J Infect Chemother 25 (2019) 225–228

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Note

Impact of alcohol-based hand sanitizers, antibiotic consumption, and other measures on detection rates of antibiotic-resistant bacteria in rural Japanese hospitals ☆

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ARTICLE INFO

Article history:
Received 30 October 2017
Received in revised form
23 July 2018
Accepted 22 August 2018
Available online 11 September 2018

Keywords:
Multidrug-resistant bacteria
Alcohol-based hand sanitizer
Antibiotic consumption
Small hospitals
Long-term care
Psychiatric hospitals

ABSTRACT

There are limited data available on the relationship between multidrug-resistant bacteria and infection control activities in small to medium-sized hospitals. Therefore, we collected data on the use of alcohol-based hand sanitizers (ABHSs), personal protective equipment, antibiotics, and the levels of detectable bacteria between April 2014 and March 2015 in 11 Japanese hospitals. Average total antibiotic consumption was 100 defined daily doses per 1000 patient-days (PD), and average use of ABHSs, masks, plastic aprons, and gloves was 5 L per 1000 PD, and 1, 2, and 26 pieces per 1 PD, respectively. Average numbers of isolated (isolation rate) *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing bacteria, and multidrug-resistant *Pseudomonas aeruginosa* (MDRP) were 107 (8% of total bacterial tests performed), 51 (4%), and 4 (0.3%), respectively. Multivariate analyses of ABHS and tazobactam/piperacillin consumption showed a significant negative association with the MRSA isolation rate (adjusted $R^2 = 0.87$). These findings suggest that hand hygiene is more important than antibiotic consumption in small to medium-sized hospitals.

Infections caused by multidrug-resistant microorganisms are strongly associated with considerable morbidity and mortality and are on the rise [1]. Among these infections, methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing bacteria, and multidrug-resistant *Pseudomonas aeruginosa* (MDRP) have become common worldwide, including in Japan [1–4]. In addition, the use of antibiotics including ceftriaxone, carbapenems, aminoglycosides, and fluoroquinolones is associated with increasing numbers of isolated multidrug-resistant bacteria [1,5,6]. In contrast, several studies have indicated that proper hand hygiene is positively associated with reductions in MRSA, ESBL-producing bacteria, and MDRP transmission [5,7,8], while the use of personal protective equipment (PPE) such as gloves and gowns does not seem to be associated with the MRSA isolation rate [9]. It should be noted, however, that it is currently unclear whether these findings can also be applied to smaller hospitals because these observations were mostly obtained from studies in large hospitals and there is a lack of similar studies in smaller hospital settings. In this study, we first attempted to summarize the current status of infection control activity in small to medium-sized hospitals in Niigata Prefecture, Japan by collecting records on the use of alcohol-based hand sanitizers (ABHSs), PPE, and antibiotic consumption in small to medium-sized hospitals. We then analyzed these data to ascertain the relationship between these preventive measures and the isolation rates of MRSA, ESBL-producing bacteria, and MDRP and evaluated the similarities to and differences from the results of previous studies in larger hospitals.

Data were collected retrospectively from 11 hospitals in Niigata Prefecture that volunteered to participate between April 2014 and March 2015. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kaetsu Hospital. Information about total intravenous antibiotic use was collected, and the defined daily dose (DDD) was assessed using the Japanese Antimicrobial Consumption Surveillance system [10]. The DDD was based on the WHO recommendation for 2014 and was normalized to 1000 patient-days (PD). Records regarding consumables were calculated based on orders placed by each hospital

