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A nationwide survey of intravenous antimicrobial use in intensive care units in Japan

Tetsu Ohnuma [a,b], Yoshiro Hayashi [c,*], Kazuto Yamashita [d], John Marquess [e], Alan Kawarai Lefor [f], Masamitsu Sanui [b] for the Japanese Survey of AntimiCRobial Use in ICU PatienTs (JSCRIPT) investigators

[a] Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan
[b] Department of Anesthesiology and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan
[c] Department of Intensive Care Medicine, Kameda Medical Center, Kamogawa, Chiba, Japan
[d] Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan
[e] Communicable Disease Unit, Queensland Health, Herston, QLD, Australia
[f] Department of Surgery, Jichi Medical University, Tochigi, Japan

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ABSTRACT

Although most patients in the intensive care unit (ICU) receive antibiotics, little is known about patterns of antibiotic use in ICUs in Japan. The objective of this study was to evaluate the pattern of antibiotic use in ICUs. A nationwide one-day cross-sectional surveillance of antibiotic use in the ICU was conducted three times between January 2011 and December 2011. All patients aged at least16 years were included. Data from 52 ICUs and 1148 patients were reviewed. There were 1028 prescriptions for intravenous antibiotics. Of 1148 patients, 834 (73%) received at least one intravenous antibiotic, and 575 had at least one known site of infection. Respiratory and intra-abdominal infections were the two most common types. Of 1028 prescriptions, 331 (34%) were for surgical or medical prophylaxis. Excluding prophylaxis, carbapenems were the most commonly prescribed agent. Infectious disease consultations, pre- and post-prescription antimicrobial stewardship, and ICU-dedicated antibiograms were available in 44%, 52%, 77%, and 21% of the ICUs, respectively. In logistic regression analysis adjusting for patient characteristics, treatment in a university hospital (adjusted odds ratio, 1.72; 95% CI, 1.05–2.84; $P = 0.033$) and an open ICU (adjusted odds ratio, 2.30; 95% CI, 1.02–5.17; $P = 0.044$) were significantly associated with greater likelihood of carbapenem use. An increase in the number of closed ICUs and more intensive care specialists may reduce carbapenem use in Japanese ICUs. Large-scale epidemiological studies of antimicrobial resistance in the ICU are needed.

1. Introduction

Most patients in the intensive care unit (ICU) receive antimicrobial therapy [1]. While antimicrobial therapy is essential for the successful treatment of bacterial infections in the critically ill, inappropriate use of antimicrobial agents often occurs [2,3]. Though many clinicians are aware that unnecessary use of antibiotics should be avoided, excluding bacterial infections is sometimes challenging in critically ill patients, resulting in inappropriate use of antibiotic agents. Antimicrobial resistance is a major concern worldwide, particularly given that the incidence of carbapenem-resistant Gram-negative bacilli is increasing [4]. Extremely-drug-resistant or pan-drug-resistant organisms are emerging in many parts of the world with no breakthrough agents in development, which indicates that more appropriate use of antibiotics is urgently needed.

Japan faces challenges related to antibiotic use. Some of the challenges include the nationwide spread of hospital-based methicillin-resistant *Staphylococcus aureus* (MRSA) since the late 1980s [5–7], an insufficient number of infectious disease specialists [8], and the inability to use antibiotics such as nafcillin or oxacillin [9]. Despite these concerns, no prior studies have described the current status of antibiotic use in Japanese ICUs.

The objective of this study was to describe the pattern of antimicrobial use in Japanese ICUs, reasons for antimicrobial use, availability of institutional antibiograms, and availability of infectious disease consultations.

* Corresponding author. Department of Intensive Care Medicine, Kameda Medical Center, Higashi-cho 929, Kamogawa, Chiba 296-8602, Japan.
E-mail address: yoshi.icu@gmail.com (Y. Hayashi).

