BMJ Open

Prevalence of antimicrobial use and active healthcare-associated infections in acute care hospitals: a multicentre prevalence survey in Japan

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ABSTRACT

Objective To determine the prevalence of antimicrobial drug use and active healthcare-associated infections (HAIs) and to evaluate the appropriateness of antimicrobial therapy in acute care hospitals in Japan.

Design A prospective multicentre cross-sectional study.

Participants All hospitalised patients on a survey day.

Main outcome measures The primary outcome was the proportion of patients receiving any antimicrobial agents. The secondary outcome was the proportion of patients with active HAIs. The reasons for antimicrobial drug use and appropriateness of antibiotic therapy were also investigated.

Results Eight hundred twenty eligible patients were identified. The median patient age was 70 years (IQR 55–80); 380 (46.3%) were women, 150 (18.3%) had diabetes mellitus and 107 (13.1%) were immunosuppressive medication users. The proportion of patients receiving any antimicrobial drugs was 33.5% (95% CI 30.3% to 36.8%). The proportion of patients with active HAIs was 7.4% (95% CI 5.6% to 9.2%). A total of 327 antimicrobial drugs were used at the time of the survey. Of those, 163 (49.8%), 101 (30.9%) and 46 (14.1%) were used for infection treatment, surgical prophylaxis and medical prophylaxis, respectively. The most commonly used antimicrobial drugs for treatment were ceftriaxone (n=25, 15.3%), followed by piperacillin–tazobactam (n=22, 13.5%) and cefmetazole (n=13, 8.0%). In the 163 antimicrobial drugs used for infection treatment, 62 (38.0%) were judged to be inappropriately used.

Conclusions The prevalence of antimicrobial use and active HAIs and the appropriateness of antimicrobial therapy in Japan were similar to those of other developed countries. A strategy to improve the appropriateness of antimicrobial therapy provided to hospitalised patients is needed.

Trial registration number UMIN000033568

Strengths and limitations of this study

► This is the first multicentre study in Japan to determine the prevalences of antimicrobial use and active healthcare-associated infections (HAIs) in hospitalised patients.
► This is the first study to evaluate the appropriateness of antimicrobial therapy in an inpatient setting in Japan.
► This study was conducted at only two hospitals in Japan with a small sample of patients.
► The presence of active HAIs and the appropriateness of antimicrobial therapy were determined based only on electric medical records.

INTRODUCTION

The prevalences of inpatient antimicrobial drug use and healthcare-associated infections (HAIs) are 30%–50%[1–12] and 3%–10%,[2 5 9 12–19] respectively. Despite the common use of antimicrobial drugs in an inpatient setting, their use is often unnecessary or inappropriate.[11 13 19–25] Given the suboptimal use of antimicrobial drugs and the burden of HAIs,[13 26 27] it is important to improve antimicrobial drug use and reduce the incidence of HAIs in inpatient settings.

Nonetheless, few studies that determine the point prevalences of inpatient antimicrobial drug use and active HAIs in Japan have been conducted.[2 28] Moreover, there are no studies evaluating the appropriateness of inpatient antimicrobial therapy in Japan.[29] Given that suboptimal use of antimicrobial drugs and HAIs are common in other countries, knowing the pattern of antibiotic prescribing practice and the prevalence of HAIs in Japan is important. Therefore, we investigated the prevalence of antimicrobial drug use and active HAIs and evaluated the appropriateness of inpatient antimicrobial therapy in acute care hospitals in Japan.

METHODS
Study design and participants

A prospective cross-sectional study was conducted at the National Hospital Organization Tochigi Medical Center (on 2 August 2018) and the Saiseikai Utsunomiya Hospital (on 6 September 2018), which are

the two largest acute care hospitals serving approximately 0.5 million individuals in Utsunomiya, Japan. These hospitals had antimicrobial stewardship teams composed of physicians, nurses, pharmacists and laboratory technicians at the time of this survey. The antimicrobial stewardship teams of both hospitals conducted weekly rounds to perform chart reviews of all hospitalised patients prescribed antimicrobial drugs for at least 2 weeks. All hospitalised patients prescribed either carbapenems or anti-methicillin-resistant *Staphylococcus aureus* drugs were also evaluated. In addition, the charts of all hospitalised patients in whom microorganisms had been isolated from blood culture were reviewed. In each weekly round, the teams recommended an appropriate type, dose and treatment duration of antimicrobial drug for each screened patient based on the results of microbial tests and antibiograms. All patients hospitalised at 08:00 on the survey day were included. Patients in the birth centre were excluded. This study was registered at the University Hospital Medical Information Network clinical registry on 31 July 2018.