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https://doi.org/10.1016/j.jiac.2018.08.013
1341-321X/

and data were expressed in liters for hand sanitizers, pieces for masks and aprons, and pairs for gloves. These data were then normalized to per 1000 PD for hand sanitizers and per 1 PD for PPE, respectively because there is no standardized surveillance system to assess PPE consumption. We also collected records of the total number of bacterial tests and the frequency of detection of MRSA, ESBL-producing bacteria (including *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*), and MDRP during the investigation period among inpatients. It should be noted that either microdilution or disk diffusion methods were used to determine antibiotic susceptibility in all hospitals involved in this study. We could not rule out that duplicated isolates with similar susceptibility profiles were obtained from the same patients because bacterial tests were outsourced by many hospitals and it is difficult to determine duplicated isolates from outsourced data. However, none of the hospitals had outbreaks of multidrug-resistant microorganisms during the study period. The isolation rates for antibiotic-resistant bacteria were calculated as the number of antibiotic resistant bacteria divided by the total number of bacterial tests. MRSA was determined by resistance to oxacillin, ESBL-producing bacteria were determined according to screening and confirmation tests suggested by the Clinical and Laboratory Standards Institute [11], and MDRP was determined by simultaneous resistance to imipenem (minimum inhibitory concentration [MIC] ≥16 μg/mL), amikacin (MIC ≥32 μg/mL), and ciprofloxacin (MIC ≥4 μg/mL) [12].

We performed simple and multiple linear regression analyses between the isolation rates of antibiotic-resistant bacteria and the variables outlined above, including antibiotic consumption and the use of ABHSs, masks, plastic aprons, and gloves. Multivariate analysis was performed using multivariate linear regression with a stepwise backward-forward selection procedure ($P < 0.25$) to identify the independent factors associated with the isolation rates of antibiotic-resistant bacteria. The partial regression coefficient (standard error) and adjusted R^2 values were calculated by a multiple linear regression analysis. Using multivariate linear regression analysis, we examined variables that showed a certain degree of association ($P < 0.2$) in the simple linear regression. Statistical significance was set at $P < 0.05$. We used JMP 9 software (SAS Institute Inc., Cary, NC) for all statistical analysis.

A summary of the data collected from the hospitals that participated in this study is shown in Table 1. Results of simple linear regression analysis of the antibiotic-resistant bacteria isolation rates are shown in Table 2. We included only those antibiotics that were associated with at least 1 of the 3 antibiotic-resistant bacteria ($P < 0.2$) in Tables 1 and 2. The average total antibiotic consumption was 100 DDDs per 1000 PD. The average use of ABHSs was 5 L per 1000 PD, and an average of 1, 2, and 26 pieces of masks, plastic aprons, and gloves were used per 1 PD, respectively. The average number of bacterial isolation tests performed within the research period was 1344, and the average numbers of isolated MRSA, ESBL-producing bacteria, and MDRP were 107 (8% of total bacterial tests performed), 51 (4%), and 4 (0.3%), respectively. Next, results of multivariate analyses of the antibiotic-resistant bacteria isolation rates are shown in Table 3. In the multivariate analyses, antibiotics without tazobactam/piperacillin were excluded by stepwise selection. The multivariate analyses demonstrated that ABHS use and tazobactam/piperacillin consumption had a significant negative association with the MRSA isolation rate (adjusted $R^2 = 0.87$), long-term care or admittance to a psychiatric bed showed a modest positive association with the ESBL-producing bacteria isolation rate (adjusted $R^2 = 0.25$), and ABHS use showed a modest negative association with the MDRP isolation rate (adjusted $R^2 = 0.15$).

The average isolation rates of MRSA (8%), ESBL-producing bacteria (4%), and MDRP (0.3%) in this study were consistent with previous studies by other Japanese groups (5–10% [2], 10% [3], and 0.5% [4], respectively), while the isolation rate for ESBL-producing bacteria (4%) was somewhat lower than those reported in other studies. Average antibiotic consumption in this study (100 DDDs per 1000 PD) was also lower than the rate reported in a nationwide survey of 203 Japanese hospitals (155 DDDs per 1000 PD)[9]. These discrepancies might reflect the abundance of hospitals with larger populations of patients in long-term and psychiatric beds in our study because their average total antibiotic consumption was lower than in hospitals with fewer of these beds. In support of this idea, a previous survey of 503 French hospitals also indicated that antibiotic use is lower in long-term care and psychiatric hospitals than in acute-care hospitals [13]. Although further studies will be needed to confirm this finding, our results indicate that the amount of antibiotics used in this study may have been small enough to suppress the emergence and/or spread of antibiotic-resistant bacteria.