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2. Materials and methods

2.1. Study design

The Japanese Survey of AntimiCRobial Use in ICU PatienTs (JSCRIPT) was a prospective three-day survey of the use of antimicrobial agents in Japanese ICUs, conducted from 1 January 2011 to 31 December 2011. Participation in JSCRIPT was voluntary. Prior to the initiation of the study, an invitation letter was sent to all ICUs accredited by the Japanese Society of Intensive Care Medicine. Multiple internet resources and medical conferences targeting intensive care specialists were used to proactively advertise JSCRIPT and encourage participation.

JSCRIPT was approved by the Institutional Review Board of Jichi Medical University Saitama Medical Center (Saitama, Japan), which served as the central research coordinating facility, on 28 February 2011 (No. 10–28). This was followed by local Institutional Review Board approval at each study site. The study was registered at the UMIN-CTR on 25 February 2011 (No. 000005122). The requirement for informed consent was waived due to the observational nature of the study.

2.2. Study population

All patients aged at least 16 years who were in the ICU at 08:00 hours on the day of the survey were included. Variables collected included patient demographics (age and sex) and clinical characteristics (the reason for ICU admission, route of admission to the ICU, use of mechanical ventilation in the past 24 h, use of renal replacement therapy in the past 48 h, sequential organ failure assessment [SOFA] score on the day of the survey, and length of ICU stay from the ICU admission to the day of the survey). Patients were admitted to the ICU from the emergency department, after elective or emergency surgery, from the regular ward, transferred from another hospital, or other. Detailed information on antimicrobial use included the use of intravenous antimicrobials (except anti-fungal) within 24 h before the survey date, the total dose (in grams) prescribed in the preceding 24 h, the reason for antibiotic use (prophylactic, empirical, or definitive), and type of infection (e.g. pneumonia, intra-abdominal, etc.). The presence of an active infection and the reason for antibiotic use were determined by treating physicians based on clinical findings. Aggregate antibiotic use was expressed as the defined daily dose (DDD), g/drug/1000 patient-days.

2.3. Data collection and management

To complete the survey, each site was provided with either a computer-based Excel (Microsoft Corporation, Redmond WA, USA) spreadsheet or a paper-based data sheet, depending on individual preferences, to record the data.

The first survey was performed at 08:00 hours on a date that was convenient for personnel at the study site. The second and the third surveys were performed in the same manner, but more than 14 days apart and on different days of the week to ensure a patient sample with diverse characteristics and to minimize the possibility of including any patient more than once.

When available, each ICU provided ICU-specific antibiograms showing resistance patterns of specific organisms to specific antibiotics used against that organism during the past year. Antibiotic susceptibility testing was performed by the microbiology laboratory at each study site or at an external central laboratory. Susceptibility breakpoints were based on the Clinical and Laboratory Standards Institute (CLSI) M100-S19 or M100-S20.

2.4. Statistical analysis

Descriptive statistics, including values and percentages with means and standard deviations, were used to analyse the data. Multivariable logistic regression analysis was performed to find predictors for the use of carbapenems using patient and hospital characteristics as covariates. We performed another multivariable logistic regression analysis to assess the association between post-prescription antibiotic stewardship program and use of prophylactic antibiotics in patients who had no infection, controlling for patient and hospital characteristics. Analyses were performed using R statistical software version 3.41 (R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of less than 0.05 was regarded as statistically significant.

3. Results

3.1. ICU characteristics

A total of 52 ICUs and 1148 patients were included in this study. The characteristics of the ICUs are shown in Table 1. Most ICUs were mixed (84.6%). Infectious disease consultation services were available in 44.2% of the ICUs. The mean number of infectious diseases specialists per 1000 beds was 1.6, with 28.8% of hospitals having a

Table 1
Characteristics of the 52 participating intensive care units (ICUs).

