$). In carbapenem-resistant *Enterobacteriaceae*, the detection rate was significantly positively correlated with fourth-generation cephalosporin use (Spearman's $\rho = 0.641$; $P = 0.003$). In fluoroquinolone-resistant *E. coli*, there were significant positive correlations between the detection rate and quinolone use (Spearman's $\rho = 0.502$; $P = 0.029$) and piperacillin/tazobactam (Spearman's $\rho = 0.518$; $P = 0.023$) and carbapenem use (Spearman's $\rho = 0.76$; $P < 0.001$). In the case of both third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, the detection rates were significantly positively correlated with carbapenem use (Spearman's $\rho = 0.54$; $P = 0.017$ and Spearman's $\rho = 0.565$; $P = 0.012$, respectively).

Table 3. The correlation between the amount of broad-spectrum antibiotic use and the detection rate of five Gram-negative resistant bacteria

Antibiotic agent	Carbapenem-resistant *Pseudomonas aeruginosa*		Carbapenem-resistant *Enterobacteriaceae*		Fluoroquinolone-resistant *Escherichia coli*		Third-generation cephalosporin-resistant *Escherichia coli*		Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	
	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
Piperacillin/tazobactam	0.14	0.567	0.4	0.09	0.518	0.023*	0.302	0.209	0.294	0.222
Third-generation cephalosporins	-0.467	0.044*	0.228	0.347	0.154	0.528	-0.035	0.887	0.032	0.898
Fourth-generation cephalosporins	-0.019	0.938	0.641	0.003**	0.17	0.486	-0.153	0.533	0.306	0.203
Carbapenems	0.551	0.015*	0.283	0.241	0.76	<0.001***	0.54	0.017*	0.565	0.012*
Aminoglycosides	-0.168	0.491	-0.044	0.859	-0.17	0.486	-0.079	0.748	0.266	0.271
Quinolones	0.279	0.248	0.353	0.138	0.502	0.029*	0.197	0.42	0.341	0.154

ρ indicates Spearman's correlation coefficient.

*, **, *** Statistically significant correlations ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively).

