



Title	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
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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

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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

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

4

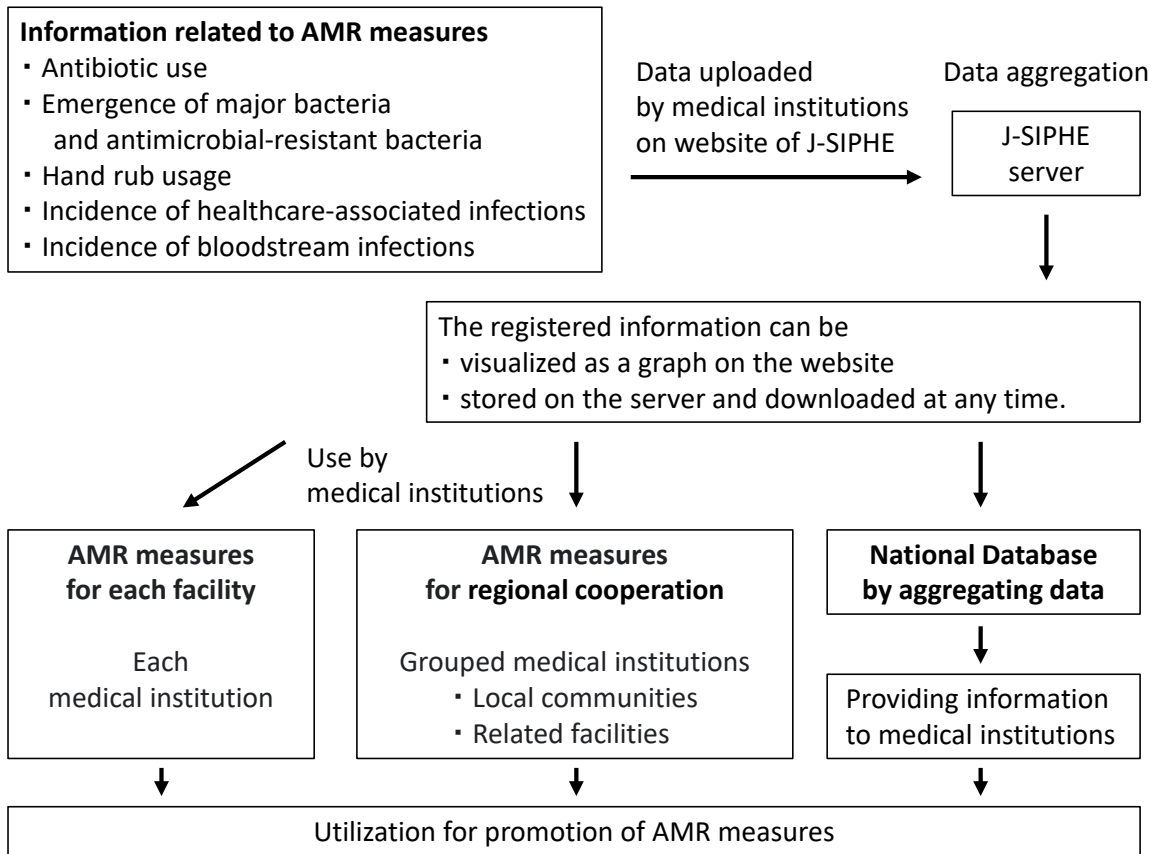
5 **Introduction**

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

13 The Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)
14 system¹³ is a national surveillance system for AMR measures. It was developed by the National
15 Center for Global Health and Medicine, the AMR Clinical Reference Center, commissioned by
16 the Japanese government in 2019, in response to adoption of the Global Action Plan on AMR
17 issued by the World Health Organization (WHO).^{14,15} The J-SIPHE system aims to aggregate
18 information related to AMR measures in medical institutions nationwide and is intended to be
19 utilized for promotion of AMR measures in participating facilities and their communities
20 (Figure 1).¹³ The aggregated information includes the status of antibiotic use, the emergence of
21 major bacteria and antimicrobial-resistant bacteria, hand rub usage, and the incidence of
22 healthcare-associated and bloodstream infections. Data are uploaded by medical institutions on
23 the website of the J-SIPHE system and aggregated in the J-SIPHE server. The registered
24 information can be visualized as a graph on the website and downloaded at any time. Each
25 medical institution, such as local communities and related facilities, can use the data when