Characteristic	n (%)
University hospital	28 (53.4)
JSICM accreditation	41 (78.8)
Hospital beds, mean ± SD	732 ± 255
ICU beds, mean ± SD	10.7 ± 6.0
Type of ICU	
Mixed	44 (84.6)
Surgical	2 (3.9)
Medical	0 (0.0)
Emergency department-based [a]	6 (11.5)
Policy of ICU [b]	
Closed	11 (21.2)
Transitional	35 (67.3)
Open	6 (11.5)
JSICM-certified intensive care specialists, mean ± SD	1.49 ± 1.60
Hospital-based Department of Clinical Infectious Diseases	15 (28.8)
Infectious disease specialists per 1000 hospital beds, mean ± SD	2.4 ± 3.3
Infectious diseases consultation available	23 (44.2)
Regular ICU rounds by infectious diseases specialists	13 (25.0)
Pre-prescription antibiotic stewardship program[c]	27 (51.9)
Pre-prescription approval for prescribing specific antibiotics	
Carbapenems	10 (19.2)
Fluoroquinolones	6 (11.5)
Vancomycin	11 (21.2)
Teicoplanin	10 (19.2)
Linezolid	24 (46.2)
Post-prescription antibiotic stewardship program[d]	40 (76.9)
Availability of antibiogram	
Hospital antibiogram	44 (84.6)
ICU-dedicated antibiogram	11 (21.2)

SD: standard deviation, ICU: intensive care unit, and JSICM: Japanese Society of Intensive Care Medicine.

[a] Emergency department-based ICU refers to an ICU (usually adjacent to the emergency rooms) in which trauma care, burn care, or primary care for critically ill patients, such as those with sepsis or post-resuscitation is provided.

[b] Closed ICU refers to an ICU in which only dedicated intensivists manage the treatment of patients 24 h a day; transitional ICU refers to an ICU in which patients are co-managed by the primary physicians and the intensivists; and open ICU refers to an ICU in which any attending physician can direct care.

[c] Pre-prescription antibiotic stewardship program refers to pre-prescription authorization in which prescribers receive appropriate information regarding antibiotic use for certain antibiotics prior to the first administration.

[d] Post-prescription antibiotic stewardship program refers to a post-prescription review with feedback system in which prescribers are advised with recommendations for stopping or adjusting antibiotic therapy if needed.

Table 2
Characteristics of 1148 patients.

Characteristic	n (%)
Age, mean ± SD	65.5 ± 16.2
Women	425 (37.1)
Weight (kg), mean ± SD	58.0 ± 13.2
SOFA score on the day of survey, mean ± SD	5.6 ± 4.0
ICU-day on the day of survey, days, median (IQR)	4 (2, 10)
Admission route	
Emergency department	364 (31.8)
Post-elective surgery	308 (26.8)
Post-emergency surgery	198 (17.3)
Ward	188 (16.4)
Other hospitals	69 (6.0)
Others	20 (1.7)
Admission diagnostic category	
Medical	
Respiratory	118 (10.3)
Cardiovascular	112 (9.8)
Neurological	88 (7.7)
Trauma	62 (5.4)
Unknown source of sepsis	61 (5.3)
Gastrointestinal	51 (4.4)
Others	68 (5.9)
Surgical	
Cardiovascular	197 (17.2)
Gastrointestinal	157 (13.7)
Neurological	72 (6.3)
Trauma	54 (4.7)
Others	96 (8.4)
Use of mechanical ventilator within 24 h of the survey	603 (52.7)
Use of renal replacement therapy within 48 h of the survey	155 (13.5)

SD: standard deviation, SOFA: sequential organ failure assessment, and ICU: intensive care unit.

Table 3
Patterns of antibiotic use (1148 patients).