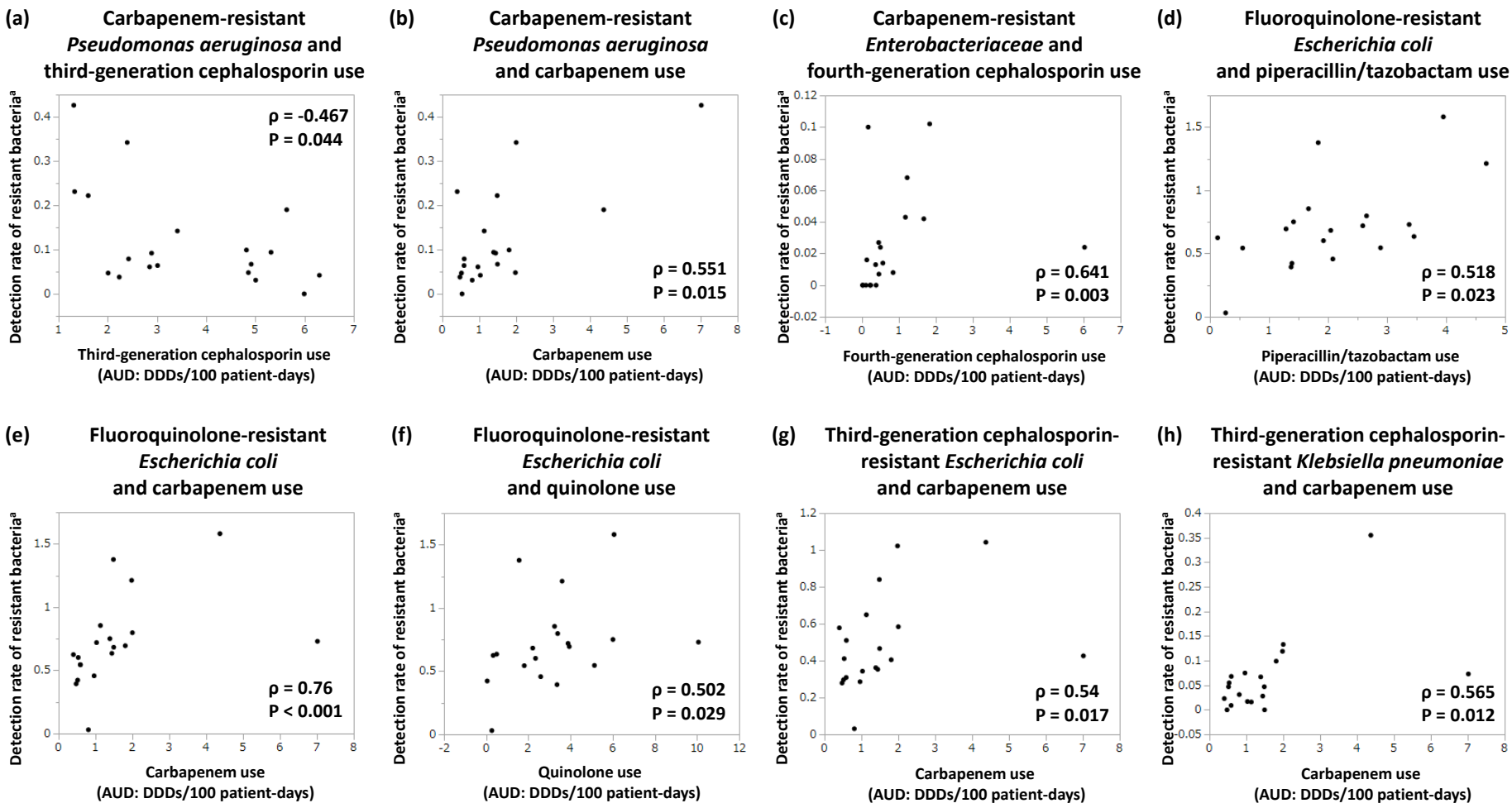

Figure 2

Figure 2. The correlation between amount of broad-spectrum antibiotic use and detection rate of (a), (b) carbapenem-resistant *Pseudomonas*

aeruginosa, (c) carbapenem-resistant *Enterobacteriaceae*, (d), (e), (f) fluoroquinolone-resistant *Escherichia coli*, (g) third-generation cephalosporin-resistant *E. coli*, and (h) third-generation cephalosporin-resistant *Klebsiella pneumoniae*. Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses.

[a] Detection rate of resistant bacteria was calculated as the number of detected resistant bacteria/1,000 patient-days.

ρ indicates Spearman's correlation coefficient

Correlation between antibiotic uses

The correlations between each antibiotic use are shown in Table 4. There were significant positive correlations between piperacillin/tazobactam use and fourth-generation cephalosporin (Spearman's $\rho = 0.468$; $P = 0.043$) and carbapenem use (Spearman's $\rho = 0.616$; $P = 0.005$). In addition, significant positive correlations were observed between quinolone use and piperacillin/tazobactam (Spearman's $\rho = 0.505$; $P = 0.027$), fourth-generation cephalosporin (Spearman's $\rho = 0.618$; $P = 0.005$), and carbapenem use (Spearman's $\rho = 0.54$; $P = 0.017$).