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

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



1
2
3
4
5
6

Figure 1

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

1 **Methods**

2

3 *Study design*

4 This cross-sectional study was conducted in Japan's Hokkaido Infection Control Group
5 (HICG). The participating hospitals were NTT Medical Center Sapporo, Kitasapporo Hospital,
6 Hokkaido Gastroenterology Hospital, KKR Sapporo Medical Center, Sapporo Hokuyu
7 Hospital, IMS Sapporo Internal Medicine Rehabilitation Hospital, Hokkaido Medical Center
8 for Child Health and Rehabilitation, Sapporo Teishinkai Hospital, Ebetsu City Hospital,
9 Hakodate Goryoukaku Hospital, Hakodate Central General Hospital, Hakodate Shintoshu
10 Hospital, Hakodate Municipal Hospital, Yakumo General Hospital, Asahikawa Red Cross
11 Hospital, Social Welfare Corporation Hokkaido Social Work Association Furano Hospital,
12 Oji General Hospital, Tomakomai City Hospital, Nemuro City Hospital, Obihiro Kosei
13 General Hospital, Kitami Red Cross Hospital, Iwamizawa Municipal General Hospital,
14 Takikawa Municipal Hospital, Hokkaido University Hospital, National Hospital Organization
15 Hokkaido Cancer Center, and NHO Hokkaido Medical Center. Each participating hospital
16 registered data related to AMR measures in the J-SIPHE system. On the website of the
17 J-SIPHE system, the amount of antibiotic use and the number of detected resistant bacteria per
18 hospitalized patient were automatically calculated. In this study involving 26 hospitals, the
19 data of 19 hospitals that registered both antibiotic use and resistant bacteria information in
20 2020 were collected from the website, and their correlations were analyzed.

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

23

24 *Antibiotic use*

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

1 the broad-spectrum antibiotic use (piperacillin/tazobactam, third-generation cephalosporins,
2 fourth-generation cephalosporins, carbapenems, aminoglycosides, and quinolones, including
3 both intravenous and oral antibiotics). Antibiotic use was evaluated based on the antibiotic use
4 density (AUD). AUD was calculated as antibiotic use (in grams)/defined daily dose (DDD) per
5 100 patient-days on the website of the J-SIPHE system. DDD is the assumed average
6 maintenance dose per day for a drug used for its main indication in adults, as assigned by the
7 World Health Organization (WHO).¹⁶

8

9 *Antibiotic resistance*

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

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

20

21 *Correlations between antibiotic use and antibiotic resistance and between use of each* 22 *antibiotic*

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

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

5

6 *Analysis by ward*

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

11

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

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

16

17 *Statistical analysis*

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

25

1 **Results**

2

3 *Participating hospitals*

4 In this study, 19 hospitals were evaluated; 3 hospitals had < 200 beds, 14 hospitals had 200–
5 500 beds, and 2 hospitals had ≥ 500 beds (Table 1). The median number of beds was 327
6 (interquartile range [IQR], 255–480). The characteristics of the wards in the 19 hospitals are
7 shown in Table 1.

8

9

10 Table 1. Characteristics of wards in 19 hospitals in the Hokkaido Infection Control Group
11 (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	–

12

13 Abbreviations: ICU, intensive care unit.

14

1 *Antibiotic use*

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

6

7 *Antibiotic resistance*

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

12

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

3

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 <i>Pseudomonas aeruginosa</i>	0.08	(0.05–0.19)
Carbapenem-resistant <i>Enterobacteriaceae</i>	0.01	(0–0.04)
Fluoroquinolone-resistant <i>Escherichia coli</i>	0.68	(0.54–0.8)
Third-generation cephalosporin-resistant <i>Escherichia coli</i>	0.41	(0.31–0.58)
Third-generation cephalosporin-resistant <i>Klebsiella pneumoniae</i>	0.05	(0.02–0.08)

4
 5 Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses.

6

7

1 *Correlation between antibiotic use and resistant bacteria*

2 The correlation between the amount of antibiotic use and the detection rate of resistant
3 bacteria is shown in Table 3 and Figure 2. In carbapenem-resistant *P. aeruginosa*, the detection
4 rate was significantly positively correlated with carbapenem use (Spearman's $\rho = 0.551$; $P =$
5 0.015) and negatively correlated with third-generation cephalosporin use (Spearman's $\rho =$
6 -0.467 ; $P = 0.044$). In carbapenem-resistant *Enterobacteriaceae*, the detection rate was
7 significantly positively correlated with fourth-generation cephalosporin use (Spearman's $\rho =$
8 0.641 ; $P = 0.003$). In fluoroquinolone-resistant *E. coli*, there were significant positive
9 correlations between the detection rate and quinolone use (Spearman's $\rho = 0.502$; $P = 0.029$)
10 and piperacillin/tazobactam (Spearman's $\rho = 0.518$; $P = 0.023$) and carbapenem use
11 (Spearman's $\rho = 0.76$; $P < 0.001$). In the case of both third-generation cephalosporin-resistant *E.*
12 *coli* and *K. pneumoniae*, the detection rates were significantly positively correlated with
13 carbapenem use (Spearman's $\rho = 0.54$; $P = 0.017$ and Spearman's $\rho = 0.565$; $P = 0.012$,
14 respectively).

