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ORIGINAL PAPER

# Efficacy of educational intervention on reducing the inappropriate use of oral third-generation cephalosporins

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## Abstract

**Purpose** This study aimed to evaluate the efficacy of an educational intervention on reducing the inappropriate use of oral third-generation cephalosporins, the prevalence of resistant bacteria, and clinical outcomes.

**Methods** A before-after study was conducted to compare the data for 1 year before and after intervention at a Japanese university hospital. Educational intervention included lectures for all medical staff on oral antibiotics and educational meetings with each medical department. The primary outcome was the use of oral third-generation cephalosporins in inpatients as measured by the monthly median days of therapy (DOTs) per 1000 patient days. Secondary outcomes included the use of each oral antibiotic in inpatients and outpatients, proportion of β-lactamase-nonproducing ampicillin-resistant *Haemophilus influenzae* (BLNAR), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and extended-spectrum β-lactamase producing *Escherichia coli* (ESBLEC), the incidence of hospital-acquired *Clostridioides difficile* infection (HA-CDI), and hospital mortality.

**Results** The use of oral third-generation cephalosporins in inpatients was significantly decreased after intervention [DOTs (interquartile range): 24.2 (23.5–25.1) vs. 3.7 (0.0–7.1), $P < 0.001$], and the value in outpatients was also decreased significantly. The use of fluoroquinolones and macrolides did not increase after intervention. The proportion of BLNAR, PRSP and ESBLEC did not change significantly during the study period. The incidence of HA-CDI was significantly decreased, and hospital mortality did not change after intervention.

**Conclusion** Educational intervention was effective in reducing the use of oral third-generation cephalosporins without increasing the use of broad-spectrum antibiotics and worsening clinical outcome. The prevalence of resistant bacteria did not change during the study period.

**Keywords** Educational intervention · Oral third-generation cephalosporins · Antibiotic stewardship · *Haemophilus influenzae* · *Streptococcus pneumoniae*

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## Introduction

The inappropriate use of antibiotics has become a global problem leading to increase antimicrobial resistance (AMR) bacteria, exacerbate clinical outcomes, and increase medical costs [1–3]. In particular, many oral antibiotic prescriptions have been reported to be inappropriate [4–6]. The Centers for Disease Control and Prevention has defined the four core elements of outpatient antibiotic stewardship as commitment, action for policy and practice, tracking and reporting, and education and expertise [7]. There are a number of reports of strategies for the appropriate use of oral antibiotics [8–11]. Accountable justification and peer comparison as behavioral interventions in primary care practices have been reported to result in lower rates of inappropriate antibiotic prescribing for acute respiratory tract infections [8]. Social norm feedback for general practitioners has been reported to reduce antibiotic prescribing at the national scale in England [9]. A systematic review reported that there was low- to moderate-strength evidence that antimicrobial stewardship programs (ASPs) in outpatient settings improve antimicrobial prescribing without adversely affecting patient outcomes [12]. However, the consumption of oral antibiotics has still not decreased by much overall and effective interventions for inappropriate prescriptions of oral antibiotics are needed [13, 14].

The Japanese antimicrobial consumption surveillance from 2009 to 2013 reported that oral antimicrobials accounted for 92.6% (mean of 2009, 2011, and 2013) of total consumption [15]. Among these, the consumption of oral third-generation cephalosporins was uniquely large compared to European countries or the United States [15–17]. Oral third-generation cephalosporins have broad-spectrum, covering Gram-positive cocci and Gram-negative bacilli [18]. In Japan, the proportions of β-lactamase-nonproducing ampicillin (ABPC)-resistant *Haemophilus influenzae* (BLNAR) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) were reported to be higher than that of European countries or the United States [19–26]; the increase of these AMR bacteria has been suggested to be due to the inappropriate use of oral third-generation cephalosporins in Japan [19, 21, 25]. In addition, extended-spectrum β-lactamase (ESBL) producing enterobacteriaceae has been reported to increase in Japan in recent years [27], and a high prevalence of community-associated ESBL producing *Escherichia coli* has also been reported [27, 28]. Moreover, the bioavailability of oral third-generation cephalosporins is low; the oral bioabailability of cefditoren-pivoxil is 17% and that of cefdinir is 25% [18]. The low bioavailability of these antibiotics is disadvantageous in terms of pharmacokinetics/pharmacodynamics theory and may lead to decrease of therapeutic response and select AMR bacteria [19, 21, 25]. Some of oral third-generation cephalosporins contain pivoxil groups to improve oral absorption, which have been reported to cause hypocarnitinemia and hypoglycemia [29–31]. Furthermore, cephalosporins have been reported as high-risk drugs for *Clostridioides difficile* infection (CDI) [32]. The reduction of the use of oral cephalosporins is one of the core of outcome indices for the national action plan on AMR of the Japanese Government; therefore, correcting their inappropriate prescribing is required urgently in Japan [25].