Table 4. The correlation between the amount of broad-spectrum antibiotic uses

Antibiotic agent	Piperacillin/tazobactam		Third-generation cephalosporins		Fourth-generation cephalosporins		Carbapenems		Aminoglycosides		Quinolones	
	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
Piperacillin/tazobactam	–	–	0.193	0.429	0.468	0.043*	0.616	0.005**	-0.012	0.96	0.505	0.027*
Third-generation cephalosporins	0.193	0.429	–	–	0.168	0.491	0.126	0.606	0.432	0.065	0.274	0.257
Fourth-generation cephalosporins	0.468	0.043*	0.168	0.491	–	–	0.439	0.06	-0.077	0.753	0.618	0.005**
Carbapenems	0.616	0.005**	0.126	0.606	0.439	0.06	–	–	-0.039	0.875	0.54	0.017*
Aminoglycosides	-0.012	0.96	0.432	0.065	-0.077	0.753	-0.039	0.875	–	–	0.102	0.679
Quinolones	0.505	0.027*	0.274	0.257	0.618	0.005**	0.54	0.017*	0.102	0.679	–	–

ρ indicates Spearman's correlation coefficient.

*, ** Statistically significant correlations ($P < 0.05$ and $P < 0.01$, respectively).

Analysis by ward

We analyzed the antibiotic use and detection rate of resistant bacteria by ward for hospitals where ward-specific information on antibiotic use and/or resistant bacteria was registered in the J-SIPHE system; antibiotic use and detection rate of resistant bacteria in hospital wards were analyzed in 16 and 14 hospitals, respectively (Table 5). Carbapenem use was significantly higher in ICU wards [median AUD (IQR), 4.84 (2.03–6.7)] than in medical [median AUD (IQR), 1.31 (0.61–2.05); P = 0.015] and surgical wards [median AUD (IQR), 1.16 (0.89–1.62); P = 0.002]. The detection rate of carbapenem-resistant *P. aeruginosa* was also higher in ICU wards [median (IQR), 0.42 (0.07–1.94]) than in medical [median (IQR), 0.06 (0.02–0.19); P = 0.105] and surgical wards [median (IQR), 0.09 (0.06–0.18); P = 0.187], although the difference was not statistically significant.

1 Table 5. Antibiotic use and detection rate of resistant bacteria in hospital wards

2

Antibiotic agent/Resistant bacteria	ICU wards (n = 11 for antibiotic use) (n = 10 for resistant bacteria)		Medical wards (n = 16 for antibiotic use) (n = 14 for resistant bacteria)		Surgical wards (n = 14 for antibiotic use) (n = 12 for resistant bacteria)		P value		
							ICU versus Medical wards	ICU versus Surgical wards	Medical versus Surgical wards
Antibiotic use (n = 16)									
(AUD: DDDs/100 patient-days)									
Piperacillin/tazobactam	4.18	(1.87–8.57)	2.62	(1.7–3.44)	1.55	(1.08–2.53)	0.391	0.217	0.283
Third-generation cephalosporins	4.45	(1.9–5.94)	5.16	(2.57–6.13)	3.39	(2.27–4.27)	0.811	0.673	0.129
Fourth-generation cephalosporins	0.31	(0.15–1.07)	0.63	(0.28–2.11)	0.32	(0.15–0.45)	0.364	1	0.108
Carbapenems	4.84	(2.03–6.7)	1.31	(0.61–2.05)	1.16	(0.89–1.62)	0.015*	0.002**	0.994
Aminoglycosides	0.11	(0–0.2)	0.1	(0.04–0.26)	0.09	(0.05–0.28)	0.837	0.847	1
Quinolones	1.97	(0.98–2.95)	4.02	(2.74–6.32)	2.85	(2.68–5.41)	0.139	0.113	0.671
The resistant bacteria detection rate (n = 14)									
(Number of detected resistant bacteria/1,000 patient-days)									
Carbapenem-resistant *Pseudomonas aeruginosa*	0.42	(0.07–1.94)	0.06	(0.02–0.19)	0.09	(0.06–0.18)	0.105	0.187	0.72
Carbapenem-resistant *Enterobacteriaceae*	0	(0–0.02)	0.01	(0–0.03)	0.02	(0–0.05)	0.592	0.338	0.953
Fluoroquinolone-resistant *Escherichia coli*	1.68	(0.8–2.93)	0.64	(0.46–0.92)	0.64	(0.5–0.9)	0.082	0.05	0.997
Third-generation cephalosporin-resistant *Escherichia coli*	1.25	(0.33–1.89)	0.39	(0.26–0.73)	0.37	(0.33–0.41)	0.138	0.07	0.997
Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	0.05	(0–0.41)	0.05	(0.02–0.13)	0.04	(0–0.1)	1	0.897	0.956

Antibiotic use in hospital wards was analyzed in the following 16 hospitals: A–K, M, N, and Q–S shown in Table 1.

