

The First Point Prevalence Survey of Healthcare-Associated Infection and Antimicrobial Use in a Japanese University Hospital: A Pilot Study

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Abstract

Background :

Point prevalence surveys (PPSs) in Japanese hospitals have not yet been reported. The purpose of this pilot PPS study was to evaluate the epidemiology of healthcare-associated infections (HAIs) and antimicrobial use in a Japanese tertiary university hospital.

Methods:

A one-day, cross-sectional PPS was performed at a Japanese University Hospital. Data on demographics, active HAIs, and antimicrobial use of all inpatients were collected using a data collection form.

Results:

Of 841 patients, 85 (10.1%) had 90 active HAIs, and 308 patients (36.6%) were administered 494 antimicrobials. Among the 90 HAIs and 58 pathogens, the

most frequent infection and isolated pathogen were pneumonia (20.0%) and Enterobacteriaceae (27.6%), respectively. Of the 118 antimicrobials used for treatment of HAIs, carbapenems were the most frequently administered category of antimicrobials (22.9%). As regards antimicrobials for surgical prophylaxis, 37 of 119 (31.1%) were administered to patients on postoperative day 3 or later, and 48 of 119 (40.3%) were administered orally.

Conclusion:

The incidence of HAIs is higher than in other developed countries. The social and medical situation in Japan may affect patient demographics, active HAIs, and antimicrobial use. Multi-center PPSs are necessary to uncover the real epidemiology of HAIs and antimicrobial use in Japan.

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Introduction

Reducing healthcare-associated infections (HAIs) and promoting antimicrobial stewardship are among the central missions of hospitals to improve patient health outcomes and reduce antimicrobial resistance. Baseline data of HAIs and antimicrobial use are essential for infection control and prevention in hospitals. A point prevalence survey (PPS) is considered a useful cross-sectional surveillance technique to evaluate HAIs and antimicrobial use. The scale of reported PPSs has become multicenter, multistate, and multinational⁽¹⁻⁴⁾.

In Japan, there have been few reports about the hospital epidemiology of infectious diseases. Although specific surveillance of hospital infections, such as catheter-related bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia, and surgical site infections at the targeted ward, is conducted, PPS data of HAIs and antimicrobial use have not yet been reported⁽⁵⁻⁸⁾. To have an overview of HAIs and antimicrobial use is essential for improving the quality of medical care. The aim of this study was to investigate the prevalence of HAIs and antimicrobial use in Nagoya University Hospital (NUH) by a PPS.

Study Design

Setting and data collection

The survey was performed at NUH in Aichi, Japan. NUH is a 1035-bed, tertiary care, university-affiliated hospital and cancer center for children and adults. The hospital provides adult, pediatric, and geriatric services, including medical and surgical subspecialties and comprehensive outpatient and ambulatory services. NUH has two intensive care units (ICUs), a maternal-fetal intensive care unit (MFICU), and a neonatal intensive/growing care unit (NICU/GCU). The numbers of beds of the general wards, psychiatric ward, ICUs, MFICU, and NICU/GCU are 917, 50, 26, 6, and 36, respectively. The 5-year (2009 - 2013) average numbers of outpatients per day, total number of operations per year, length of hospital stay (days), and bed occupation rate (%) were 2350, 8035, 13.4, and 85.1%, respectively.

The PPS was performed using a standardized PPS questionnaire on July 3, 2014. The

NUH PPS protocol 2014 was created with some modification to the European Center for Diseases Prevention and Control (ECDC) surveillance protocol ⁽⁹⁾. All inpatients as of 8:00 am on the survey day at NUH were included in the present study. Fifteen investigators (seven doctors, one junior resident, four pharmacists, and three nurses) participated in the study. Doctors and pharmacists reviewed the medical records on the survey day to collect demographic and clinical data. Nurses collected patient data from the devices in place on the morning of the survey day, including: peripheral venous catheters, central venous catheters/ports (CVCs), urinary catheters, and tracheal/tracheostomy tubes. All investigators checking medical records were instructed about study protocol and definitions of HAIs before PPS, and all patients with HAIs were judged by two independent trained investigators.

