Spinal Cord (2020) 58:705–710
https://doi.org/10.1038/s41393-020-0416-8

ARTICLE

Use of oral third generation cephalosporins and quinolones and occurrence of antibiotic-resistant strains in the neurogenic bladder (NB) outpatient setting: a retrospective chart audit

Koichi Kitagawa [1,2] · Katsumi Shigemura [2,3] · Masashi Nomi [4] · Nozomi Takami [4] · Naoki Yamada [2] · Masato Fujisawa [3]

Received: 27 August 2019 / Revised: 2 January 2020 / Accepted: 6 January 2020 / Published online: 21 January 2020

Abstract

Study design A retrospective chart audit.

Objectives Neurogenic bladder (NB), a risk factor for urinary tract infection, has not been comprehensively studied in terms of antimicrobial stewardship. In this study, we studied the relationship between the use of oral third generation cephalosporins and quinolones, and the occurrence of antibiotic-resistant strains.

Setting Hyogo Prefectural Central Rehabilitation Hospital, Hyogo, Japan.

Methods We retrospectively investigated antibiotic-resistant bacteria and the amount of antibiotics prescribed in outpatients with NB caused by spinal cord injury between 2012 and 2017. We intervened in urological departments whose physicians often prescribed third generation cephalosporins and fluoroquinolone, and analyzed the number of prescriptions and the amount of Cefdinir (CFDN) and Levofloxacin (LVFX), and studied changes of ratios in antibiotic-resistant strains such as extended-spectrum β-lactamases (ESBLs) and quinolone-resistant *Escherichia coli* and *Klebsiella pneumoniae*.

Results The number of CFDN prescriptions per year significantly decreased from 463 cases to 130 cases over 6 years ($p = 0.012$). The number of LVFX prescriptions per year decreased from 640 cases to 171 cases ($p = 0.025$). The incidence rate of ESBL-producing *K. pneumoniae* decreased from 25% to 7% of total *K. pneumoniae* ($p < 0.001$). The incidence of LVFX-resistant *E. coli* and *K. pneumoniae* significantly decreased in 2017 compared with 2012 ($p = 0.03$ and $p = 0.016$, respectively).

Conclusions Antimicrobial stewardship interventions decreased the use of CFDN and LVFX for outpatients with NB. Our findings suggested that the reduction in the use of third generation cephalosporins and quinolones correlates with observed decrease in the occurrence of antibiotic-resistant, ESBL-producing, and quinolone-resistant bacteria.

Introduction

Neurogenic bladder is one of the risk factors for urinary tract infection (UTI) because these patients often have complications such as disturbances in urination, catheterization, urinary tract obstruction, and residual urine lead to the emergence of bacteriuria or pyuria. During UTI management, antibiotic use needs to be monitored since uncontrolled use may lead to the emergence of antibiotic-resistant strains and also involves unnecessarily high institutional costs [1]. Antimicrobial stewardship (ASW) programs have become more common as a way to address these problems [2]. ASW programs have emphasized the prevention of antibiotic-resistant strains from unnecessary broad-spectrum antibiotic use, long duration use, insufficient doses, or inappropriate spectrum coverage [3]. The related researchers have spread this concept and increased the number of specialists managing these issues [4, 5], including the UTI field. In particular, outpatients with NB require special attention because most patients with NB have urination disturbances and a high risk of catheter-associated UTI (CAUTI) leading to the increased likelihood

✉ Katsumi Shigemura
katsumi@med.kobe-u.ac.jp

1 Division of Advanced Medical Science, Kobe University Graduate School of Science, Technology and Innovation, Kobe, Japan

2 Division of Infectious Diseases, Department of International Health, Kobe University Graduate School of Health Sciences, Kobe, Japan

3 Division of Urology, Kobe University Graduate School of Medicine, Kobe, Japan

4 Infection Control Team, Hyogo Prefectural Central Rehabilitation Hospital, Hyogo, Japan

of antibiotic-resistant bacterial infection owing to frequent antibiotic exposure for chronic pyuria or bacteriuria. Antibiotic treatments are contraindicated for patients without UTI in many clinical settings [6]. Outpatients with NB specifically need to be studied for antibiotic consumption, antibiotic stewardship intervention, and changes in the emergence of antibiotic-resistant bacteria.