The detection rate of resistant bacteria in hospital wards was analyzed in the following 14 hospitals: A–H, K, M, O, and Q–S shown in Table 1.

Data are presented as medians (interquartile ranges).

*, ** Statistically significant differences ($P < 0.05$ and $P < 0.01$, respectively).

Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses; ICU, intensive care unit.

Analysis by the presence or absence of certified nurses in infection control

We analyzed antibiotic use and the detection rate of resistant bacteria in hospitals with and without certified nurses in infection control (Table 6). There were no significant differences in antibiotic use between hospitals with and without certified nurses in infection control. Among resistant bacteria, the detection rate of carbapenem-resistant *P. aeruginosa* was significantly higher in hospitals with certified nurses in infection control [median (IQR), 0.09 (0.06–0.21]) than in those without certified nurses in infection control [median (IQR), 0.03 (0–0.05)] (P = 0.022).

Table 6. Antibiotic use and detection rate of resistant bacteria in hospitals with and without certified nurses in infection control

Antibiotic agent/Resistant bacteria	Hospitals with certified nurses in infection control (n = 16)		Hospitals without certified nurses in infection control (n = 3)		P value
Antibiotic use (AUD: DDDs/100 patient-days)					
Piperacillin/tazobactam	1.94	(1.38–2.83)	1.92	(0.27–4.68)	0.955
Third-generation cephalosporins	2.87	(2.06–4.89)	5.01	(4.86–5.99)	0.083
Fourth-generation cephalosporins	0.41	(0.14–1.21)	0.45	(0.38–0.5)	0.955
Carbapenems	1.26	(0.59–1.73)	0.81	(0.53–1.98)	0.78
Aminoglycosides	0.09	(0.03–0.22)	0.46	(0.03–0.95)	0.199
Quinolones	3.3	(1.62–4.83)	2.34	(0.27–3.6)	0.467
The resistant bacteria detection rate (Number of detected resistant bacteria/1,000 patient-days)					
Carbapenem-resistant *Pseudomonas aeruginosa*	0.09	(0.06–0.21)	0.03	(0–0.05)	0.022*
Carbapenem-resistant *Enterobacteriaceae*	0.01	(0–0.04)	0.02	(0–0.03)	1
Fluoroquinolone-resistant *Escherichia coli*	0.69	(0.54–0.79)	0.6	(0.03–1.21)	0.615
Third-generation cephalosporin-resistant *Escherichia coli*	0.42	(0.32–0.58)	0.41	(0.03–1.02)	0.955
Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	0.05	(0.02–0.07)	0.06	(0.03–0.12)	0.538

Data are presented as medians (interquartile ranges).

* Statistically significant difference ($P < 0.05$).

Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses.

Discussion

This is the first multicenter study to investigate the correlation between antibiotic use and antibiotic resistance based on the J-SIPHE system data.[13] Although this correlation has been investigated in several studies, data from single institutions were used, producing controversial results.[4-12] Therefore, a multicenter study is needed to clarify this correlation. In the current multicenter study, we showed several correlations between antibiotic use and the detection rate of resistant bacteria.

The J-SIPHE system can aggregate information related to AMR measures in participating medical institutions nationwide.[13] The aggregated information includes antibiotic use, antibiotic resistance, and other information, such as approaches to and structure of infection control, hand rub usage, and incidence of healthcare-associated and bloodstream infections. Therefore, using this system enables a multicenter study focusing not only on antibiotic use and antibiotic resistance but also on several additional factors useful for the promotion of AMR measures.