Data collection and patient characteristics

Physicians (JK, TO, TY and MK) reviewed the electronic medical records and retrieved information on patient age, gender, residence before the index admission, medical history and medication use. Infection control nurses at each hospital collected information on the devices in place during the morning of the survey day. Information on antimicrobial drugs was retrieved from drug prescription data from electronic medical records. Based on a previous study,[1] the reasons for use of each antimicrobial drug were recorded and classified into the following five categories: treatment of infection, surgical prophylaxis, medical prophylaxis, a non-infection-related reason or unknown reason. Empirical antimicrobial therapy for suspected infectious disease was considered treatment. When there was no documentation regarding the reason for antimicrobial drug use in medical records (described in online supplementary table S1), the investigators attempted to infer the reason according to the following procedures. If there were any vital signs, physical signs, laboratory findings or microbial tests that met a case definition of infection,[30] the purpose of the antimicrobial drug use was judged to be treatment for infectious disease. If the patient did not have active infectious disease but there was evidence for use for prophylaxis or non-infection reasons, the purpose of the antimicrobial drug use was judged to be prophylaxis for infectious disease or non-infection reasons. If there was no evidence of active infectious disease or other reason for antimicrobial drug use, the purpose of the antimicrobial drug use was judged to be unknown. For patients who received antimicrobial therapy or had active HAIs, information on the anatomical site and type of infection and the results of microbial tests and cultures were collected. For antimicrobial drugs used for surgical prophylaxis, the duration and type of antimicrobial use were evaluated.

Outcome measures

The primary outcome was the proportion of patients who received antimicrobial drugs on the survey date. Investigators reviewed electronic medical records to determine whether the patients were receiving antimicrobial drugs. Based on a previous study,[1] a patient was considered to receive an antimicrobial drug if one of the following criteria was met: (1) the patient was prescribed or scheduled to be prescribed any antimicrobial drug on the survey date or the calendar day before the survey date and (2) the patient was undergoing dialysis and was prescribed or scheduled to receive parenteral vancomycin or an aminoglycoside during the 4 days before the survey date. Topical antimicrobial drugs and drugs used to treat HIV or viral hepatitis were excluded based on the previous study.[1]

One secondary outcome was the proportion of patients who had active HAIs. HAIs were defined as the following: (1) infections occurring after the third day of the index admission, (2) surgical site infections related to surgery performed within the prior 30 days or within 1 year if an implant was in place during the surgery, (3) *Clostridioides* (*Clostridium*) *difficile* infection related to a previous hospitalisation within 28 days before specimen collection[4 20 30 31] or (4) infections related to a previous hospitalisation in an acute care hospital within the previous 48 hours. We included infections related to previous hospitalisations in acute care hospitals other than the studied hospitals because we wanted to determine the pattern of antimicrobial drug use for all acute care hospital-related infections. Infections that were symptomatic or treated with antimicrobial drugs on the survey date were considered active.

The other secondary outcome was the proportion of antimicrobial drugs that were judged to be used appropriately among all antimicrobial drugs used for treatment. There is no consensus regarding a definition of appropriate antimicrobial drug use.[32] Based on past studies,[19–23 33 34] the appropriateness of antimicrobial drug use for treatment was determined by evaluating the following points: (1) Indication: Does the patient have an infection that needs antimicrobial drugs? (2) Dose and timing: Is the dose or timing of the antimicrobial drug appropriate? (3) Duration: Is the duration of antimicrobial therapy appropriate? (4) Choice: Is the selected antimicrobial drug effective? (5) Spectrum: Are there no alternative antimicrobial drugs that are equally effective and have narrower spectrum activity? Antimicrobial therapy was judged to be appropriate if the answer to all five questions was 'yes'. Members of infection control teams of each hospital (including JK, TY and TO) assessed the appropriateness of antimicrobial drug use for treatment based on the results of microbial tests at the time of the survey, antibiograms of each hospital and the Infectious Diseases Society of America Practical Guidelines.[35]

Statistical analysis

Descriptive statistics were used to describe the study population. Individual antimicrobial drugs were considered unique based on the World Health

Organization Anatomical Therapeutic Chemical classification and were analysed. Based on a previous study,[1] the following antimicrobial drugs were considered distinct drugs according to the formulations (enteral and parenteral): vancomycin, metronidazole, colistin, polymyxin B, amphotericin B, streptomycin and neomycin. For the primary outcome, the proportion of patients receiving any antimicrobial drugs on the survey date was calculated. For the secondary outcome, the proportion of patients who had any HAIs on the survey date was calculated. Regarding the appropriateness of antimicrobial therapy, the proportion of antimicrobial drugs that were judged to be used appropriately was calculated. The proportion of individual antimicrobial drugs among all antimicrobial drugs given to treat infection was also calculated according

to subgroups that were used to treat community-onset infections and HAIs. Based on a previous study,[1] community-onset infections were defined as infections for which signs and symptoms began in community settings, including nursing facilities and rehabilitation facilities. However, community-onset infections that met the definition of HAIs were excluded. The 95% CIs were also calculated for these outcomes. Continuous and categorical variables were compared in patients receiving or not receiving any antimicrobial drugs using the Mann-Whitney U test and Fisher's exact test, respectively. These analyses were performed using the Excel statistical software package V.2.11 (Bellcurve for Excel; Social Survey Research Information Co., Tokyo, Japan) or Stata V.15, and the level of significance was set at 5%.