We previously reported the long-term efficacy of ASPs centered on weekly prospective audit and feedback (PAF), which targeted mainly parenteral antibiotics [33]. In this study, we aimed to reduce the inappropriate use of oral third-generation cephalosporins principally in inpatients and implemented educational intervention from July 2017 consisting of lectures for the all medical staff and educational meetings with each medical department. We evaluated the efficacy of educational intervention on use of oral third-generation cephalosporins and other antibiotics, the prevalence of resistant bacteria, and clinical outcomes.

## Methods

### Study design and setting

Kobe University Hospital is one of the national university hospitals with 934 beds in Japan. A before-after study was conducted to compare the data before (from July 2016 to June 2017) and after (from July 2017 to June 2018) educational intervention. At the start of intervention, the oral third-generation cephalosporins available to inpatients and/or outpatients in our hospital were cefcapene-pivoxil, cefditoren-pivoxil, cefteram-pivoxil, and cefdinir. The study protocol was approved by the Ethics Committee of Kobe University Hospital (No. 160165).

### Educational intervention

Educational intervention was conducted from July to August 2017 by a multidisciplinary team consisting of infectious disease physicians, pharmacists, nurses, and microbiology technologists, and included lectures for the all medical staff on the appropriate use of oral antibiotics and educational meetings with each medical department.

Lectures on the appropriate use of oral antibiotics were held four times in 2 weeks of July 2017 with the same contents. The subjects of the lectures were all medical staff in our hospital, and it was mandatory to attend one out of four lectures. The lecture included the following contents: the national action plan on AMR in Japan, typical cases that used oral antibiotics inappropriately (use for the prevention of surgical site infection after surgery, prevention of developing pneumonia after transient aspiration, infective endocarditis prophylaxis before dental procedures in unnecessary case, treatment of asymptomatic bacteriuria, and treatment of soft-tissue infection), low bioavailability and side effects of oral third-generation cephalosporins, and problems of AMR bacteria.

An educational meeting was held on July 2017, attended by representative physicians from all medical departments in our hospital, then individual meetings were also conducted from July to August 2017 with each representative physician of the medical departments that were frequently using oral third-generation cephalosporins in inpatients. At the meetings, our intervention team discussed the use of oral third-generation cephalosporins in each medical department, typical cases used oral third-generation cephalosporins in our hospital, and their alternatives. For example, oral third-generation cephalosporins have been prescribed frequently after the administration of parenteral antibiotics for prophylaxis in orthopedic surgery, so then we suggested that an additional prescription of them is unnecessary [34]. Oral third-generation cephalosporins have been prescribed frequently in oral therapy of skin and soft-tissue infections, so then we suggested that first-generation cephalosporins are appropriate in many cases of them. Oral third-generation cephalosporins also have been prescribed frequently in dental procedures for prophylaxis of infective endocarditis, so then we recommended that antibiotic prophylaxis is unnecessary in cases without high-risk cardiac conditions and penicillins are appropriate if prophylaxis is needed [35]. The main targets of our educational intervention were the inpatients, and we considered that most diseases which oral third-generation cephalosporins were used could be treated with narrower oral antibiotics such as penicillins or first-generation cephalosporins, or without antibiotics, then we did not present the indications for oral third-generation cephalosporins in the meetings.