We demonstrated that the J-SIPHE system could facilitate analysis of the correlation between antibiotic use and antibiotic resistance in multiple centers in local communities. Furthermore, sharing such analyzed information with each regional facility may contribute to developing regional AMR measures.

In the current study, quinolones were used most often, followed by third-generation

cephalosporins, piperacillin/tazobactam, carbapenems, fourth-generation cephalosporins, and aminoglycosides (Table 2). This trend was almost consistent with a previous multicenter study in Europe,[18] except that aminoglycosides were used more often than piperacillin/tazobactam in the European study.

Some reports from Asia and Europe noted a positive correlation between carbapenem-resistant *P. aeruginosa* and carbapenem use[12,19-21] but some did not.[4-8,22] In our study, a significant positive correlation was observed between carbapenem use and the detection rate of carbapenem-resistant *P. aeruginosa*, supporting the results of previous studies showing this correlation. Third-generation cephalosporin use was negatively correlated with the detection rate of carbapenem-resistant *P. aeruginosa*. This reason could not be revealed from our study. However, it is unlikely that this correlation was caused by a negative correlation between carbapenem and third-generation cephalosporin use (Table 4).

Some studies have demonstrated a positive correlation between the detection rate of carbapenem-resistant *Enterobacteriaceae* and carbapenem use[4,9,10,19]; although there was no significant association between these in our study, this might be explained by the small sample size involved in it. The detection rate of carbapenem-resistant *Enterobacteriaceae* was lower than other bacteria evaluated in this study (Table 2); this bacterium was not detected in 6 of the 19 hospitals. This low detection rate of carbapenem-resistant *Enterobacteriaceae* in the participating institutions is consistent with the result of a previous study in Europe, where this

bacterium was not detected at the investigated hospital in a seven-year study.[22] However, it is unknown why carbapenem-resistant *Enterobacteriaceae* was positively correlated with fourth-generation cephalosporins use.

Our study indicated that quinolone use was correlated with the detection rate of fluoroquinolone-resistant *E. coli*, which is consistent with the results of previous studies.[4,7,11,23] The detection rate of fluoroquinolone-resistant *E. coli* was also correlated with piperacillin/tazobactam and carbapenem use. This might be explained by the fact quinolone use was associated with piperacillin/tazobactam and carbapenem use in our data (Table 4); piperacillin/tazobactam and carbapenem use may have been confounding factors. Our finding on the correlation between quinolone use and fluoroquinolone-resistant *E. coli* was also consistent with the results from a Spanish multicenter study investigating the relationship between antibiotic use and the prevalence of *Enterobacteriaceae* resistant to fluoroquinolones from 1999 to 2010.[24] On the other hand, our result was not consistent with the results of a study conducted at a university hospital in the Czech Republic from 2000 to 2011, which demonstrated no correlation between quinolone use and fluoroquinolone-resistant *E. coli*.[25] In the Czech study, the authors discussed that the resistance to fluoroquinolones probably occurred due to the circulation of resistance genes in bacterial populations, and was not affected by quinolone use. Therefore, when interpreting our results, effects other than antimicrobial use on resistant bacteria should also be considered.

Our study showed that third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae* were correlated with carbapenem use. Meyer et al.[26] investigated changes in antibiotic consumption and antibiotic resistance over 8 years and demonstrated that an increase in occurrence of third-generation cephalosporin-resistant *E. coli*, indicating an increase in occurrence of extended-spectrum β-lactamase (ESBL)-producing bacteria, was associated with an increase in carbapenem use. They discussed that this was due to the increase in occurrence of third-generation cephalosporin-resistant *E. coli*. Therefore, the correlation between the detection rate of third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae* and the use of carbapenem might indicate the use of carbapenem to treat ESBL-producing bacteria.