Multivariate linear regression analyses indicated that there was a significant negative association between ABHS use and MRSA isolation rates and a modest negative association between ABHS use and MDRP isolation rates. These findings suggest that hand hygiene decreased the isolation rates of MRSA and MDRP by reducing the spread of antibiotic-resistant bacteria among patients in small and medium-sized hospitals. Previous studies have found that ABHS use is negatively associated with the isolation rates of MRSA, ESBL-producing bacteria, and MDRP when their use exceeds approximately 15 L [7], 60 L [5], and 30 L [8] per 1000 PD, respectively. The fact that we did not detect an association between ABHS use and ESBL-producing bacteria might reflect the difference in the amount of consumption in our study compared with others; the average consumption of ABHSs in this study (5 L per 1000P D, Table 1) was far lower than the previously reported values [5].

Multivariate linear regression analysis also showed a significant negative association between tazobactam/piperacillin consumption and MRSA isolation rates, but we did not find a similar association between antibiotic use and ESBL-producing bacteria or MDRP isolation rates. Tazobactam/piperacillin showed low rates of MRSA colonization and infection compared with cefepime [14]. Therefore, high tazobactam/piperacillin consumption might reduce the isolation rates of MRSA and decrease the use of other antimicrobials like carbapenems and broad-spectrum cephalosporins. However, even simple linear regression analyses indicate that there is a negative association between most antibiotics and these three multidrug-resistance bacteria. Thus, our observations suggest that the low consumption of antibiotics in small to medium-sized hospitals has little impact on multidrug-resistance bacteria. This is contrary to the findings of a previous study, which suggested a positive association between MRSA isolation rates and the consumption of quinolones, glycopeptides, cephalosporins, and β lactams [1], between ESBL-producing bacteria isolation rates and the consumption of anti-pseudomonal β-lactams and fluoroquinolones [6], and between MDRP isolation rates and the consumption of carbapenems, fluoroquinolones, and aminoglycosides [6]. The fact that we did not detect this association might reflect differences in the amounts of antibiotics used in each study because our antibiotic consumption rate appeared to be lower than the rates reported in other studies [1,6,13].

Our multivariate linear regression analyses found a modest positive association between the isolation rates of ESBL-producing bacteria and the percentage of long-term care or psychiatric bed use. A study of a long-term care facility in the Netherlands found a high level of endemic ESBL-ST131 colonization that persisted despite the antimicrobial measures taken, while colonization with other ESBL-EC returned to a relatively normal level over time. The authors of that study theorized that the sustained high prevalence of ESBL-ST131 was likely due to prolonged gut colonization [15]. Our observations of long-term care facilities in Japan were similar, and average length of hospital stay in these hospitals was high in our

Table 1
Hospital characteristics, use of antibiotics, ABHSs, and PPE, and clinical isolation of antibiotic-resistant bacteria.

No.	Establishment of ICT	Employment of ICD	Employment of ICN	Employment of board-certified pharmacist	Employment of ICMT	Microbiology laboratory
1	Yes	No	No	Yes	No	No
2	Yes	Yes	Yes	No	No	No
3	Yes	Yes	No	Yes	No	No
4	No	No	No	No	No	No
5	No	No	No	Yes	No	No
6	Yes	No	No	No	No	No
7	Yes	Yes	Yes	Yes	Yes	Yes
8	Yes	No	No	No	No	No
9	Yes	Yes	No	Yes	No	Yes
10	Yes	Yes	Yes	No	No	Yes
11	Yes	Yes	No	Yes	No	Yes