The collected data included each patient's background characteristics (age, sex, duration of hospital stay, underlying diseases), McCabe score ⁽¹⁰⁾, devices in place, detection history of drug-resistant (DR) microorganisms within three months, active HAIs, antimicrobial use and any consultations with the infection control team (ICT) within the last month such as for treatment advice, infection control, or vaccination, including any remarks from a member of the ICT team. If a patient had any active HAIs or received at least one antimicrobial, further information was collected.

This study adhered to the Japanese ethical guidelines for epidemiologic studies, and the study protocol was approved by the institutional review board of Nagoya University Graduate School of Medicine (No. 4386).

Drug-resistant microorganisms

DR-microorganisms were defined as follows: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate/resistant *Staphylococcus aureus* (VIRA/VRSA), vancomycin-resistant Enterococci (VRE), toxin A/B-producing *Clostridium difficile* as defined according to the Clinical and Laboratory Standards Institute (CLSI) M100-S24 ⁽¹¹⁾, and *C. difficile* toxin as checked by *C. DIFF* QUIK CHEK COMPLETE[®] (Tech Lab, Blacksburg, VA, USA). DR Gram-negative rods (GNRs) were defined by the following criteria: 1. Enterobacteriaceae: resistant to any 3rd-generation cephalosporins (3GC: cefotaxime, ceftriaxone, or ceftazidime) or non-susceptible to imipenem or meropenem; 2. *Acinetobacter* spp. or *Pseudomonas aeruginosa*: resistant to at least two classes among any fluoroquinolones, any aminoglycosides, any carbapenems, or beta-lactams (resistant to at least two of piperacillin, ceftazidime, and cefepime); 3. non-fermenting GNRs other than *Acinetobacter* spp. and *P. aeruginosa*: resistant to any carbapenems; and 4. *Bacteroides* spp.: resistant to any carbapenems.

Case definitions

HAI was defined as follows: 1. infection occurring on Day 3 or later after admission (Day 1: day of admission); 2. infections related to a prior hospitalization in an acute care hospital within the preceding 48 hours; 3. *C. difficile* infection related to a previous hospitalization in an acute care hospital within 28 days before diagnosis; or 4. surgical site infection related to surgery within 30 days of the operation (or within 1 year in cases of implant infection).

Active HAI was defined as HAI with signs and symptoms present on the survey day, or HAIs with antimicrobial therapy still being given. Febrile neutropenia, which was defined according to the 2010 clinical practice guideline⁽¹²⁾, was separated from clinical sepsis in adults and children in our protocol. Febrile neutropenia and clinical sepsis were selected only when a case was diagnosed as having infectious diseases that did not meet any corresponding diagnostic criteria.

Information about device-associated infection (the term is only used for pneumonia, bloodstream infection, and urinary tract infection) and HAI-causative organisms detected was collected from all patients with active HAIs.

Antimicrobial use

For patients receiving at least one dose of antimicrobials on the survey day or antimicrobials for surgical prophylaxis within 24 hours, additional data were collected as follows: antimicrobial category, purpose of antimicrobial use, and route of systemic administration (intravenous, oral, inhaled, and anal). The purpose of antimicrobial use was divided into treatment for active HAIs, treatment for community/nursing care facility-associated infections, medical prophylaxis (e.g. co-trimoxazole for prevention of pneumocystis pneumonia), surgical prophylaxis, and others. Data on antimicrobial use for surgical prophylaxis were collected if antimicrobials were given within 24 hours before the survey day.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics⁽¹³⁾.

Comparisons of patients with and without HAIs were performed. Continuous variables were analyzed using the Mann-Whitney *U* test. Categorical variables were analyzed using the chi-squared test or Fisher's exact test, as appropriate. A *P* value <0.05 was considered significant.