Due to the nature of multicenter research, this study was likely biased by different institutional characteristics. In order to consider the different characteristics of hospitals, we investigated the characteristics of wards in each hospital and analyzed the antibiotic use and detection rate of resistant bacteria by ward (Tables 1 and 5). As a result, piperacillin/tazobactam and carbapenem use in the ICU was higher than that in the medical and surgical wards. This trend was consistent with a previous ward-level multicenter study performed in Europe.[18] Notably, the detection rates of carbapenem-resistant *P. aeruginosa* and third-generation cephalosporin-resistant *E. coli* were also higher in the ICU than in medical and surgical wards. This might be related to the result of the higher use of carbapenem in the

ICU, considering the fact carbapenem use was positively correlated with the detection rate of carbapenem-resistant *P. aeruginosa* and third-generation cephalosporin-resistant *E. coli* (Table 3 and Figure 2). In the current study, differences were observed in the proportion of ICU to other wards in each hospital. Therefore, the above-mentioned ward characteristics should be considered when interpreting our results.

Various factors are involved in the development of AMR. Therefore, the results of the current study may be affected by several biases, including infection control practices. To consider different infection control measures implemented in participating hospitals, we analyzed antibiotic use and the detection rate of resistant bacteria in hospitals with and without certified nurses in infection control (Table 6). Unexpectedly, the detection rate of carbapenem-resistant *P. aeruginosa* was significantly higher in hospitals with certified nurses in infection control than in those without. This reason could not be revealed from our study. In the current study, hospitals without certified nurses in infection control had fewer beds. Therefore, it is possible that hospital characteristics other than infection control, including the number of beds, might have been confounding factors.

This is the ecological study that cannot fully prove a causative relationship between antibiotic use and resistance. AMR is related not only to antibiotic use, but also to multiple factors, such as antimicrobial stewardship intervention, infection control strategy, clonal spread of strains, occurrence of outbreaks due to resistant organisms, inter-hospital transfer of

resistance, and community contribution.[22,25,26] Considering this, the complex nature of the spread and emergence of AMR could, at least partly, explain the results of the current study. Therefore, the involvement of these factors should be considered when interpreting our results.

Although several studies have investigated the correlation between antibiotic use and resistance, the results of these studies are controversial.[4-12] In this study, we showed several correlations between antibiotic use and resistant bacteria. This is the first multicenter study to investigate this correlation using the J-SIPHE system, and showed that using the J-SIPHE system can easily be used to monitor and evaluate the relationship between antibiotic use and antibiotic resistance in local communities. As mentioned above, the spread and emergence of AMR is multifaceted, and is not only affected by antibiotic use.[22,25,26] However, monitoring of antibiotic use and resistant bacteria constitutes an essential part of antimicrobial stewardship programs,[27] and recognizing this correlation is considered to be a useful tool for developing antimicrobial stewardship policies.[22] We believe that the current study has the added value and future perspectives that could contribute to promote the use of the J-SIPHE system for other local communities and encourage AMR measures such as antimicrobial stewardship implementation in their facilities in the future.

Despite the importance of multicenter studies, this study has several limitations. First, this retrospective study did not consider differences between participating hospitals, such as bed

numbers, clinical departments, patient parameters, infection control strategies, antimicrobial stewardship interventions, and the occurrence of outbreaks due to resistant organisms. Second, this study investigated the correlation between antibiotic use and antibiotic resistance in the same period and did not take into account the time lag of the change in bacterial resistance rate. Third, AUD measurements are useful for benchmarking, but may not fully correlate with AMR due to intrinsic biases; for example in the case of low-dose administration in pediatric patients or individuals with renal dysfunction.[28] Finally, we did not conduct multivariable analysis and could not exclude confounding factors, such as the correlation associated with use of different antibiotics. These limitations should be considered when interpreting our results.