Variable	n (%)
Presence of bacterial infection	575 (50.1)
Intravenous antibiotics administered	834 (72.6)
Reason for antibiotic use (1010 antibiotic prescriptions)	
Prophylaxis	331 (32.8)
Empirical therapy	435 (43.1)
Definitive therapy	244 (24.2)
Source of infection in 575 patients with suspected bacterial infection[a]	
Respiratory	283 (49.3)
Intra-abdominal	108 (18.8)
Unknown source	63 (11.0)
Skin and soft tissue	52 (8.9)
Catheter-related blood stream	34 (2.8)
Urinary tract	27 (2.2)
Infective endocarditis	13 (1.1)
Central nervous system	9 (0.7)
Osteomyelitis	5 (0.4)
Other known source of infection	42 (3.5)

[a] Some patients had more than one source of infection; therefore, the total exceeds 100%.

separate Department of Clinical Infectious Diseases. While the hospital antibiogram was available in 84.6% of the ICUs, 21.2% of the ICUs had unit-dedicated antibiograms. Half of the ICUs had prior-to-prescribe restrictions for antibiotic use and 76.9% had post-prescription antibiotic stewardship programs. Missing data occurred for three variables: weight (9.4%), SOFA score (2.1%), and ICU days (0.3%).

3.2. Cohort characteristics

Table 2 shows the characteristics of the patient sample. The mean age of the patients was 65.5 ± 16.2 years and 425 (37.1%) were female. Of 575 patients with suspected bacterial infections, respiratory infections (n = 283, 49.3%) and intra-abdominal infections (n = 108, 18.8%) were most common. The reasons for antibiotic use are shown in Table 3.

3.3. Patterns of antibiotic use

Details of antibiotic use are shown in Table 4. Of 1028 total prescriptions for intravenous antibiotics in the 834 patients who received them, 331 (33.9%) were for prophylaxis. The five most commonly used antibiotics for surgical prophylaxis were cefazolin, ampicillin-sulbactam, cefmetazole, flomoxef, and ceftriaxone and cefotiam (tie), while the five most commonly used for medical prophylaxis were cefazolin, ampicillin-sulbactam, meropenem, ceftriaxone, and flomoxef and ciprofloxacin (tie), as shown in Supplemental Table S1. In logistic regression analysis adjusting for patient and hospital characteristics, the presence of a post-prescription antibiotic stewardship program (adjusted odds ratio, 0.39; 95% CI, 0.23–0.65; $P < 0.001$) was significantly associated with lower odds for the use of prophylactic antibiotics.

When prophylactic use was excluded, however, carbapenems (136 prescriptions, 19.5% of therapeutic use) were prescribed most frequently. There was a wide variation in use patterns by center or type of infection (Supplemental Figs S1, S2, and S3). Prescription patterns did not vary in hospitals with or without Infectious Disease consultation services (Supplemental Table S2).

In logistic regression analysis adjusting for patient characteristics, treatment in a university hospital (adjusted odds ratio, 1.72; 95% CI, 1.05–2.84; $P = 0.033$) and an open ICU (adjusted odds ratio, 2.30; 95% CI, 1.02–5.17; $P = 0.044$) were significantly associated with a greater likelihood of carbapenem use (Supplemental Table S3).

3.4. Antimicrobial susceptibility

Unit-dedicated antibiograms were obtained from 42 (80.8%) participating ICUs as shown in Table 5. The oxacillin-susceptible rate of *Staphylococcus aureus* was 48.1%. Fluoroquinolone-susceptible rate of *E. coli* was 70.2%, and *K. pneumoniae* was 95.4%. *P. aeruginosa* was least susceptible to carbapenems among the anti-pseudomonal agents. The lowest susceptibility rates of *E. coli* and *K. pneumoniae* to carbapenems among the study sites were 40.0% and 62.5%, respectively.

4. Discussion

4.1. Summary of key findings

The key findings of this study are that most patients admitted to ICUs in Japan received intravenous antibiotics (72.6%), and one-third of the antibiotic prescriptions were for prophylaxis. Excluding prophylactic use, carbapenems were the most commonly prescribed antibiotics. Infectious disease consultation services were available in only 44.2% of the ICUs. *P. aeruginosa* was least susceptible to carbapenems among the anti-pseudomonal agents. Treatment in a university hospital and an open ICU were significantly associated with greater odds of carbapenem use.