Results

On the day of the survey, 841 patients were hospitalized and enrolled in this survey. Table 1 shows the patient demographic and clinical characteristics. The median age of the patients was 61 years, and patients over 65 years old accounted for 43.3%. According to the McCabe score, 292 (34.7%) had ultimately fatal diseases (estimated prognosis: 1 to 5 years) or rapidly fatal diseases (less than 1 year). DR-GNR, MRSA, and toxin A/B-producing *C. difficile* were detected in 3.2%, 3.9%, and 1.2% of all patients, respectively. None of carbapenem-resistant Enterobacteriaceae, multidrug-resistant *P. aeruginosa*, multidrug-resistant *Acinetobacter* spp., VRE, or VISA/VRSA were detected within the three-month study period. The ICT was involved in some way in the care of 98 patients (11.7%), such as by commenting on treatment or infection control in the patients' medical records within the last month.

Overall, 85 patients (10.1%) had at least one active HAI. Active HAIs occurred significantly more frequently in male than female patients, patients with hematological malignancy and hematopoietic stem cell transplantation, and patients with CVCs or tracheal or tracheostomy tubes. The median duration of hospital stay was 31 days in patients with active HAIs, which was significantly longer than in those without active HAIs (9 days). Patients with active HAIs tended to be carriers of DR-GNR, MRSA, or toxin A/B-producing *C. difficile*. Overall, 48.2% of patients with active HAIs received a consultation from the ICT team.

Table 2 shows the prevalence of active HAIs and antimicrobial use by specialty. The incidence of active HAIs differed by specialty: from 0% for psychiatry to 38.1% for intensive care. Device-associated infections occurred in 15 (1.8%) patients. A total of 308 (36.6%) patients received at least one antimicrobial, and the proportion of patients with antimicrobial use ranged from 0% for psychiatry to 85.7% for intensive care.

Pneumonia and surgical site infection were the top two active HAIs (Table 3). Due to inadequate descriptions in the medical records and/or examinations, febrile neutropenia and clinical sepsis accounted for 10 (11.1%) and 7 cases (7.8%), respectively. The number of HAIs with positive blood cultures was 17 (18.9%), including 4 catheter related infections.

The causative microorganisms of active HAIs are shown in Table 4. A total of 58 microorganisms were detected in this survey. Enterobacteriaceae (27.6%), *Staphylococcus aureus* (15.5%), and *Enterococcus* spp. and *P. aeruginosa* (10.3%) were the common microorganisms of active HAIs. MRSA and 3GC-resistant Enterobacteriaceae accounted for 55.6% and 20.0% (excluding strains of unknown susceptibility) of all *S. aureus* and Enterobacteriaceae, respectively. Of the 17 microorganisms detected by blood culture, *S. aureus* was the most frequent (35.3%).

Table 5 shows the indications for antimicrobial use. Of the 494 antimicrobials, 118 were given for HAIs, 69 for community/nursing care facility-associated infections, 182 for medical prophylaxis, 119 for surgical prophylaxis, and 6 for others (including unknown purposes). Carbapenems were the antimicrobials most frequently used for treatment of active HAIs. As

for the 119 antimicrobials given for surgical prophylaxis, 48 (40.3%) were given orally, and 37 (31.1%) were administered to patients on postoperative day 3 or later.

Discussion

To the best of our knowledge, this is the first PPS report on hospital epidemiology in a Japanese university hospital. This survey showed that 10.1% of patients in NUH had at least one active HAI, and 36.6% of patients received at least one antimicrobial. Baseline characteristics of inpatients, antimicrobial use, categories of active HAIs, and causative microorganisms were also reported in this cross-sectional study.