## Outcomes

The primary outcome was the total use of oral third-generation cephalosporins in hospitalized inpatients. Secondary outcomes included the use of oral third-generation cephalosporins in outpatients, use of other oral antibiotics (penicillins, other cephalosporins, penems, fluoroquinolones, macrolides, tetracyclines, lincosamides, and sulfamethoxazole and trimethoprim) in inpatients and outpatients, the proportion of BLNAR among all isolates of *H. influenzae*, the proportion of PRSP among all isolates of *S. pneumoniae*, the proportion of ESBL producing *E. coli* among all *E. coli*, incidence of hospital-acquired CDI (HA-CDI), and hospital mortality. Outcomes compared the data before and after educational intervention. Oral third-generation cephalosporins have been removed from the formulary for inpatients in our hospital since January 2018.

According to our previous study [31], the use of oral antibiotics was evaluated by recording the days of therapy (DOTs) per 1000 patient days. For outpatients, total number of outpatients in each period was used as the denominator, and DOTs per 1000 outpatients were calculated. DOTs were calculated as the monthly medians or averages for each period and compared before and after educational intervention. Oral antibiotics were classified according to the World Health Organization's Anatomical Therapeutic Chemical classification system. The proportion of BLNAR among all isolates of *H. influenzae* and the proportion of PRSP among all isolates of *S. pneumoniae* were counted as the number of strains from any culture. The susceptibility of *H. influenzae* was classified according to the Clinical Laboratory Standards Institute (CLSI) 2012 criteria [36]: β-lactamase-nonproducing strains with ABPC minimum inhibitory concentration (MIC) of $\geq 4.0$ μg/mL were classified as BLNAR, β-lactamase-producing strains with ABPC MIC of $\geq 4.0$ μg/mL and amoxicillin/clavulanate MIC of $\leq 4.0$ μg/mL were classified as β-lactamase-producing ampicillin-resistant *H. influenzae*, and β-lactamase-producing strains with ABPC MIC of $\geq 4.0$ μg/mL and amoxicillin/clavulanate MIC of $\geq 8.0$ μg/mL were classified as β-lactamase-producing amoxicillin/clavulanate-resistant *H. influenzae*. The nitrocefin test was used to detect β-lactamase production. To compare with the prevalence of PRSP in the previous reports in Japan [24–26], the susceptibility of *S. pneumoniae* was classified according to the CLSI 2012 criteria (parenteral penicillin, meningitis) [36]: strains with PCG MIC of $\geq 0.12$ μg/mL were classified as PRSP. ESBL production in *E. coli* was confirmed by Double Disk Synergy Test. Patients with multiple detections for each of ESBL producing or non-producing *E. coli* were counted only once. The incidence of HA-CDI was determined as the number of inpatients with microbiologically confirmed *C. difficile* toxin production $\geq 72$ h after admission to hospital. Patients with multiple confirmations were counted only once. An enzyme immunoassay was used to confirmed *C. difficile* toxin production (C. DIFF QUIK CHEK COMPLETE, Abbott). The number of inpatients ordered *C. difficile* toxin tests was also evaluated before and after intervention.

## Statistical analysis

The statistical significance of the difference in median values between the two groups was analyzed by Mann–Whitney *U*-test if the data were not normally distributed (oral third-generation cephalosporins both inpatients and outpatients, and lincosamides in outpatients).

The difference in mean values between the two groups was analyzed by Student's *t* test if the data were normally distributed (other oral antibiotics). Chi-square test were used for the comparison of the proportions of categorical variables between the groups (proportion of BLNAR, proportion of PRSP, proportion of ESBL producing *E. coli*, incidence of HA-CDI, and hospital mortality). $P<0.05$ was considered to indicate statistical significance. All statistical analyses were performed with GraphPad Prism 6 (La Jolla, CA, USA).

## Results

### Antibiotic use

Change of monthly days of therapy per 1000 patient days of oral third-generation cephalosporins in inpatients is shown in Fig. 1. The monthly median (interquartile range) use of oral third-generation cephalosporins in inpatients was 24.2 (23.5–25.1) DOTs per 1000 patient days before intervention and 3.7 (0.0–7.1) DOTs per 1000 patient days after intervention, and the value after intervention was significantly lower than before intervention ($P<0.001$; Table 1). The value in outpatients was 30.2 (25.4–32.1) DOTs per 1000 outpatients before intervention and 13.3 (9.6–17.1) DOTs per 1000 outpatients after intervention, and there was also statistically significant difference ($P<0.001$; Table 1).