4.2. Contrast with previous studies

As documented in studies performed in ICUs in other countries [1,10–12], respiratory and intra-abdominal infections were more common in the present study and accounted for approximately 70% of all cases of confirmed infections. Increasing consumption of carbapenems [13] and the global spread of carbapenem-resistant organisms have recently become urgent global health issues, because

Table 4
Use of intravenous antibiotics.

	All Patients N = 1028		Non-prophylactic Purpose N = 697	
Antibiotics	Prescriptions n (%)	DDD per 1000 patient-days	Prescriptions n (%)	DDD per 1000 patient-days
Cefazolin	218 (21.2)	149.6	28 (4.0)	22.7
Carbapenems[a]	145 (14.1)	121.5	136 (19.5)	111.3
Ampicillin/sulbactam	121 (11.7)	319.1	80 (11.4)	190.1
Piperacillin/tazobactam	95 (9.2)	72.2	90 (12.9)	63.5
Vancomycin	88 (8.6)	57.1	84 (12.3)	53.7
Fluoroquinolones[b]	61 (5.9)	50.2	54 (7.7)	46.8
Ceftriaxone	43 (4.2)	36.9	34 (4.9)	28.5
Ceftazidime	31 (3.0)	23.9	30 (4.3)	21.0
Cefepime	13 (1.3)	13.5	10 (1.5)	12.2
Ampicillin	11 (1.1)	38.2	10 (1.4)	30.4
Others	202 (19.6)	–	141 (20.2)	–

DDD denotes defined daily dose (g/drug/1000 patient-days).
[a] Five intravenous carbapenem agents with anti-pseudomonal properties available in Japan in 2011 included meropenem, imipenem/cilastatin, doripenem, biapenem, and panipenem/betamipron.
[b] Three intravenous fluoroquinolones available in Japan in 2011 included ciprofloxacin, levofloxacin, and pazufloxacin.

the carbapenem class of antibiotics is considered to be the last resort for the treatment of severe infections, particularly those caused by extended-spectrum β-lactamases (ESBLs) or AmpC-producing Enterobacteriaceae. The use of carbapenems is associated with the isolation of carbapenem-resistant organisms [4,14,15]. Daiokos et al. also reported that carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections are an independent risk factor for mortality (hazard ratio, 2.83; 95% CI, 1.08–7.41) [16]. In the present study, excluding prophylactic use, carbapenems (19.5%) were the most commonly prescribed antibiotics, and emerging carbapenem-resistant organisms were noted.

Limited access to infectious disease specialists and limited utilization of antimicrobial stewardship programs were found in this study (Table 1). The benefits of involving infectious disease specialists to deal with issues related to infectious diseases in ICUs are well documented [17–19]. Rimawi et al. illustrated the impact of infectious disease specialists on the reduction of antibiotic overuse in medical ICUs without increasing mortality [17]. Antimicrobial stewardship programs are also an important strategy to improve the quality of antibiotic use. Taggart et al. showed that antibiotic stewardship programs in the ICU reduce antibiotic use by 28% [20]. Gentry et al. compared data from before and after implementation of antibiotic stewardship periods, showing that the length-of-stay in the ICU decreased significantly from 15.0 to 12.8 days ($P < 0.001$) [21]. While many acute care hospitals in Japan had infection control teams that provided post-prescription antibiotic stewardship programs [22], it is a concern that even those hospitals had few infectious diseases specialists [8]. Therefore, there is a pressing need to train a sufficient number of infectious disease specialists and to establish infectious disease consultation services and/or antimicrobial stewardship programs in acute care hospitals in Japan. Developing other tools to assist clinicians in the ICU (e.g. guidelines, telemedicine, computer-based decision support systems) [23,24], increasing the number of intensivists, and/or including infectious disease training during intensive care training are important to improve this situation.