Table 1 Clinical and demographic characteristics of surveyed patients who received antimicrobial drugs and those who did not receive antimicrobial drugs*

Characteristics	Total n=820	Received antimicrobial drugs n=275	Did not receive antimicrobial drugs n=545	P value†
Age, year, median (IQR)	70 (55–80)	69 (54–80)	71 (56–80)	0.51
Women	380 (46.3)	126 (45.8)	254 (46.6)	1.00
Residence before the index admission‡				
Home	747 (91.1)	261 (94.9)	486 (89.2)	0.01
Nursing care facility	27 (3.3)	7 (2.5)	20 (3.7)	0.54
Other hospitals	23 (2.8)	6 (2.2)	17 (3.1)	0.51
Medical history				
Ischaemic heart disease	57 (7.0)	19 (6.9)	38 (7.0)	1.00
Stroke	89 (10.9)	25 (9.1)	64 (11.7)	0.29
Dementia	39 (4.8)	11 (4.0)	28 (5.1)	0.60
Liver cirrhosis	19 (2.3)	6 (2.2)	13 (2.4)	1.00
Diabetes mellitus	150 (18.3)	53 (19.3)	97 (17.8)	0.63
Dialysis	26 (3.2)	13 (4.7)	13 (2.4)	0.09
Immunosuppressive drug use	107 (13.1)	41 (14.9)	66 (12.1)	0.27
Location in hospitals				
Ward	777 (94.8)	255 (92.7)	522 (95.8)	0.07
Critical care unit	43 (5.2)	20 (7.3)	23 (4.2)	0.07
Central line in place on survey date	54 (6.6)	24 (8.7)	30 (5.5)	0.10
Peripheral line in place on survey date	284 (34.6)	149 (54.2)	135 (24.8)	<0.001
Urinary catheter in place on survey date	121 (14.8)	61 (22.2)	60 (11.0)	<0.001
Intubated or tracheal tube in place on survey date	25 (3.1)	17 (6.2)	8 (1.5)	<0.001
Drainage tube in place on survey date	49 (6.0)	27 (9.8)	22 (4.0)	0.002
Median days to survey date from admission (IQR)	9 (3–23)	6 (2–19)	10 (3–26)	<0.001

*Values are the numbers of patients; the numbers in parentheses are percentages of the total number of patients unless stated otherwise.
†The Mann-Whitney U test or Fisher's exact test were used for comparison between patients who were and were not prescribed any antimicrobial drugs. The threshold for statistical significance was set at p<0.05.
‡Twenty-three patients who were born at the surveyed hospitals were excluded.

Table 2 The reasons for antimicrobial drug use according to the survey site*

Reasons	Total n=327	Site A n=79	Site B n=248
Treatment for infection	163 (49.8)	43 (54.4)	120 (48.4)
Prophylaxis			
Surgical	101 (30.9)	28 (35.4)	73 (29.4)
Medical	46 (14.1)	5 (6.3)	41 (16.5)
Non-infectious reasons	3 (0.9)	1 (1.3)	2 (0.8)
Unknown reasons	14 (4.3)	2 (2.5)	12 (4.8)

*Values are the number of antimicrobial drugs, with the percentage of the total number of antimicrobial drugs in parenthesis according to the site.

Patient and public involvement statement

No patients were involved in determining the research question or outcome measures, nor were they involved in developing plans to design or implement the study. No patients were asked for advice during the interpretation or writing up of the results. There are no plans to disseminate the results of this research to study participants or the relevant patient community.

RESULTS

On the survey date, 828 patients were identified. After excluding eight patients hospitalised in the birth centre, a total of 820 patients were included. The baseline characteristics of the surveyed patients are shown in table 1. The median number of days to the survey date from the index admission was nine (IQR 3–23). The median patient age was 70 years (IQR 55–80), 380 (46.3%) were women, 150 (18.3%) had diabetes mellitus and 107 (13.1%) were immunosuppressive drug users (online supplementary table S2).

A total of 327 antimicrobial drugs were given to 275 patients. The proportion of patients who received any antimicrobial drugs was 33.5% (95% CI 30.3% to 36.8%) (online supplementary table S3). Patients receiving

Table 3 Type of antimicrobial drugs representing more than one percent of antimicrobial drugs given to treat community-onset and HAIs*

Type	Total	Community-onset infections†	Healthcare-associated infections
Total antimicrobial drugs	163 (100.0)	93 (100.0)	70 (100.0)
Ceftriaxone	25 (15.3)	19 (20.4)	6 (8.6)
Piperacillin–tazobactam	22 (13.5)	10 (10.8)	12 (17.1)
Cefmetazole	13 (8.0)	11 (11.8)	2 (2.9)
Cefazolin	12 (7.4)	4 (4.3)	8 (11.4)
Ampicillin–sulbactam	12 (7.4)	7 (7.5)	5 (7.1)
Meropenem	9 (5.5)	3 (3.2)	6 (8.6)
Vancomycin (parenteral)‡	8 (4.9)	0 (0.0)	8 (11.4)
Levofloxacin	6 (3.7)	4 (4.3)	2 (2.9)
Cefozopran	6 (3.7)	2 (2.2)	4 (5.7)
Ampicillin	5 (3.1)	5 (5.4)	0 (0.0)
Cefoperazone–sulbactam	4 (2.5)	4 (4.3)	0 (0.0)
Ceftazidime	3 (1.8)	1 (1.1)	2 (2.9)
Trimethoprim–sulfamethoxazole	3 (1.8)	2 (2.2)	1 (1.4)
Amoxicillin	2 (1.2)	2 (2.2)	0 (0.0)
Amoxicillin–clavulanate	2 (1.2)	1 (1.1)	1 (1.4)
Piperacillin	2 (1.2)	2 (2.2)	0 (0.0)
Cefcapene	2 (1.2)	2 (2.2)	0 (0.0)
Minocycline	2 (1.2)	0 (0.0)	2 (2.9)
Rifampicin	2 (1.2)	2 (2.2)	0 (0.0)
Micafungin	2 (1.2)	0 (0.0)	2 (2.9)

*Values are the number of antimicrobial drugs, with the percentage of the total number of antimicrobial drugs in parenthesis according to the type of infections.
†Community-onset infections were defined as infections for which signs and symptoms began in community settings, including nursing facilities and rehabilitation facilities. However, community-onset infections that met the definition of healthcare-associated infections were excluded.
‡Parenteral formulation of the drug.