The amount of each class of oral antibiotics is also shown in Table 1. The use of first-generation cephalosporins in inpatients and outpatients was significantly increased after intervention than before intervention. The use of penicillins with extended spectrum (amoxicillin) was significantly increased after intervention in inpatients only. In outpatients, the use of fluoroquinolones and sulfamethoxazole and trimethoprim was significantly decreased, whereas the use of tetracyclines was significantly increased after intervention. The use of macrolides and lincosamides did not change significantly during the study period. The total use of oral antibiotics in inpatients did not change significantly, whereas in outpatients was significantly decreased after intervention.

### Antibiotic resistance

The proportion of BLNAR among all *H. influenzae* was 41.9% before intervention and 30.9% after intervention, although the difference between them was not statistically significant (Table 2). The proportion of PRSP among all *S. pneumoniae* was 51.2% before intervention and 39.5% after intervention, and no significant difference was observed between them. (Table 3). The proportion of ESBL producing

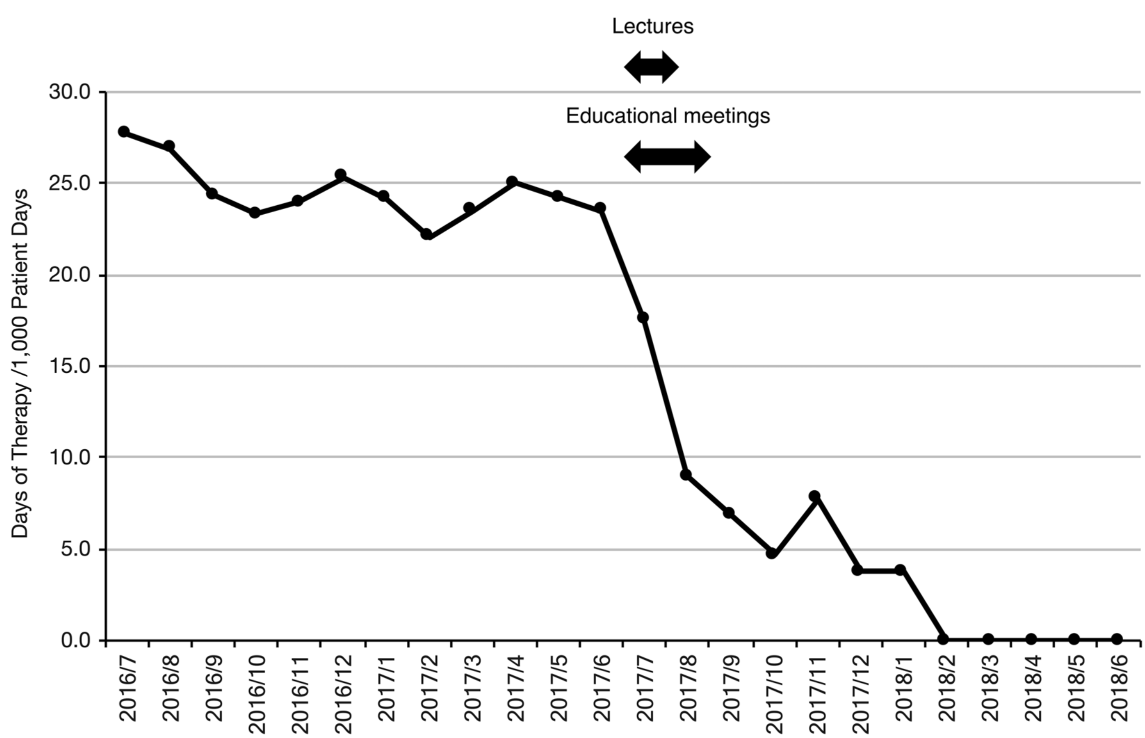


**Fig. 1** Monthly days of therapy per 1000 patient days of oral third-generation cephalosporins in inpatients. The time at which each measure of educational intervention was implemented is shown in the figure. Oral third-generation cephalosporins have been removed from the formulary for inpatients in our hospital since January 2018