Indications for prophylactic antibiotics are very limited; this study shows that 32.8% of antibiotic prescriptions were for prophylaxis and approximately 20.5% of the prophylactic antibiotic prescriptions (6.7% of all antibiotic prescriptions) were for prophylaxis in patients with medical conditions. Even for perioperative prophylaxis, current guidelines [25] recommend less than 24 h of administration, except for cardiothoracic procedures for which extended prophylaxis of up to 48 h has been accepted without sufficient evidence. The currents study shows that 60% of antibiotics for surgical prophylaxis were for non-cardiothoracic procedures, and 42.7% of antibiotics given for surgical prophylaxis were given on or after the second day in the ICU. Although routine administration for prophylaxis for these procedures is not recommended, some patients who underwent percutaneous coronary interventions, endoscopic retrograde cholangio-pancreatography, or dental procedures may have received prophylactic antibiotics categorized as medical conditions. These findings indicate that there is significant room to reduce prophylactic antibiotic use in ICUs in Japan.

Table 5
Susceptibility of common nosocomial organisms from 42 ICU-dedicated antibiograms.

Organism	N	Antibiotic names	Average susceptibility rate (%)	Minimum susceptibility rate (%)
S. aureus	3217	Oxacillin	48.1	8.3
E. faecalis	899	Vancomycin	100	0.0
E. faecium	257	Vancomycin	99.5	66.7
E. coli	1363	Cefotaxime	80.0	40
		Ceftazidime	79.6	40
		Fluoroquinolone [a]	70.2	40
		Carbapenem [b]	97.0	40
K. pneumoniae	1012	Cefotaxime	92.5	62.5
		Ceftazidime	92.6	62.5
		Fluoroquinolone [a]	95.4	62.5
		Carbapenem [b]	96.8	62.5
P. aeruginosa	1636	Piperacillin	85.3	50.0
		Ceftazidime	81.8	8.3
		Cefepime	81.8	50.0
		Carbapenem [b]	78.6	28.6
		Fluoroquinolone [a]	84.1	28.6
Acinetobacter spp.	345	Carbapenem [b]	92.9	14.3

[a] Ciprofloxacin or levofloxacin.
[b] Imipenem or meropenem.

4.3. Strengths and limitations

This study has significant strengths. To the best of our knowledge, this is the first study to describe the nationwide use of intravenous antibiotics in ICUs in Japan. We pooled the data of a large and diverse patient population from a wide range of ICUs, and observed large differences in various health care systems, ICU facilities, and local practices for treating infections.

This study has some acknowledged limitations. First, the voluntary nature of participation in the study may provide a degree of selection bias and might not be representative of all ICUs in Japan. Second, laboratory testing was performed at each participating hospital; therefore, susceptibility testing, molecular testing of strain relatedness, or confirmation of specific resistance mechanisms was

not standardized. Third, evaluation of whether hospital antibiotic choices were made based on antibiogram data was unavailable because pathogen data for each patient was not available. Fourth, there may be duplicate data due to study design, although we suggest that the proportion is small. Fifth, the delay in publication of this study was caused by several circumstantial factors. We believe that there have been no major changes in this field of medical practice in Japan since data were collected, and that these results are applicable to current clinical practice. Lastly, in this prospective cross-sectional survey, associations between antibiotic use and patient outcomes were not evaluated.

4.4. Future research

Strategies to limit antibiotic use for two major types of infection (e.g. shorter course of antibiotics [26], procalcitonin-guidance [27]) are worth investigating in Japanese ICUs, particularly because a successful strategy to limit antibiotic use in another country does not guarantee a favorable effect in Japan due to inherent differences in practice. These findings will be used to guide future trials to assess the efficacy of limiting antibiotic use on respiratory and intra-abdominal infections.