The prevalence of active HAIs was significantly higher than in other multicenter reports: 4.0% in the USA, 6.0% in Europe, 3.5% in China, and 7.8% in Vietnam ($p < 0.05$, chi-squared test) ⁽¹⁻⁴⁾. Pneumonia and surgical site infection were common HAIs, similar to previous reports ^(1, 2). This high prevalence of HAIs in NUH can be explained as follows. First, hospitalized patients in NUH had high-risk factors for HAIs: about half of the patients had malignant diseases, and they received more intensive chemotherapy or invasive surgery than patients in local hospitals. Second, Japanese public healthcare insurance, which was featured by Lancet in 2011 ⁽¹⁴⁾, provides inexpensive and easy-to-access medical care. Ironically, this medical situation leads to the longest average length of hospital stay in the world ⁽¹⁵⁾. Some patients developed HAIs during longer hospital stays. Third, NUH is one of the largest pediatric oncology centers in Japan. Most pediatric patients had hematological malignancies or solid tumors and received intensive chemotherapy, hematopoietic stem cell transplantation, or surgery with CVCs. Infants in the NICU/GCU were mostly very or extremely low birth weight or had congenital abnormalities, and they received intensive care and surgery. Longer hospital stays among pediatric patients lead to a higher proportion of HAIs than in adult patients. Finally, the total proportion of febrile neutropenia and clinical sepsis (18.9%) was higher than that of clinical sepsis in ECDC reports 2011-2012 (5.4%). Most patient records of febrile neutropenia and clinical sepsis did not contain sufficient information to determine the focus of infection retrospectively. Some cases of febrile neutropenia and clinical sepsis might have been of non-infectious etiology, which may have led to an overestimate of HAIs in NUH. Even if these cases ($n=15$, two cases had clinical sepsis and *C. difficile* infection) were excluded from active HAIs, the prevalence of active HAIs (8.3%) was still higher than in the USA, Europe, and China ($p < 0.05$, chi-squared test) ⁽¹⁻⁴⁾.

The frequency of DR-pathogens isolated from patients with active HAIs has been unclear in Japan. This cross-sectional PPS reported, for the first time, the frequency of 3GC-resistant Enterobacteriaceae and MRSA as causative agents of HAIs in a Japanese hospital. The

Japan Nosocomial Infection Surveillance (JANIS) presents the national laboratory-based surveillance data of DR-pathogens in Japan, but this surveillance is based on the monthly data of the isolates first recovered from both hospitalized patients and those from outpatient clinics. Moreover, it was not possible to determine whether these isolates truly caused infectious diseases. According to 2013 JANIS data, cefotaxime-resistant *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* accounted for 19.4%, 6.1%, and 27.2%, respectively ⁽¹⁶⁾. Despite advanced tertiary medicine and high-risk patients in NUH, the frequency of 3GC-resistant Enterobacteriaceae (20%) was close to the JANIS data and relatively low compared to the ECDC report ^(2, 16). Sequential PPSs are needed to confirm the changing epidemiology of HAI pathogens in NUH.

As for antimicrobial use, the proportion of patients with antimicrobial use was 36.6%, which was similar to the previous reports ^(1, 2, 17). Carbapenems were the predominant antimicrobials prescribed for active HAI treatment, although the frequency of DR-pathogens for which carbapenems were necessary was moderate. This showed that promotion of antimicrobial stewardship is essential to decrease further emergence of DR-pathogens in NUH. As for surgical prophylaxis, this study showed distinctive characteristics in NUH: longer duration and oral administration. Selecting appropriate antimicrobials and shortening the duration of surgical prophylaxis based on guidelines are among the highest priority issues for hospital infection prevention and control ⁽¹⁸⁾.

This study has several limitations. First, this study was conducted in only one hospital. To evaluate actual hospital epidemiology of HAI and antimicrobial use in Japan, a multicenter PPS is necessary. Second, some patient records were insufficient to judge the diagnosis of infectious diseases retrospectively, which might have affected the PPS results. Finally, this was the “first snapshot survey” in NUH, and the weekly or seasonal selection of survey day might affect the results. To reveal more exact and changing hospital epidemiology in NUH, sequential surveys are necessary ^(19, 20).