Table 4 The appropriateness* of antimicrobial therapy†

	Total n=163	Site A n=43	Site B n=120
Appropriate	101 (62.0)	26 (60.6)	75 (62.5)
Inappropriate	62 (38.0)	17 (39.4)	45 (37.5)
Reasons for inappropriateness‡			
No infection	15 (9.2)	7 (16.3)	8 (6.7)
Inappropriate dose or timing	14 (8.6)	9 (20.9)	5 (4.2)
Inappropriate duration	2 (1.2)	0 (0.0)	2 (1.7)
Inappropriate choice	10 (6.1)	0 (0.0)	10 (8.3)
Inappropriate spectrum§	27 (16.6)	2 (4.7)	25 (20.8)

*The appropriateness of antimicrobial therapy was determined by members of the infection control team of each hospital based on the results of microbial tests at the time of the survey, antibiograms of each hospital, and the Infectious Diseases Society of America Practical Guidelines.
†Values are shown as numbers of antimicrobial drugs, with the percentage of the total number of antimicrobial drugs in parenthesis according to the type of infections.
‡Antimicrobial drugs could be given for more than one reason.
§Antimicrobial therapy was considered inappropriate if there were alternative antimicrobial drugs that were equally effective and had narrower spectrum activity.

antimicrobial drugs were more likely than patients not receiving antimicrobial drugs to be admitted from home. Of all antimicrobial drugs administered to the patients, 163 (49.8%), 101 (30.9%) and 46 (14.1%) were used for treatment, surgical prophylaxis and medical prophylaxis, respectively (table 2). The first- and third-generation cephalosporins and penicillin combinations accounted for approximately half of all prescribed antimicrobial drugs (online supplementary table S4).

Of the 163 antimicrobial drugs used for treatment, 25 (15.3%) were ceftriaxone, 22 (13.5%) were piperacillin–tazobactam, 13 (8.0%) were cefmetazole, 12 (7.4%) were cefazolin and 12 (7.4%) were ampicillin–sulbactam (table 3 and online supplementary table S5). These five antimicrobial drugs accounted for half of the antimicrobial drugs used for treatment. The most common infection site for which patients received antimicrobial therapy was the lower respiratory tract (n=44, 27%), followed by the bloodstream (n=32, 19.6%), urinary tract (n=25, 15.3%) and hepatobiliary system (n=23, 14.1%) (online supplementary table S6). The most common specialty of physicians who prescribed antimicrobial drugs for treatment was internal medicine (n=73, 44.8%), followed by general surgery (n=33, 20.2%) (online supplementary table S7). The antimicrobial drugs prescribed by physicians of these two specialties accounted for approximately two-thirds of all antimicrobial drugs used for treatment.

Of 163 antimicrobial therapies, 62 (38.0%) were judged as inappropriate antibiotic use (table 4). The most

common reasons for inappropriate use for antimicrobial drugs were unnecessary prescription of a broader spectrum of antimicrobial drugs and treatment without indications. The prevalence of inappropriate therapeutic use of ceftriaxone, piperacillin–tazobactam, cefmetazole, cefazolin and ampicillin–sulbactam was 48.0%, 40.9%, 30.8%, 8.3% and 50.0%, respectively (online supplementary table S7). The prevalence of inappropriate therapeutic use for lower respiratory tract infection, bloodstream infection, urinary tract infection and hepatobiliary system infection was 29.6%, 21.9%, 44.0% and 34.8%, respectively. The prevalence of inappropriate antimicrobial therapy provided by physicians of internal medicine and general surgery was 28.8% and 48.5%, respectively.

A total of 101 antimicrobial drugs were given to 99 patients for surgical prophylaxis (online supplementary table S8). The median duration of surgical prophylaxis was 2 days (IQR 1–3). Of those, 70 (69.3%) were administered on two or more consecutive days. Cefazolin accounted for approximately half of the antimicrobial drugs used for surgical prophylaxis.

The proportion of patients who had active HAIs was 7.4% (95% CI 5.6% to 9.2%). Sixty-one patients had 63 active HAIs. The most common type of HAI was pneumonia (n=15, 23.8%), followed by clinical sepsis (n=10, 15.9%) and urinary tract infection (n=8, 12.7%) (table 5). The causative organisms were reported in 30 (47.6%) of all active HAIs. The most common causative organism was *Klebsiella pneumoniae* or *K. oxytoca* (n=7, 11.1%), followed by *Escherichia coli* (n=6, 9.5%), *S. aureus* (n=4, 6.3%) and *Candida* species (n=3, 4.8%) (online supplementary table S9). The most commonly used antimicrobial drugs given to treat HAIs were piperacillin – tazobactam (n=12, 17.1%), parenteral vancomycin (n=8, 11.4%) and cefazolin (n=8, 11.4%), while those given to treat community-onset infections were ceftriaxone (n=19, 20.4%), cefmetazole (n=11, 11.8%) and piperacillin–tazobactam (n=10, 10.8%) (online supplementary table S10).