15

16

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 <i>Pseudomonas aeruginosa</i>		Carbapenem-resistant <i>Enterobacteriaceae</i>		Fluoroquinolone-resistant <i>Escherichia coli</i>		Third-generation cephalosporin-resistant <i>Escherichia coli</i>		Third-generation cephalosporin-resistant <i>Klebsiella pneumoniae</i>	
	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).

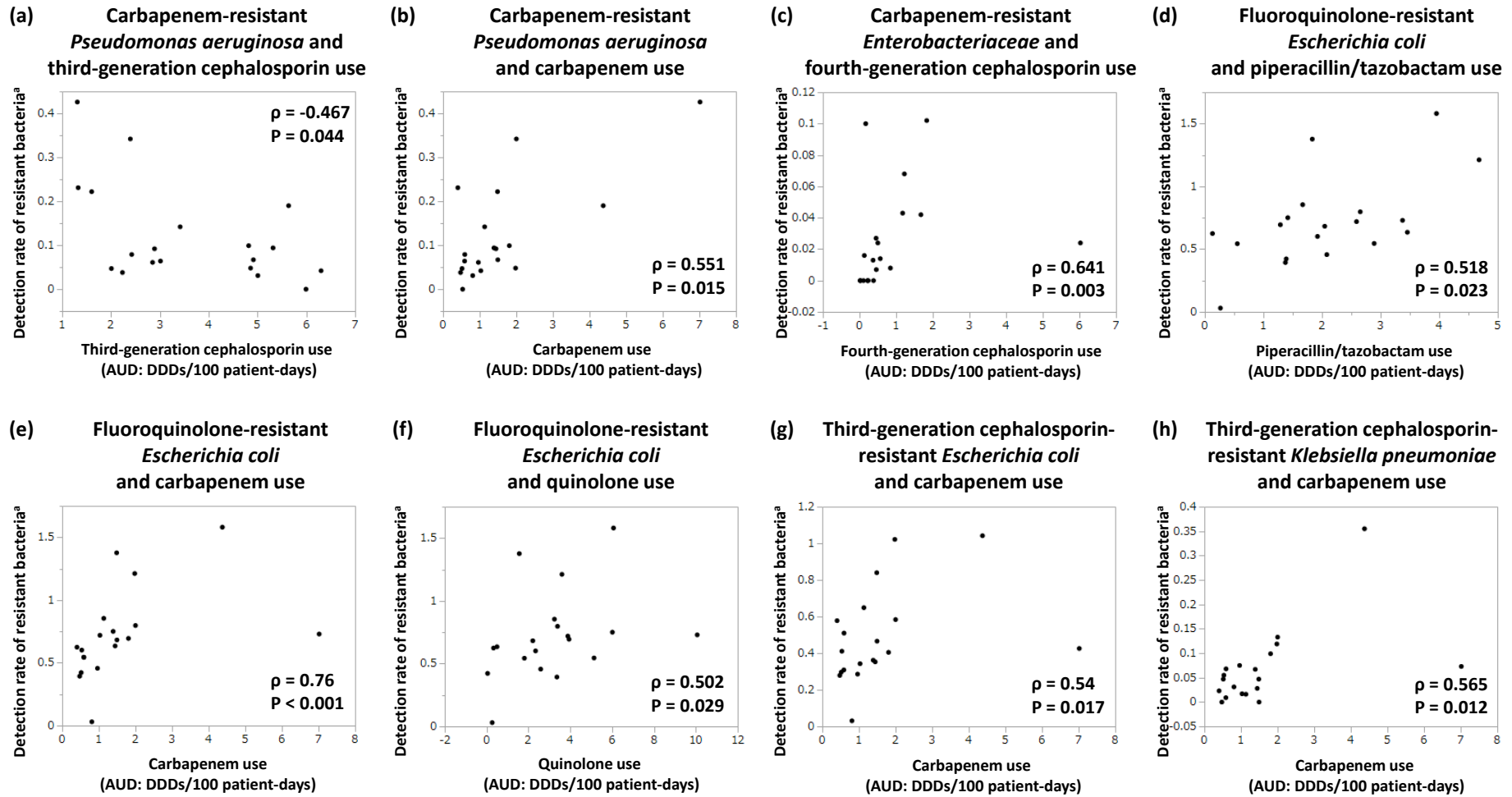


Figure 2

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).