In conclusion, this first PPS conducted in Japan showed that 10.1% of hospitalized patients in NUH had at least one HAI, which was relatively higher than in other developed countries. The categories of active HAIs and resistance profiles of detected pathogens were comparable to the previous reports. Unnecessary prescription of broad-spectrum antimicrobials to HAIs and inappropriate surgical prophylaxis were found, for which corrective interventions are necessary. We believe the present study can provide reference data on hospital epidemiology in Japanese tertiary care hospitals. Further multicenter studies are warranted to identify the changing Japanese hospital epidemiology and improve the quality of care in Japanese hospitals.

Conflicts of interests

All authors declare that they have no conflicts of interest.

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Table 1. Demographic and Clinical Characteristics of patients 1						
	All patients (n=841)	% (IQR)	patients with active HAI (n=85)	% (IQR)	patients without active HAI (n=756)	% (IQR)
General information						
Age, median years (IQR)	61	(37-62)	58	(20-71)	62	(39-72)
Age category						
0-15 years, n (%)	110	(13.1)	18	(21.2)	92	(12.2)
16-40 years, n (%)	120	(14.3)	9	(10.6)	111	(14.7)
41-64 years, n (%)	247	(29.4)	25	(29.4)	222	(29.4)
65- years, n (%)	364	(43.3)	33	(38.8)	331	(43.8)
Gender, male (n, %)	462	(54.9)	57	(67.1)	405	(53.6)
Type of admission, emergency (n, %)	239	(28.4)	23	(27.1)	216	(28.6)
Duration of hospital stay, median days (IQR)	10	(3-29)	31	(17-70)	9	(3-27)
Category of duration of hospital stay						
0-7 days, n (%)	321	(38.2)	3	(3.5)	318	(42.1)
8-14 days, n (%)	161	(19.1)	11	(12.9)	150	(19.8)
15-30 days, n (%)	160	(19.0)	27	(31.8)	133	(17.6)
31-90 days, n (%)	137	(16.3)	28	(32.9)	109	(14.4)
91- days, n (%)	62	(7.4)	16	(18.8)	46	(6.1)
Baseline disease						
Carcinoma/Sarcoma, n (%)	335	(39.8)	41	(48.2)	294	(38.9)
Hematological malignancy, n (%)	73	(8.7)	18	(21.2)	55	(7.3)
Hematopoietic stem cell transplantation, n (%)	19	(2.3)	6	(7.1)	13	(1.7)
Solid organ transplantation, n (%)	8	(1.0)	2	(2.4)	6	(0.8)
Diabetes, n (%)	138	(16.4)	11	(12.9)	127	(16.8)
CKD without HD (eGFR <60/mL), n (%)	123	(14.6)	12	(14.1)	111	(14.7)
CKD on HD, n (%)	12	(1.4)	3	(3.5)	9	(1.2)
McCabe Score (estimated prognosis)						
Non fatal (>5 years), n (%)	483	(57.4)	30	(35.3)	453	(59.9)
Ultimately fatal (1-5 years), n (%)	235	(27.9)	22	(25.9)	213	(28.2)
Rapidly fatal (< 1 years), n (%)	57	(6.8)	14	(16.5)	43	(3.0)
Unknown, n (%)	66	(7.8)	19	(22.4)	47	(11.8)
Devices in place on survery date						
Central venous catheter/port, n (%)	131	(15.6)	41	(48.2)	90	(11.9)
Peripheral venous catheter, n (%)	251	(29.8)	37	(43.5)	214	(28.3)
Tracheal/tracheostomy tube, n (%)	31	(3.7)	8	(9.4)	23	(3.0)
Urinary catheter, n (%)	99	(11.8)	10	(11.8)	89	(11.8)
Detection of microorganisms, within 3 months						
Drug resistant GNR, n (%)	27	(3.2)	8	(9.4)	19	(2.5)
MRSA, n (%)	33	(3.9)	7	(8.2)	26	(3.4)
Toxin A/B producing <i>Clostridium difficile</i> , n (%)	10	(1.2)	8	(9.4)	2	(0.3)