DISCUSSION
Prevalence, rationale and type of antimicrobial drug use
The present study found that exposure of hospitalised patients to antimicrobial agents was common in Japan. Our findings are similar to those of European studies[3 4 6–8 12] and recent Chinese[9] and Japanese studies[2] showing that approximately one-third of hospitalised patients were receiving antimicrobial drugs. However, the prevalence of antimicrobial drug use reported in this study is lower than that of recent studies conducted in the USA,[1] China[10] and Southeast Asia.[5 11]

Similar to recent studies,[1 2 4 5 8] the present study found that treatment for infection and surgical prophylaxis were the predominant reasons for inpatient antimicrobial drug use. The five most commonly used antimicrobial drugs for infection treatment were ceftriaxone, piperacillin–tazobactam, cefmetazole, cefazolin and ampicillin–sulbactam. Compared with their reported use in the US

Table 5 Distribution of 63 healthcare-associated infections among 61 patients*

Type of infection	Total	Site A	Site B
Total infections	63 (100.0)†	13 (100.0)	50 (100.0)†
Pneumonia	15 (23.8)†	1 (7.7)	14 (28.0)†
Ventilator-associated	5 (7.9)	1 (7.7)	4 (8.0)
Clinical sepsis	10 (15.9)	0 (0.0)	10 (20.0)
Urinary tract infection	8 (12.7)	3 (23.1)	5 (10.0)
Device-associated‡	4 (6.3)	1 (7.7)	3 (6.0)
Primary bloodstream infection	7 (11.1)	3 (23.1)	4 (8.0)
Central catheter related	4 (6.3)	2 (15.4)	2 (4.0)
Surgical site infection	7 (11.1)	2 (15.4)	5 (10.0)
Hepatobiliary system infection	6 (9.5)	2 (15.4)	4 (8.0)
Device-associated	4 (6.3)	2 (15.4)	2 (4.0)
Gastrointestinal infection	3 (4.8)	0 (0.0)	3 (6.0)
Clostridioides (*Clostridium*) *difficile* infection	2 (3.2)	0 (0.0)	2 (4.0)
Eye, ear, nose, throat or mouth infection	3 (4.8)	1 (7.7)	2 (4.0)
Skin and soft tissue infection	1 (1.6)	0 (0.0)	1 (2.0)
Bone and joint infection	1 (1.6)	1 (7.7)	0 (0.0)
Central nervous system infection	1 (1.6)	0 (0.0)	1 (2.0)
Cardiovascular system infection	1 (1.6)	0 (0.0)	1 (2.0)

*Values are the number of infections, with the percentage of the total number of healthcare-associated infections in parentheses according to the survey site.
†One infection was related to a previous hospitalisation in an acute care hospital other than one of the studied hospitals.
‡One infection was a urethral stent-associated infection, and three were urethral catheter-associated infections.

survey,[1] the use of levofloxacin and vancomycin was less common in the present study. The four most common infection sites for which patients received antimicrobial therapy were the lower respiratory tract, bloodstream, urinary tract and hepatobiliary system. Thus, focusing the target of antimicrobial stewardship on the antimicrobial drugs used for these infections and surgical antimicrobial prophylaxis may address the problems of inpatient antimicrobial drug use in the region around the studied hospitals.

Prevalence, type and causative organisms of active HAIs
This study found that one in every 14 patients had at least one HAI. This prevalence of HAIs is similar to that reported in past studies.[2 5 9 12–19] The most common types of HAIs were pneumonia, clinical sepsis, urinary tract infection, bloodstream infection and surgical site infection. These five infections accounted for more than two-thirds of all HAIs. The most common causative organisms were *K. pneumoniae* or *K. oxytoca*, *E. coli* and *S. aureus*, consistent with past studies,[5 12 15] whereas *Pseudomonas aeruginosa* seemed to be isolated less frequently in the present study than in previous studies. Given that isolation of *P. aeruginosa* is uncommon in this study, the use of anti-*Pseudomonas* penicillins, such as piperacillin with or without tazobactam, can be reduced.

Appropriateness of antimicrobial drug use
The proportion of antimicrobial drugs that were used inappropriately was 38.0%. Our results are consistent with those of past studies[11 19–25] showing that inappropriate or unnecessary antimicrobial therapy is common, although the methods of assessing the appropriateness of antimicrobial therapy differ among studies. The most common reasons for inappropriateness of antimicrobial drug use were the drug's spectrum and its use without indications. This result is consistent with past studies showing that antimicrobial use without indication[11 19–25] and unnecessary use of antimicrobial drugs with broad spectrums[21] are common.