5. Conclusion

The JSCRIPT study shows that most ICU patients in Japan receive antibiotics. The widespread use of carbapenems and resulting carbapenem resistance are of concern. Treatment in a university hospital and an open ICU are associated with higher odds of carbapenem use. An increased number of closed ICUs and more intensive care specialists are targets to reduce the use of carbapenems in the Japanese ICUs. Large-scale epidemiological studies of antimicrobial resistance in the ICU are needed.

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K. Andoh, Sendai City Hospital, Miyagi; M. Egi, Okayama University Hospital, Okayama; M. Fujita, Tohoku University Hospital, Miyagi; S. Fujitani, St. Marianna University School of Medicine, Kanagawa; Y. Gushima, Saiseikai Kumamoto Hospital, Kumamoto; K. Hagiya, University of Tsukuba Hospital, Ibaraki; H. Hagiya, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama; T. Ide, Hyogo College of Medicine, Hyogo; Y. Iizuka, T. Ohnuma, Jichi Medical University, Saitama Medical Center, Saitama; T. Itagaki, The University of Tokushima Graduate School, Tokushima; T. Ito, Takamatsu Red Cross Hospital, Kagawa; M. Ito, Tonami General Hospital, Toyama; Y. Iwashita, Mie University Hospital, Mie; J. Izawa, Jikei University School of Medicine, Tokyo; S. Izuta, Kobe University Hospital, Hyogo; K. Kabutan, National Hospital Organization Okayama Medical Center, Okayama; M. Kamochi, University Hospital, University of Occupational and Environmental Health, Fukuoka; M. Kashiura, Tokyo Metropolitan Bokutoh Hospital, Tokyo; K. Matsuo, Misato Kenwa Hospital, Saitama; H. Matsushima, Dokkyo Medical University, Tochigi; D. Miyazaki, Japanese Redcross Maebashi Hospital, Gunma; M. Miyazu, Nagoya City University Graduate School of Medical Sciences, Nagoya; I. Nagata, T. Takei, Yokohama City Minato Red Cross Hospital, Kanagawa; H. Nagatani, Teikyo University Hospital, Tokyo; M. Nakagawa, Kinan Hospital, Wakayama; M. Nakane, Yamagata University Hospital, Yamagata; K. Nishi, Kansai Medicai University, Osaka; M. Noguchi, Tokyo Medical University, Tokyo; T. Nomura, Juntendo University Nerima Hospital, Tokyo; S. Nunomiya, Jichi Medical University, Tochigi; T. Obayashi, Isesaki Munical Hospital, Gunma; T. Oda, Iizuka Hospital, Fukuoka; T. Oda, Showa General Hospital, Tokyo; K. Oe, Asahi General Hospital, Chiba; K. Ota, Hiroshima University Hospital, Hiroshima; N. Saito, Chiba-Hokusoh Hospital, Nippon Medical School, Chiba; S. Sako, Asahikawa Medical University, Hokkaido; M. Sekino, Nagasaki University Hospital, Nagasaki; R. Seo, Kobe City Medical Center General Hospital, Hyogo; Y. Shiino, Kawasaki Medical School, Okayama; N. Shime, National Hospital Organization Kyoto Medical Center, Kyoto; K. Shimizu, General hospital social insurance Tokuyama central hospital, Yamaguchi; K. Takada, Toyonaka Municipal hospital, Osaka; K. Takimoto, Graduate School of Medicine, Osaka University, Osaka; M. Taneda, Japanese Red Cross Medical Center, Tokyo; K. Uehara, Hiroshima City Hospital, Hiroshima; K. Unemoto, Nippon Medical School Tamanagayama Hospital, Tokyo; T. Yamada, Saga University Hospital, Saga; H. Yasuda, Japanese Red Cross Musashino Hospital, Tokyo.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.01.022.

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