**Table 1** Days of therapy with each oral antibiotic by class for 1 year before and after intervention

| | Inpatients | | | Outpatients | | |
|---|---|---|---|---|---|---|
| | DOTs (IQR) | | *P* | DOTs (IQR) | | *P* |
| | Before intervention | After intervention | | Before intervention | After intervention | |
| Penicillins with extended spectrum | 16.8 (13.5–18.2) | 19.3 (18.2–24.2) | 0.021 | 22.8 (21.2–25.5) | 27.6 (23.7–29.1) | 0.10 |
| Combinations of penicillins, including β-lactamase inhibitors | 10.0 (8.8–11.3) | 12.5 (10.6–14.0) | 0.16 | 10.6 (8.2–12.9) | 11.3 (10.3–12.9) | 0.27 |
| First-generation cephalosporins | 8.1 (6.2–8.8) | 18.0 (17.4–20.1) | < 0.001 | 7.1 (5.9–9.2) | 14.4 (10.1–15.9) | < 0.001 |
| Second-generation cephalosporins[a] | | | | 1.3 (0.9–1.6) | 1.3 (1.1–1.4) | 0.89 |
| Third-generation cephalosporins | 24.2 (23.5–25.1) | 3.7 (0.0–7.1) | < 0.001 | 30.2 (25.4–32.1) | 13.3 (9.6–17.1) | < 0.001 |
| Other cephalosporins and penems[a] | | | | 2.2 (1.9–2.8) | 2.4 (1.6–2.8) | 0.89 |
| Macrolides | 10.8 (9.5–12.7) | 13.2 (11.9–14.8) | 0.051 | 112.6 (106.2–117.2) | 109.3 (103.2–122.9) | 0.82 |
| Fluoroquinolones | 26.7 (25.0–28.5) | 25.3 (23.3–27.9) | 0.81 | 41.1 (39.3–44.5) | 35.1 (32.8–40.3) | 0.008 |
| Tetracyclines | 11.9 (10.3–13.0) | 14.3 (11.3–16.8) | 0.10 | 44.7 (38.9–46.9) | 50.1 (43.8–52.9) | 0.029 |
| Lincosamides | 1.5 (0.5–2.4) | 1.1 (0.5–1.5) | 0.35 | 3.9 (2.9–4.2) | 3.9 (3.4–4.2) | 0.79 |
| Sulfamethoxazole and trimethoprim | 83.5 (79.0–90.6) | 86.4 (80.5–94.5) | 0.27 | 339.6 (330.9–347.5) | 315.6 (306.3–324.3) | 0.019 |
| Total | 195.1 (182.4–203.4) | 190.4 (186.9–212.6) | 0.62 | 609.8 (603.4–619.7) | 578.2 (575.2–600.3) | 0.032 |

DOTs (per 1000 outpatients for outpatients) expressed as monthly median (IQR)

*DOTs* days of therapy per 1000 patient days, *IQR* interquartile range

[a]Classes of antibiotics not available for inpatients

**Table 2** Proportion of BLNAR among all isolates of *H. influenzae*

| | Number of strains (%) | | *P* |
|---|---|---|---|
| | Before the intervention | After the intervention | |
| BLNAR/total | 26/62 (41.9) | 25/81 (30.9) | 0.17 |

*BLNAR* β-lactamase-nonproducing ampicillin-resistant *H. influenzae*

**Table 3** Proportion of PRSP among all isolates of *S. pneumoniae*

| | Number of strains (%) | | *P* |
|---|---|---|---|
| | Before the intervention | After the intervention | |
| PRSP/total | 22/43 (51.2) | 15/38 (39.5) | 0.29 |

*PRSP* penicillin-resistance *Streptococcus pneumoniae*

*E. coli* among all *E. coli* was 20.5% before intervention and 23.4% after intervention, and no significant difference was observed between them. (Table 4).