More than 30% of antimicrobial therapy involving ceftriaxone, piperacillin–tazobactam, cefmetazole and ampicillin–sulbactam was inappropriate; these drugs were four of the five most common antimicrobial drugs used for treatment in this study. Most cefazolins, which represented one of the five most common types of antimicrobial drugs used for treatment, were appropriately used for treatment. These results are similar to those of a past study[22] reporting that narrow-spectrum cephalosporines were associated with a lower risk of inappropriate use of antimicrobial drugs and that amoxicillin–clavulanic acid was associated with a higher risk of inappropriate use of antimicrobial drugs. Given that the prevalences of the therapeutic use of ceftriaxone, piperacillin–tazobactam,

cefmetazole and ampicillin–sulbactam are high, these four antimicrobial drugs may serve as suitable targets of antimicrobial stewardship interventions.

Among the four most common sites of infection, urinary tract infection had the highest proportion of inappropriate antimicrobial therapy in the present study, although several past studies reported that appropriateness of antimicrobial therapy for urinary tract infection was higher than that for other site infections.[23 36] In this study, most antimicrobial therapies were provided by physicians of internal medicine and general surgery. Consistent with previous studies,[3 11 20 24 25 36] our study found that the rate of inappropriate antimicrobial therapy was higher for physicians of general surgery than for those of internal medicine. Thus, focusing antimicrobial stewardship interventions on urinary tract infections and the specialty of general surgery may be useful.

We did not collect information on surgeries in which antimicrobial drugs were used for surgical prophylaxis. Therefore, the appropriateness regarding the choice of antimicrobial drugs for surgical prophylaxis remains unknown. However, more than two-thirds of the antimicrobial drugs used for surgical prophylaxis were administered for durations longer than 1 day, whereas a duration of antimicrobial drugs for surgical prophylaxis of 1 day or less has been found to be sufficient in most cases.[37] Moreover, given that antimicrobial surgical prophylaxis beyond 48 hours may be associated with acquired antimicrobial resistant organisms,[38] it is problematic that more than a third of the drugs were administered for more than 2 days. An unnecessarily long duration of surgical antimicrobial prophylaxis was found to be common in past studies investigating the antimicrobial drug use for surgical prophylaxis.[2–5 39–42] Given that approximately 30% of all inpatient antimicrobial drugs were given for surgical prophylaxis, it is important to improve the duration of surgical antimicrobial prophylaxis. Moreover, additional studies investigating the appropriateness of the choice of antimicrobial drugs for surgical prophylaxis in Japan are needed.

Strength and weakness
This study was the first multicentre survey in Japan to determine the prevalences of antimicrobial drug use and active HAIs. Furthermore, it was also the first to evaluate the appropriateness of antimicrobial therapy provided to hospitalised patients in Japan. In addition, we included all patients except those hospitalised in a birth centre.

Nonetheless, these results presented here should be interpreted in the context of several limitations. First, we did not confirm the administration of antimicrobial drugs directly but determined the antimicrobial drug use by reviewing electronic medical records. Therefore, the prevalence of antimicrobial drug use might be overestimated if some antimicrobial drugs were ordered but not administered. Second, we investigated the outcomes over a 2-day period. Therefore, antimicrobial drugs that were used for a longer period might be overrepresented

relative to those used for a shorter period.[1] Third, we did not contact the patients directly to collect data. Therefore, the prevalence of active HAIs might be underestimated unless the primary physicians caring for the patients noticed and documented a sign of HAIs appropriately. However, a past study reported that reviewing the medical records only did not yield results different from those obtained from the direct evaluation of patients to detect HAIs.[43] Fourth, we investigated only two hospitals located in one region of Japan. Moreover, the hospitals surveyed in this study did not care for patients who needed organ transplantation. Given the variation in antimicrobial drug use and its appropriateness,[19 44 45] our results cannot be generalised to other hospitals. However, in a recent Japanese study using sales data, which covered 98% of the total sales for antimicrobial drugs in Japan, the first- and third-generation cephalosporines and penicillin combinations, which were the most commonly used antimicrobial drugs in the present study, accounted for the top three antimicrobial drugs consumed.[28] Fifth, the frequency of isolation of *P. aeruginosa* was less frequent in this study (online supplementary table S11) than in past studies.[2 5 12 15] Moreover, the surveyed hospitals already had antimicrobial stewardship teams. Therefore, our results may not be applicable to other hospitals without antimicrobial stewardship teams. Sixth, primary physicians caring for the patients were not contacted. Given that no reasons were documented in approximately 30% of all patients surveyed in this study, rationales for antimicrobial drug use and assessment of appropriateness for antimicrobial therapy might be inaccurate. However, past studies also reported poor documentation of the reasons for antimicrobial drug use.[1–3 12 23 46] This poor documentation of reasons for antimicrobial drug use needs to be improved in the future. Seventh, the appropriateness of not receiving antimicrobial therapy was not evaluated in this study. Therefore, the appropriateness of antimicrobial therapy may be underestimated. However, past studies reported that the inadvertent omission of antimicrobial therapy to patients was uncommon.[19 22] Eighth, we did not evaluate the appropriateness of the choice of antimicrobial drugs for surgical prophylaxis, medical prophylaxis, non-infection or unknown reasons. Ninth, we did not determine the proportion of antimicrobial drugs used for treatment after receiving microbial tests among all the antimicrobial drugs used for treatment. Finally, we included infections related to previous hospitalisations in acute care hospitals other than the studied hospitals as HAI. Therefore, the prevalence of HAIs in the present study might be overestimated relative to that reported in previous studies. However, only one of 63 active HAIs was attributed to previous hospitalisation in another acute care hospital.