No.	Number of admissions per year	Number of beds	Number of long-term care or psychiatric beds (rate)	Average length of hospital stay (days)	ABHSs	Masks	Plastic aprons	Gloves	Number of bacterial tests	Isolated MRSA (rate)	Isolated ESBL-producing bacteria (rate)	Isolated MDRP (rate)
1	40548	145	99 (68)	301	6	1.09	0.24	13	838	31 (4)	63 (8)	0 (0)
2	41177	197	0 (0)	31	6	2.27	5.94	32	2039	106 (5)	46 (2)	2 (0.1)
3	53421	174	0 (0)	75	5	0.74	0.87	23	848	90 (11)	57 (7)	2 (0.2)
4	57463	166	120 (72)	157	2	0.03	0.06	10	554	72 (13)	4 (1)	0 (0)
5	64068	180	180 (100)	395	1	0.60	1.70	15	34	7 (21)	10 (29)	1 (3)
6	70222	210	210 (100)	339	4	0.80	0.48	6	270	36 (13)	75 (28)	0 (0)
7	92100	261	0 (0)	23	7	1.02	3.70	21	2031	205 (10)	98 (5)	10 (0.5)
8	93115	299	299 (100)	257	3	0.97	1.61	25	298	42 (14)	1 (0.3)	3 (1)
9	44504	321	0 (0)	18	10	1.90	2.12	107	1768	84 (5)	17 (1)	3 (0.2)
10	99770	312	0 (0)	19	7	1.73	3.43	19	3100	283 (9)	113 (4)	5 (0.2)
11	119008	354	0 (0)	17	1	No data	0.01	18	3000	226 (8)	78 (3)	15 (0.5)
Ave.	70491	238	83	148	5	1.11	1.83	26	1344	107 (8)	51 (4)	4 (0.3)
S.D.	26690	73	107	148	3	0.67	1.87	28	1098	90	39	5

No.	Antibiotic consumption	Sulbactam/ampicillin	Tazobactam/piperacillin	Ceftriaxone	Cefoperazone	Sulbactam/cefoperazone	Cefepime	Meropenem	Ciprofloxacin	Amikacin
1	57	6	21	10	6	1	0	6	0	0.6
2	158	43	32	36	1	2	9	10	0	0.0
3	93	14	11	16	0	5	0	7	0	0.2
4	50	16	0	5	0	6	0	5	0	0.0
5	12	0	0	0	0	2	0	2	0	0.0
6	6	1	0	0	0	0	2	0	0	0.0
7	163	56	1	26	0	3	8	24	0	0.0
8	21	0	1	5	0	1	0	2	0	0.0
9	129	55	4	11	0	4	9	15	5	0.1
10	162	48	7	20	0	6	2	11	0	0.0
11	252	44	18	17	0	2	7	26	3	0.0
Ave.	100	26	9	13	1	3	4	10	1	0.1
S.D.	79	23	11	11	2	2	4	9	2	0.2

ICT, infection control team; ICD, infection control doctor; ICN, infection control nurse; ICMT, infection control microbiological technologist. Board-certified pharmacist includes "Board Certified Infection Control Pharmacy Specialist", "Board Certified Pharmacist in Infection Control" and "Infectious Disease Chemotherapy Pharmacist". Antibiotic use is expressed in DDD/1000 PD, ABHS use is expressed in L/1000 PD, and PPE use is expressed in pieces/1 PD. Isolation rates of MRSA, ESBL-producing bacteria, and MDRP are expressed as percent total antimicrobial tests.

Table 2
Simple linear regressions analysis of antibiotic-resistant bacteria isolation rates.[a]