**Table 4** Proportion of ESBL producing *E. coli* among all isolates of *E. coli*

| | Number of strains (%) | | *P* |
|---|---|---|---|
| | Before the intervention | After the intervention | |
| ESBL/total | 114/557 (20.5) | 138/591 (23.4) | 0.24 |

*ESBL* extended-spectrum β-lactamase

## Clostridioides difficile infection

The incidence of HA-CDI was 0.14 per 1000 patient days before intervention and 0.09 per 1000 patient days after intervention, and the value after intervention was significantly lower than before intervention ($P = 0.029$; Fig. 2). The number of inpatients ordered *C. difficile* toxin tests was 435 before intervention and 430 after intervention.

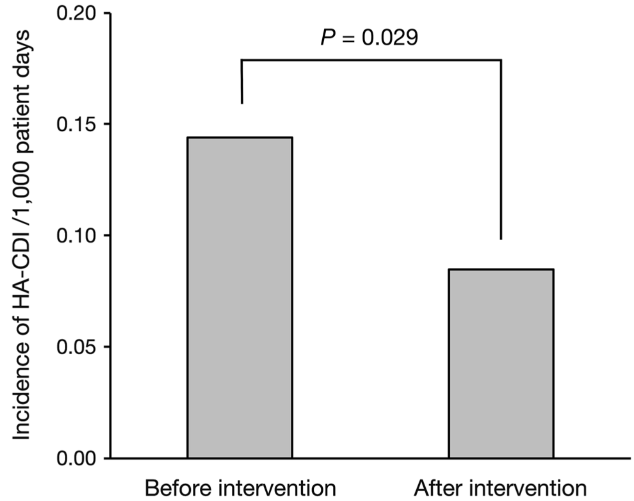


**Fig. 2** Incidence of HA-CDI per 1000 patient days. HA-CDI, hospital-acquired *Clostridioides difficile* infection

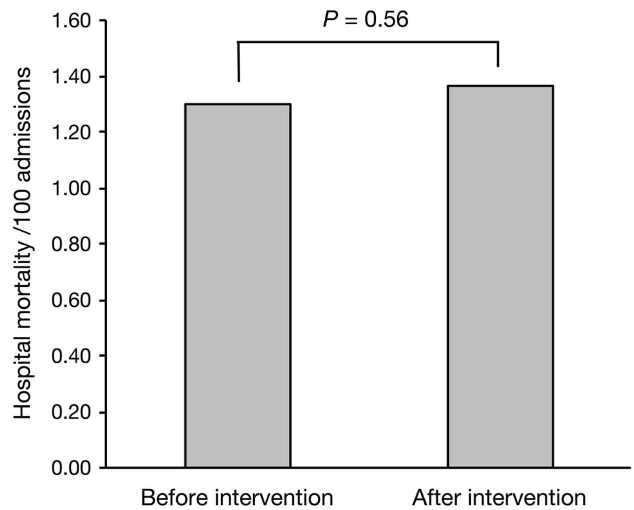


**Fig. 3** Hospital mortality

### Hospital mortality

Hospital mortality did not change significantly before and after intervention ($P = 0.56$; Fig. 3).

## Discussion

Our study suggested the efficacy of educational intervention on reducing the use of oral third-generation cephalosporins in inpatients and outpatients. The use of oral third-generation cephalosporins decreased for 6 months after intervention, and then, those have been removed from formulary for inpatients in our hospital since January 2018. Meanwhile, the use of broad-spectrum oral antibiotics, such as fluoroquinolones or macrolides, did not change before and after educational intervention. The Japanese antimicrobial consumption surveillance reported that oral antimicrobials accounted for 92.6% of total consumption and oral third-generation cephalosporins accounted for 23.8% of all oral antimicrobials in 2013 [15]. Another Japanese nationwide study of outpatient oral antimicrobial utilization patterns for children reported that oral third-generation cephalosporins accounted for 35.6% of all antimicrobials dispensed in 2013–2016 [37]. Unlike in European countries or the United States, the consumption of oral third-generation cephalosporins has been particularly high in Japan [15–17], although those were suggested to increase AMR [19, 21, 25], cause hypocarnitinemia particularly in children [29–31], and be an important risk factor for CDI [32]. The national action plan on AMR of the Japanese Government aims to reduce the use of oral cephalosporins, quinolones, and macrolides per day per 1000 inhabitants by 50% in 2020 from the level in 2013 [25]. Our educational intervention to the inappropriate use of oral third-generation cephalosporins may contribute to the achievement of this goal.