In conclusion, this is the first study to investigate the correlation between antibiotic use and antibiotic resistance in a multicenter study using the J-SIPHE system.[13] Using this system, several correlations between antibiotic use and antibiotic resistance were observed. Although the correlations between antibiotic use and antibiotic resistance were controversial in previous studies,[4-12] we showed the possibility that an increase in carbapenem and quinolone use was associated with an increase in carbapenem-resistant *P. aeruginosa* and fluoroquinolone-resistant *E. coli*, respectively. However, further studies using the J-SIPHE system are needed to elucidate the correlation between antibiotic use and antibiotic resistance more accurately.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Cao H, Phe K, Laine GA, Russo HR, Putney KS, Tam VH. An institutional review of antimicrobial stewardship interventions. J Glob Antimicrob Resist 2016;6:75–7. https://doi.org/10.1016/j.jgar.2016.03.006.

2. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis 2006;42;Supplement 2:S82–9. https://doi.org/10.1086/499406.

3. Roberts RR, Hota B, Ahmad I, Scott 2nd RD, Foster SD, Abbasi F, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis 2009;49:1175–84. https://doi.org/10.1086/605630.

4. Guo W, Sun F, Liu F, Cao L, Yang J, Chen Y. Antimicrobial resistance surveillance and prediction of Gram-negative bacteria based on antimicrobial consumption in a hospital setting: A 15-year retrospective study. Medicine 2019;98:e17157. https://doi.org/10.1097/MD.0000000000017157.

5. Guo W, He Q, Wang Z, Wei M, Yang Z, Du Y, et al. Influence of antimicrobial consumption on gram-negative bacteria in inpatients receiving antimicrobial resistance therapy from 2008–2013 at a tertiary hospital in Shanghai, China. Am J Infect Control 2015;43:358–64. https://doi.org/10.1016/j.ajic.2014.12.010.

6. Hao Y, Chen S, Chang H, Yan X, Zhou W, Cao X, et al. Temporal association between carbapenems usage and antimicrobial resistance in gram-negative bacteria at a tertiary hospital in Nanjing, China. Diagn Microbiol Infect Dis 2020;98:115083. https://doi.org/10.1016/j.diagmicrobio.2020.115083.

7. Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991–2003 at a university hospital in Taiwan. Int J Antimicrob Agents 2005;26:463–72. https://doi.org/10.1016/j.ijantimicag.2005.08.016.

8. Lai CC, Wang CY, Chu CC, Tan CK, Lu CL, Lee YC, et al. correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. J Antimicrob Chemother

2011;66:1374–82. https://doi.org/10.1093/jac/dkr103.

9. Lee HS, Loh YX, Lee JJ, Liu CS, Chu C. Antimicrobial consumption and resistance in five Gram-negative bacterial species in a hospital from 2003 to 2011. J Microbiol Immunol Infect 2015;48:647–54. https://doi.org/10.1016/j.jmii.2014.04.009.

10. Prakobsrikul N, Malathum K, Santanirand P, Chumnumwat S, Piebpien P, Montakantikul P. Correlation between antimicrobial consumption and the prevalence of carbapenem-resistant *Escherichia coli* and carbapenem-resistant *Klebsiella pneumoniae* at a university hospital in Thailand. J Clin Pharm Ther 2019;44:292–9. https://doi.org/10.1111/jcpt.12791.

11. Wu HH, Liu HY, Lin YC, Hsueh PR, Lee YJ. Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant *Escherichia coli*. J Microbiol Immunol Infect 2016;49:424–9. https://doi.org/10.1016/j.jmii.2011.12.019.

12. Xu J, Duan X, Wu H, Zhou Q. Surveillance and correlation of antimicrobial usage and resistance of *Pseudomonas aeruginosa*: a hospital population-based study. PLOS ONE

2013;8:e78604. https://doi.org/10.1371/journal.pone.0078604.

13. National Center for Global Health and Medicine, AMR Clinical Reference Center. Japan surveillance for infection prevention and healthcare epidemiology (J-SIPHE) annual report 2019. [Cited 31 Oct 2021]. Available from: https://j-siphe.ncgm.go.jp/files/JSIPHE_AnnualReport_2019en.pdf.