Implications for clinical practice
The exposure of hospitalised patients to antimicrobial drugs in Japan is common, consistent with findings in other countries. Nonetheless, the appropriateness of

antimicrobial therapy is suboptimal, and the duration of surgical antimicrobial prophylaxis seems unnecessarily long. Given that the majority of antimicrobial drugs are used for antimicrobial therapy and surgical prophylaxis, some efforts to improve inpatient antimicrobial drug use are needed. Our findings suggest that focusing the antimicrobial stewardship on the spectrum of antimicrobial drugs and indication of their use may be effective. Regarding the spectrum of antimicrobial drugs, antibiotic de-escalation based on the results of microbial tests may be useful.[47] Furthermore, given that the isolation of *P. aeruginosa* appears infrequently and that the use of anti-*Pseudomonas* penicillins is common, reducing the use of anti-*Pseudomonas* penicillins as an initial empirical therapy may be effective. Regarding the indications for antimicrobial drug use, monitoring and feedback by antimicrobial stewardship teams may be useful.[48]

CONCLUSIONS

In Japan, one in every three hospitalised patients is exposed to antimicrobial drugs, and 1 in every 14 hospitalised patients has active HAIs. The most common reasons for antimicrobial drug use are infection treatment and surgical prophylaxis. Because the appropriateness of antimicrobial therapy and surgical antimicrobial prophylaxis is suboptimal, some efforts to improve inpatient antimicrobial drug use for these purposes are needed. Nonetheless, given the limitation due to the small sample size of the present study, further large studies should be conducted to investigate the prevalence and appropriateness of antimicrobial drug use in Japan.

REFERENCES

1. Magill SS, Edwards JR, Beldavs ZG, *et al*. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. *JAMA* 2014;312:1438–46.
2. Morioka H, Hirabayashi A, Iguchi M, *et al*. The first point prevalence survey of health care-associated infection and antimicrobial use in a Japanese university hospital: a pilot study. *Am J Infect Control* 2016;44:e119–23.
3. Zarb P, Amadeo B, Muller A, *et al*. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009. *J Antimicrob Chemother* 2011;66:443–9.
4. Ansari F, Erntell M, Goossens H, *et al*. The European surveillance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. *Clin Infect Dis* 2009;49:1496–504.
5. Cai Y, Venkatachalam I, Tee NW, *et al*. Prevalence of Healthcare-Associated Infections and Antimicrobial Use Among Adult Inpatients in Singapore Acute-Care Hospitals: results from the first national point prevalence survey. *Clin Infect Dis* 2017;64:S61–S67.
6. Robert J, Péan Y, Varon E, *et al*. Point prevalence survey of antibiotic use in French hospitals in 2009. *J Antimicrob Chemother* 2012;67:1020–6.
7. Amadeo B, Zarb P, Muller A, *et al*. European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. *J Antimicrob Chemother* 2010;65:2247–52.
8. Gharbi M, Doerholt K, Vergnano S, *et al*. Using a simple point-prevalence survey to define appropriate antibiotic prescribing in hospitalised children across the UK. *BMJ Open* 2016;6:e012675.
9. Ren N, Zhou P, Wen X, *et al*. Point prevalence survey of antimicrobial use in Chinese hospitals in 2012. *Am J Infect Control* 2016;44:332–9.
10. Xie DS, Xiang LL, Li R, *et al*. A multicenter point-prevalence survey of antibiotic use in 13 Chinese hospitals. *J Infect Public Health* 2015;8:55–61.
11. Thu TA, Rahman M, Coffin S, *et al*. Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *Am J Infect Control* 2012;40:840–4.
12. Zarb P, Coignard B, Griskeviciene J, *et al*. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. *Euro Surveill* 2012;17.
13. Ling ML, Apisarnthanarak A, Madriaga G. The Burden of Healthcare-Associated Infections in Southeast Asia: A Systematic Literature Review and Meta-analysis. *Clin Infect Dis* 2015;60:1690–9.
14. Bagheri Nejad S, Allegranzi B, Syed SB, *et al*. Health-care-associated infection in Africa: a systematic review. *Bull World Health Organ* 2011;89:757–65.
15. Magill SS, Edwards JR, Bamberg W, *et al*. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198–208.
16. Charrier L, Argentero PA, Farina EC, *et al*. Surveillance of healthcare-associated infections in Piemonte, Italy: results from a second regional prevalence study. *BMC Public Health* 2014;14:558.
17. Deptuła A, Trejnowska E, Ozorowski T, *et al*. Risk factors for healthcare-associated infection in light of two years of experience with the ECDC point prevalence survey of healthcare-associated infection and antimicrobial use in Poland. *J Hosp Infect* 2015;90:310–5.
18. Chen Y, Zhao JY, Shan X, *et al*. A point-prevalence survey of healthcare-associated infection in fifty-two Chinese hospitals. *J Hosp Infect* 2017;95:105–11.
19. Willemsen I, van der Kooij T, van Benthem B, *et al*. Appropriateness of antimicrobial therapy: a multicentre prevalence survey in the Netherlands, 2008-2009. *Euro Surveill* 2010;15.
20. Kunin CM, Tupasi T, Craig WA. Use of antibiotics. A brief exposition of the problem and some tentative solutions. *Ann Intern Med* 1973;79:555–60.
21. Hecker MT, Aron DC, Patel NP, *et al*. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med* 2003;163:972–8.
22. Willemsen I, Groenhuijzen A, Bogaers D, *et al*. Appropriateness of antimicrobial therapy measured by repeated prevalence surveys. *Antimicrob Agents Chemother* 2007;51:864–7.
23. Cotta MO, Robertson MS, Upjohn LM, *et al*. Using periodic point-prevalence surveys to assess appropriateness of antimicrobial

prescribing in Australian private hospitals. *Intern Med J* 2014;44:240–6.