In our hospital, the typical cases that used oral third-generation cephalosporins inappropriately were as follows: prophylaxis in orthopedic surgery, treatment of soft-tissue infection, prophylaxis for infective endocarditis before dental procedures, and treatment of asymptomatic bacteriuria or urinary tract infection. Our educational intervention included lectures and educational meetings focused on the appropriate use of antibiotics in these cases. Moreover, the prescribing pattern in outpatients was also improved, although the main targets of our educational intervention were the inpatients. Several studies also reported the efficacy of educational intervention [10, 11]. Multifaceted intervention, which included physician focus group meetings, workshops, seminars, and practice campaigns, was reported to reduce the annual antibiotic prescription rates for 4 years in a community pediatric setting [10]. Educational programs, which included practice-based seminars, online educational elements, and practicing consulting skills, were reported to reduce oral antibiotic dispensing over the subsequent year with no significant change in admissions to hospital, reconsultations, or costs [11]. The guidelines for implementing ASPs have recommended that passive educational activities, such as lectures should be used to complement other stewardship activities [38]. In our educational intervention, lectures were given in combination with educational meetings in each medical department. It was difficult to conduct individualized intervention such as PAF in all cases prescribed with oral antibiotics inappropriately; therefore, educational intervention focused on typical cases could be useful in correcting antibiotic prescription patterns. In addition, implementation of intervention by a multidisciplinary team consisting of infectious disease specialists may have led to smooth acceptance of our recommendations and its immediate efficacy. In our study, the use of broad-spectrum antibiotics such as fluoroquinolones or macrolides did not change, whereas the use of narrow-spectrum antibiotics such as first-generation cephalosporins or penicillins was increased, and the total use of oral antibiotics in inpatients did not decrease before and after educational intervention. Although the inappropriate use of oral third-generation cephalosporins has decreased, the remaining inappropriate or unnecessary other oral antibiotics needs to be corrected.

The prevalence of BLNAR in Japan has increased in recent years and was reported to account for 38–64% of all *H. influenzae* strains in the reports after 2010 [19–21]. Its prevalence was higher than that in European countries or the United States [19–23], and it was suggested to be due to the inappropriate use of oral third-generation cephalosporins in Japan [19, 21]. However, there has been no report to improve the prevalence of BLNAR by reducing the use of oral third-generation cephalosporins. Regarding *S. pneumoniae*, nationwide survey conducted from 2000 to 2012 in the pediatric field in Japan reported that the sum of the isolation rates for penicillin-intermediate *S. pneumoniae* (PISP) and PRSP were 49.5–76.9%, according to the CLSI 2007 criteria (non-meningitis, oral penicillin): PCG sensitivity of 0.12–1.0 µg/mL was classified as PISP and sensitivity of ≥ 2.0 µg/mL was classified as PRSP [24]. Meanwhile, the Annual Open Report 2016 of the Japanese Nosocomial Infection Surveillance (JANIS) system reported that the proportion of PRSP in all *S. pneumoniae* other than cerebrospinal fluid was 0.4%, according to the CLSI 2012 criteria: PCG sensitivity of 4.0 µg/mL was classified as PISP and sensitivity of ≥ 8.0 µg/mL was classified as PRSP [39]. The discrepancy in the prevalence of PRSP between that in the previous reports [24–26] and that in the JANIS report of 2016 [39] was considered to be due to the differences in the criteria applied in each study. In our study, the prevalence of BLNAR and PRSP after educational intervention was lower than that in previous reports in Japan [19–21, 24], whereas no significant difference was observed before and after educational intervention. One of the reasons why the difference was not deemed to be statistically significant in the proportion of BLNAR among all *H. influenzae* and PRSP among all *S. pneumoniae* may have been their small sample sizes. Our study was a single-center study; therefore, our intervention did not directly affect the use of antibiotics in the community. However, our educational intervention may have positive ripple effects on the inappropriate use of oral third-generation cephalosporins in the community, because our hospital has an educational role as a university hospital. Whether the prevalence of the BLNAR or PRSP could be decreased by reducing the consumption of oral third-generation cephalosporins throughout the community needs to be examined in the future.