Table 2. Prevalence of healthcare-associated infections and antimicrobial use, and the number of antimicrobials

Specialty	All patients (n=841)	Patients with HAI (n=85)		Patients with device- associated HAI (n=15)		Patients with antimicrobial use (n=308)	
	n	n	%	n	%	n	%
Medicine	246	23	9.3	2	0.8	95	38.6
Surgery	403	34	8.4	5	1.2	130	32.3
Intensive care	21	8	38.1	5	23.8	18	85.7
Pediatrics	85	18	21.2	2	2.4	49	57.6
Obstetrics and Gynecology	51	2	3.9	1	2.0	16	31.4
Psychiatrics	35	0	0	0	0	0	0

HAI: healthcare-associated infections

Table 3. Distribution active health-care associated infections in 85 patients

Type of Infection	Number of HAI (n=90) [#]	
	n	%
Pneumonia	18	20.0
Surgical site infection	15	16.7
Bloodstream infection	10	11.1
Febrile Neutropenia	10	11.1
Clinical sepsis	7	7.8
Intra-abdominal infection	6	6.7
Urinary tract infection	5	5.6
Catheter related infection	4	4.4
<i>Clostridium difficile</i> infection	4	4.4
Others	11	12.2

HAI: healthcare-associated infection, BSI: Bloodstream infection. [#] Five patients had two HAIs

Table 4. Microorganisms of healthcare-associated infections				
	No. of detected pathogens (n=58)	%	No. of detected pathogens from blood culture (n=17)	%
Enterobacteriaceae				
3GC S, meropenem S	12	27.6	3	23.5
3GC R, meropenem S	3		1	
unknown susceptibility	1		0	
<i>Staphylococcus aureus</i>				
MSSA	4	15.5	3	35.3
MRSA	5		3	
<i>Enterococcus</i> spp. (vancomycin S)	6	10.3	3	17.6
<i>Pseudomonas aeruginosa</i>				
all S	5	10.3	0	0
unknown susceptibility	1		0	
<i>Streptococcus</i> spp.	4	6.9	1	5.9
<i>Clostridium difficile</i>	3	5.2	0	0
Others	14	24.1	3	17.6
S: susceptible, R: resistant, 3GC: third generation cephalosporins, S: susceptible, R: resistant, MSSA: methicillin-susceptible <i>Staphylococcus aureus</i> , MRSA: methicillin-resistant <i>Staphylococcus aureus</i>				

Table 5. Indications of antimicrobials for use

Indication of Antimicrobials	Treatment (n=187)		Prophylaxis (n=301)			Others (n=6)	Total (n=494)
	HAI (n=118)	C/NCAI (n=69)	Medical (n=182)	Surgical (n=119)			
				≤ POD 2 (n=82)	≥ POD 3 (n=37)		
Antibiotics							
Beta-lactams							
Penicillins (IV), n	12	14	0	3	1	1	31
Cephems (IV), n	22	19	0	48	17	2	108
Cephems (PO), n	3	2	3	30	17	0	55
Carbapenems (IV), n	27	2	1	0	1	1	32
Fluoroquinolones (IV + PO), n	10	3	2	0	0	0	15
Co-Trimoxazole (PO) , n	0	0	74	0	0	0	74
Anti-MRSA agents (IV + PO), n	18	4	0	0	0	0	22
Antivirals (IV + PO), n	4	5	24	0	0	0	33
Antifungals (IV + PO + IH), n	12	7	55	0	0	0	74
Others (IV + PO + IH), n	10	13	23	1	1	2	50

HAI: healthcare-associated infection, C/NCAI: community-/nursing care facilities-associated infection, POD: post operative day, IV: intravenous, PO: per os, IH: inhalation, HAI: healthcar Anti-MRSA agents: vancomycin, teicoplanin, daptomycin, linezolid