	MRSA isolation rate		ESBL-producing bacteria isolation rate		MDRP isolation rate	
	R	*P*	R	*P*	R	*P*
Number of beds	−0.20	0.56	−0.39	0.24	−0.05	0.89
Percent long-term care or psychiatric bed use	0.64	0.04	0.57	0.07	0.42	0.20
Total antibiotic use	−0.58	0.06	−0.55	0.08	−0.31	0.35
Sulbactam/ampicillin	−0.58	0.06	−0.55	0.08	−0.35	0.29
Tazobactam/piperacillin	−0.68	0.02	−0.32	0.34	−0.33	0.32
Ceftriaxone	−0.59	0.06	−0.53	0.09	−0.36	0.27
Cefoperazone	−0.51	0.11	−0.05	0.88	−0.23	0.49
Sulbactam/cefoperazone	−0.07	0.84	−0.44	0.17	−0.24	0.48
Cefepime	−0.58	0.06	−0.36	0.27	−0.26	0.44
Meropenem	−0.46	0.15	−0.48	0.14	−0.20	0.56
Ciprofloxacin	−0.42	0.19	−0.28	0.40	−0.12	0.72
Amikacin	−0.48	0.13	−0.06	0.87	−0.25	0.47
ABHSs	−0.66	0.03	−0.35	0.30	−0.48	0.13
Masks	−0.06	0.04	−0.34	0.34	−0.26	0.46
Plastic aprons	−0.25	0.46	−0.23	0.50	−0.00	1.00
Gloves	−0.41	0.20	−0.36	0.28	−0.11	0.74

[a] Values shown are correlation coefficients.

Table 3
Multiple linear regression analysis of the antibiotic-resistant bacteria isolation rates.[a]

	MRSA isolation rate	*P*	ESBL-producing bacteria isolation rate	*P*	MDRP isolation rate	*P*
Percent long-term care or psychiatric bed use	–		0.57 (0.06)	0.07	–	
Tazobactam/piperacillin	−0.56 (0.0007)	0.01	–		–	
ABHSs	−0.92 (0.004)	<0.01	–		−0.48 (0.0009)	0.13
Masks	0.36 (0.02)	0.15	–		–	
Adjusted R^2	0.87		0.25		0.15	

[a] Values shown are partial regression coefficients (standard error); blank spaces indicate that these values were not selected in the model.

study. Thus, the high levels of ESBL-producing bacteria isolates might be associated with the length of hospital stay. However, we did not exclude duplicated isolates among the bacterial tests, so it should be borne in mind that there may be many duplicated isolates from the same patients in long-term care or psychiatric facilities.

We were unable to find any association between the use of PPE and MRSA, ESBL-producing bacteria, or MDRP isolation rates; therefore, the effectiveness of PPE in the prevention of infection at smaller hospitals remains unclear. However, in this study, small to medium-sized hospitals including long-term care or psychiatric facilities provided fewer treatments and less physical care for patients. Thus, it would be difficult to assess the effect of PPE in these hospitals because of low PPE use. This is not surprising, considering that several previous reviews have pointed out the difficulty in determining the efficacy of individual PPE for infection control [16].

Our study has some limitations. These include the small sample size and the limited geographic area. Additionally, we did not exclude duplicated isolates in bacterial tests and active surveillance. However, although duplicate isolates generally may be greater in surveys, it has also been reported that the effect of exclusion of duplicate isolates was minor in MRSA and *E. coli* in elderly patients, similar to the present research [17]. Moreover, we did not assess the numbers of days of antimicrobial therapy. Furthermore, hospitals where all beds are solely for long-term or psychiatric care had a low number of the bacterial tests, likely because patients in these hospitals have low rates of infectious disease compared with acute care patients. Also, if these patients develop a serious infection, they are likely to be transferred to an acute care hospital. Thus, antibiotic-resistant bacteria isolation rates might be low compared with real isolation rates in these hospitals, and confounders might be included in the multivariable models. Therefore, more robust studies including active surveillance are needed to confirm these findings.

Our observations showed that ABHSs were associated with MRSA and MDRP isolation rates, but that antibiotics and PPE were not associated with multidrug-resistant bacteria. These findings suggest that hand hygiene is more important than antibiotic use and other antimicrobial measures in small to medium-sized hospitals, including long-term care or psychiatric facilities.

Conflicts of interest

The authors declare no conflicts of interest.

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

Acknowledgments

We are grateful to the hospital pharmacists who participated in the survey.

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