14. World Health Organization (WHO). Global action plan on antimicrobial resistance. [Cited 31 Oct 2021]. Available from: http://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf.

15. The Government of Japan. National action plan on antimicrobial resistance (AMR); 2016–2020. [Cited 31 Oct 2021]. Available from: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf.

16. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignments; 2020. [Cited 31 Oct 2021]. Available from: https://www.whocc.no/atc_ddd_index/.

17. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty-first informational supplement M100-S21. Wayne, PA: CLSI; 2011.

18. Muller A, Bertrand X, Rogues AM, Péfau M, Alfandari S, Gauzit R, et al. ATB-RAISIN network steering committee. Higher third-generation cephalosporin prescription proportion is associated with lower probability of reducing carbapenem use: a nationwide retrospective study. Antimicrob Resist Infect Control 2018;7:11. https://doi.org/10.1186/s13756-018-0302-8.

19. Yang P, Chen Y, Jiang S, Shen P, Lu X, Xiao Y. Association between antibiotic consumption and the rate of carbapenem-resistant Gram-negative bacteria from China based on 153 tertiary hospitals data in 2014. Antimicrob Resist Infect Control 2018;7:137. https://doi.org/10.1186/s13756-018-0430-1.

20. Mladenovic-Antic S, Kocic B, Velickovic-Radovanovic R, Dinic M, Petrovic J, Randjelovic G, et al. Correlation between antimicrobial consumption and antimicrobial resistance of Pseudomonas aeruginosa in a hospital setting: a 10-year study. J Clin Pharm

Ther 2016;41:532-7. https://doi.org/10.1111/jcpt.12432.

21. Lepper PM, Grusa E, Reichl H, Högel J, Trautmann M. Consumption of imipenem correlates with beta-lactam resistance in Pseudomonas aeruginosa. Antimicrob Agents Chemother 2002;46:2920-5. https://doi.org/10.1128/AAC.46.9.2920-2925.2002.

22. Mascarello M, Simonetti O, Knezevich A, Carniel LI, Monticelli J, Busetti M, et al. Correlation between antibiotic consumption and resistance of bloodstream bacteria in a University Hospital in North Eastern Italy, 2008–2014. Infection 2017;45:459-67. https://doi.org/10.1007/s15010-017-0998-z.

23. Yang P, Chen Y, Jiang S, Shen P, Lu X, Xiao Y. Association between the rate of fluoroquinolones-resistant gram-negative bacteria and antibiotic consumption from China based on 145 tertiary hospitals data in 2014. BMC Infect Dis 2020;20:269. https://doi.org/10.1186/s12879-020-04981-0.

24. Asensio A, Alvarez-Espejo T, Fernandez-Crehuet J, Ramos A, Vaque-Rafart J, Bishopberger C, et al.; Estudio de Prevalencia de las Infecciones Nosocomiales en España (EPINE) Working Group. Trends in yearly prevalence of third-generation

cephalosporin and fluoroquinolone resistant *Enterobacteriaceae* infections and antimicrobial use in Spanish hospitals, Spain, 1999 to 2010. Euro Surveill 2011;16:19983. https://doi.org/10.2807/ese.16.40.19983-en.

25. Sedláková MH, Urbánek K, Vojtová V, Suchánková H, Imwensi P, Kolář M. Antibiotic consumption and its influence on the resistance in *Enterobacteriaceae*. BMC Res Notes 2014;7:454. https://doi.org/10.1186/1756-0500-7-454.

26. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14:R113. https://doi.org/10.1186/cc9062.

27. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clin Infect Dis 2016;62:e51-77. https://doi.org/10.1093/cid/ciw118.

28. Morris AM. Antimicrobial stewardship programs: appropriate measures and metrics to

study their impact. Curr Treat Options Infect Dis 2014;6:101-12.

https://doi.org/10.1007/s40506-014-0015-3.