ESBL-producing *E. coli* has been reported to increase in healthcare facilities and communities in Japan [27, 28]. A long-term study of outpatients in a Japanese single facility reported that the detection rates of ESBL-producing *E. coli* increased from 1.2% in 2003 to 14.3% in 2011 [27]. The Annual Open Report 2016 of the JANIS system reported that the proportion of cefotaxime resistant *E. coli* was 26.0% [39]. In our study, the proportion of ESBL producing *E. coli* did not change before and after intervention, and it was unclear whether a decrease of the use of oral third-generation cephalosporins could reduce the prevalence of ESBL producing *E. coli*. The retrospective study investigating the characteristics of ESBL producing *E. coli* at a national center in Japan reported that community-associated ESBL producing *E. coli* accounted for 26% of all patients with ESBL-producing *E. coli*, and 85% of them were not exposed to antimicrobials in the past 3 months [28]. In addition to reducing the inappropriate use of antibiotics in healthcare facilities, measures in communities may be necessary to prevent a spread of ESBL producing *E. coli* [28].

ASPs has been reported to significantly reduce the incidence of CDI in hospital inpatients [40]. The guidelines for implementing ASPs have recommended interventions to reduce the use of antibiotics associated with a high-risk of CDI [38]. The incidence of HA-CDI decreased after educational intervention in our study. Previously reported ASPs in our hospital were simultaneously implemented during the study period [33]. The main contents of the ASPs included weekly PAF targeting parenteral antipseudomonal agents, anti-methicilin-resistant *Staphylococcus aureus* agents and antifungals, mandatory preauthorization when using linezolid and daptomycin, and consultation on bacteremia patients by infectious disease physicians [33]. Although the ASPs have not included measures targeting oral third-generation cephalosporins, which may have also affected the incidence of HA-CDI. Additionally, the incidence of HA-CDI may have been underestimated because only the number of inpatients with microbiologically confirmed *C. difficile* toxin production was counted. However, the method for the evaluation of the incidence of HA-CDI was not changed during the study period, and the number of inpatients ordered *C. difficile* toxin tests did not increase after intervention. Meanwhile, hospital mortality did not change significantly in this study. Although these results did not reflect the exact mortality among all subjects of our study, as outpatients were not included, it was suggested that educational intervention did not, at least, cause clinical harm in our study.

Our study has several limitations. First, it was a before-after study conducted at a single university hospital in Japan. As mentioned above, the use of oral third-generation cephalosporins was uniquely high in Japan compared to European countries or the United States [15–17]. Hence, our results may not be generalizable to other antibiotics, care settings, or countries. However, our results will be helpful to many Japanese healthcare facilities required to correct the inappropriate use of oral third-generation cephalosporins [25]. Second, we could not exclude the effects of the factors other than educational intervention on the outcomes of the prevalence of BLNAR and PRSP, the incidence of HA-CDI, and hospital mortality. ASPs for parenteral antibiotics in our hospital [33] and the use of antibiotics in our community might affect these outcomes. In particular, the impacts of the decrease on the community usage of oral third-generation cephalosporins on the prevalence of AMR should be verified with a large-scale research in the future.

In conclusion, our study suggested the efficacy of educational intervention consisting of lectures and educational meetings on reducing the use of oral third-generation cephalosporins. The use of broad-spectrum oral antibiotics, such as fluoroquinolones or macrolides, did not change during the study period. There were no significant differences in the prevalence of BLNAR, PRSP, and ESBL-producing *E. coli* between before and after intervention. The incidence of HA-CDI decreased after intervention, whereas hospital mortality did not change significantly during the study period. Many healthcare facilities in Japan have been required to correct the inappropriate use of oral third-generation cephalosporins [25]; therefore, our educational intervention may contribute to their correction.

## Compliance with ethical standards

**Conflict of interest** T. Miyara has received grant support from Shionogi & Co., Ltd. The other authors reported no conflicts of interest relevant to this article.

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