1 *Analysis by ward*

2 We analyzed the antibiotic use and detection rate of resistant bacteria by ward for
3 hospitals where ward-specific information on antibiotic use and/or resistant bacteria was
4 registered in the J-SIPHE system; antibiotic use and detection rate of resistant bacteria in
5 hospital wards were analyzed in 16 and 14 hospitals, respectively (Table 5). Carbapenem use
6 was significantly higher in ICU wards [median AUD (IQR), 4.84 (2.03–6.7)] than in medical
7 [median AUD (IQR), 1.31 (0.61–2.05); $P = 0.015$] and surgical wards [median AUD (IQR),
8 1.16 (0.89–1.62); $P = 0.002$]. The detection rate of carbapenem-resistant *P. aeruginosa* was
9 also higher in ICU wards [median (IQR), 0.42 (0.07–1.94)] than in medical [median (IQR),
10 0.06 (0.02–0.19); $P = 0.105$] and surgical wards [median (IQR), 0.09 (0.06–0.18); $P = 0.187$],
11 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		Medical wards		Surgical wards		P value		
	(n = 11 for antibiotic use) (n = 10 for resistant bacteria)		(n = 16 for antibiotic use) (n = 14 for resistant bacteria)		(n = 14 for antibiotic use) (n = 12 for resistant bacteria)		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 <i>Pseudomonas aeruginosa</i>	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 <i>Enterobacteriaceae</i>	0	(0–0.02)	0.01	(0–0.03)	0.02	(0–0.05)	0.592	0.338	0.953
Fluoroquinolone-resistant <i>Escherichia coli</i>	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 <i>Escherichia coli</i>	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 <i>Klebsiella pneumoniae</i>	0.05	(0–0.41)	0.05	(0.02–0.13)	0.04	(0–0.1)	1	0.897	0.956

- 1 Antibiotic use in hospital wards was analyzed in the following 16 hospitals: A–K, M, N, and Q–S shown in Table 1.
- 2 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.
- 3 Data are presented as medians (interquartile ranges).
- 4 *, ** Statistically significant differences ($P < 0.05$ and $P < 0.01$, respectively).
- 5 Abbreviations: AUD, antibiotic use density; DDDs, defined daily doses; ICU, intensive care unit.

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

2 We analyzed antibiotic use and the detection rate of resistant bacteria in hospitals with and
3 without certified nurses in infection control (Table 6). There were no significant differences
4 in antibiotic use between hospitals with and without certified nurses in infection control.
5 Among resistant bacteria, the detection rate of carbapenem-resistant *P. aeruginosa* was
6 significantly higher in hospitals with certified nurses in infection control [median (IQR), 0.09
7 (0.06–0.21)] than in those without certified nurses in infection control [median (IQR), 0.03
8 (0–0.05)] ($P = 0.022$).

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

2

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 <i>Pseudomonas aeruginosa</i>	0.09	(0.06–0.21)	0.03	(0–0.05)	0.022*
Carbapenem-resistant <i>Enterobacteriaceae</i>	0.01	(0–0.04)	0.02	(0–0.03)	1
Fluoroquinolone-resistant <i>Escherichia coli</i>	0.69	(0.54–0.79)	0.6	(0.03–1.21)	0.615
Third-generation cephalosporin-resistant <i>Escherichia coli</i>	0.42	(0.32–0.58)	0.41	(0.03–1.02)	0.955
Third-generation cephalosporin-resistant <i>Klebsiella pneumoniae</i>	0.05	(0.02–0.07)	0.06	(0.03–0.12)	0.538

3 Data are presented as medians (interquartile ranges).

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

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

1 **Discussion**

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

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

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

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

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

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

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

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

4 Our study indicated that quinolone use was correlated with the detection rate of
5 fluoroquinolone-resistant *E. coli*, which is consistent with the results of previous studies.^{4,7,11,23}
6 The detection rate of fluoroquinolone-resistant *E. coli* was also correlated with
7 piperacillin/tazobactam and carbapenem use. This might be explained by the fact quinolone
8 use was associated with piperacillin/tazobactam and carbapenem use in our data (Table 4);
9 piperacillin/tazobactam and carbapenem use may have been confounding factors. Our finding
10 on the correlation between quinolone use and fluoroquinolone-resistant *E. coli* was also
11 consistent with the results from a Spanish multicenter study investigating the relationship
12 between antibiotic use and the prevalence of *Enterobacteriaceae* resistant to fluoroquinolones
13 from 1999 to 2010.²⁴ On the other hand, our result was not consistent with the results of a
14 study conducted at a university hospital in the Czech Republic from 2000 to 2011, which
15 demonstrated no correlation between quinolone use and fluoroquinolone-resistant *E. coli*.²⁵ In
16 the Czech study, the authors discussed that the resistance to fluoroquinolones probably
17 occurred due to the circulation of resistance genes in bacterial populations, and was not
18 affected by quinolone use. Therefore, when interpreting our results, effects other than
19 antimicrobial use on resistant bacteria should also be considered.

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

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

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

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

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

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

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

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

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

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

19

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