24. Scheckler WE, Bennett JV. Antibiotic usage in seven community hospitals. *JAMA* 1970;213:264–7.

25. Castle M, Wilfert CM, Cate TR, *et al*. Antibiotic use at Duke University Medical Center. *JAMA* 1977;237:2819–22.

26. Zimlichman E, Henderson D, Tamir O, *et al*. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013;173:2039–46.

27. Lamarsalle L, Hunt B, Schauf M, *et al*. Evaluating the clinical and economic burden of healthcare-associated infections during hospitalization for surgery in France. *Epidemiol Infect* 2013;141:2473–82.

28. Muraki Y, Yagi T, Tsuji Y, *et al*. Japanese antimicrobial consumption surveillance: First report on oral and parenteral antimicrobial consumption in Japan (2009-2013). *J Glob Antimicrob Resist* 2016;7:19–23.

29. The Ministry of Health, Labour and Welfare. Government of Japan. Manual of Antimicrobial Stewardship (1st Edition). http:// www.mhlw. go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000193504. pdf (Accessed 14 Oct 2018).

30. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Protocol version 5.3. https://ecdc.europa.eu/sites/portal/files/media/en/publications/ Publications/PPS-HAI-antimicrobial-use-EU-acute-care-hospitals- V5-3.pdf (Accessed 1 Apr 2019).

31. McDonald LC, Coignard B, Dubberke E, *et al*. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol* 2007;28:140–5.

32. DePestel DD, Eiland EH, Lusardi K, *et al*. Assessing appropriateness of antimicrobial therapy: in the eye of the interpreter. *Clin Infect Dis* 2014;59(Suppl 3):S154–1.

33. Gyssens IC, van den Broek PJ, Kullberg BJ, *et al*. Optimizing antimicrobial therapy. A method for antimicrobial drug use evaluation. *J Antimicrob Chemother* 1992;30:724–7.

34. Achong MR, Wood J, Theal HK, *et al*. Changes in hospital antibiotic therapy after a quality-of-use study. *Lancet* 1977;2:1118–22.

35. Infectious Diseases Society of America. IDSA Practice Guidelines. https://www.idsociety.org/PracticeGuidelines/?q=&page=4&ref=#/ date_na_dt/DESC/0/+/ (Accessed 1 Apr 2019).

36. Ceyhan M, Yildirim I, Ecevit C, *et al*. Inappropriate antimicrobial use in Turkish pediatric hospitals: a multicenter point prevalence survey. *Int J Infect Dis* 2010;14:e55–61.

37. Bratzler DW, Dellinger EP, Olsen KM, *et al*. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013;70:195–283.

38. Harbarth S, Samore MH, Lichtenberg D, *et al*. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation* 2000;101:2916–21.

39. Ng RS, Chong CP. Surgeons' adherence to guidelines for surgical antimicrobial prophylaxis - a review. *Australas Med J* 2012;5:534–40.

40. Miliani K, L'Hériteau F, Astagneau P. INCISO Network Study Group. Non-compliance with recommendations for the practice of antibiotic prophylaxis and risk of surgical site infection: results of a multilevel analysis from the INCISO Surveillance Network. *J Antimicrob Chemother* 2009;64:1307–15.

41. Hohmann C, Eickhoff C, Radziwill R, *et al*. Adherence to guidelines for antibiotic prophylaxis in surgery patients in German hospitals: a multicentre evaluation involving pharmacy interns. *Infection* 2012;40:131–7.

42. Musmar SM, Ba'ba H, Owais A. Adherence to guidelines of antibiotic prophylactic use in surgery: a prospective cohort study in North West Bank, Palestine. *BMC Surg* 2014;14:69.

43. Brusaferro S, Regattin L, Faruzzo A, *et al*. Surveillance of hospital-acquired infections: a model for settings with resource constraints. *Am J Infect Control* 2006;34:362–6.

44. Gerber JS, Newland JG, Coffin SE, *et al*. Variability in antibiotic use at children's hospitals. *Pediatrics* 2010;126:1067–73.

45. Huttner B, Jones M, Huttner A, *et al*. Antibiotic prescription practices for pneumonia, skin and soft tissue infections and urinary tract infections throughout the US Veterans Affairs system. *J Antimicrob Chemother* 2013;68:2393–9.

46. Kass EH. Antimicrobial drug usage in general hospitals in Pennsylvania. *Ann Intern Med* 1978;89(5 Pt 2 Suppl):800–1.

47. Liu P, Ohl C, Johnson J, *et al*. Frequency of empiric antibiotic de-escalation in an acute care hospital with an established Antimicrobial Stewardship Program. *BMC Infect Dis* 2016;16:751.

48. Davey P, Marwick CA, Scott CL, *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017;2:CD003543.