In this study, we retrospectively examined outpatients with NB at risk for CAUTI after intervention for appropriate use of antibiotics, and analyzed the amounts of antibiotics prescribed and the incidence rate of antibiotic-resistant bacteria over a 6-year period in a rehabilitation hospital to investigate the effect of our ASW program [7] in decreasing the use of oral third generation cephalosporins and quinolones, and to reduce the occurrence of antibiotic-resistant bacteria.

Methods

Study setting

We retrospectively investigated the amount of oral antibiotics used for outpatients in Hyogo Prefectural Rehabilitation Central Hospital, Hyogo, Japan from 2012 to 2017. This is a rehabilitation hospital with 7 inpatient wards (two rehabilitation wards, one internal medicine and neurology ward, two orthopedic wards, one spinal cord injury ward, and one pediatric rehabilitation ward) with 330 beds, 70 days of average hospitalization, an average 630 cases of yearly surgery, and 30 full-time doctors (orthopedics, urology, internal medicine, rehabilitation, neurology, rheumatology, pediatric orthopedics, and pediatric sleep disorders) [8]. This hospital is one of the hospitals that had been referred in our previous study [8]. We had found that there had been significant correlations between antibiotic resistance of UTI-causing bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* and both annual number of days of antibiotic use and days of therapy in the hospital. There were 28,973 drug prescriptions for outpatients and 31,874 prescriptions for inpatients in 2017, all of which were prepared in the hospital. Two hundred five prescriptions were provided per working day. Our infection control team (ICT) consists of a pharmacologist (team leader), physician, medical technologist, and nurses based on Japanese Ministry of Health, Labor, and Welfare standards for intervention initiated in 2016. The ICT suggests that physicians limit or stop the use of third generation cephalosporins and fluoroquinolones. Penicillin or first generation cephalosporins or sulfamethoxazole–trimethoprim (ST) is often recommended for use as de-escalation. We began intervening in Urology Department use of third generation cephalosporins and fluoroquinolones at the initiation of the study. Most of the patients with NB and UTI in this study were caused by spinal cord injury. The number of patients with indwelling catheter or intermittent catheterization was 100 cases and 350 cases, respectively. In total, 103 patients were routinely changed with urethral catheter or cystostomy catheter. The frequency of outpatient clinical attendance and the indication for attendance was once per 1–3 months.

Antibiotic-resistant bacteria

In this study, we particularly focused on extended-spectrum β-lactamase (ESBL) producing-*E. coli*, ESBL-producing-*K. pneumoniae*, and multi-drug resistant *Pseudomonas aeruginosa*, since these are representative UTI-causative bacteria with a high likelihood of antibiotic resistance and are likely to well represent the whole spectrum of antibiotic resistance. ESBL-producing and multidrug resistant *P. aeruginosa* were primarily screened by the cefotaxime and ceftazidime disk diffusion method. Isolates, which showed an inhibition zone of 27 mm for cefotaxime and 22 mm for ceftazidime were investigated for ESBL enzyme production. The suspected isolates were further assessed by the double disc method [9, 10]. A multidrug-resistant *P. aeruginosa* phenotype is defined as resistance to three or more antipseudomonal antimicrobial classes: carbapenems, fluoroquinolones, penicillins/cephalosporins, and aminoglycosides [10].

Particularly, we focused on the quantity of cefdinir (CFDN) and levofloxacin (LVFX), two antibiotics that were especially heavily used in the Urology Department and whose use has been remarkably reduced over the 6-year study period. We also investigated the incidence rate of antibiotic-resistant bacteria in urine cultures from outpatients over the 6-year study period. This study was approved by the ethics board of Hyogo Prefectural Rehabilitation Central Hospital.

Statistical analysis

Data were analyzed by Statcel 3 (OMS publishing Inc., Tokyo, Japan) to compare the changes in parameters between the first three years and the last three years. Welch's t test was used for comparison because of non-normal distribution. The Spearman's correlation coefficient by the rank test was conducted to determine the correlation between years and the following parameters for CFDN and LVFX: number of prescriptions, dosing periods, dosages, total number of antibiotics used, number of prescriptions in the Urology Department, and dosages in the Urology Department. The proportion of resistant bacteria was analyzed using the χ^2 test to compare 2012 and 2017. Statistical differences among means were considered significant when $p < 0.05$.

Table 1 Change in prescriptions of cefdinir in the urological outpatient setting.

Years	2012	2013	2014	2015	2016	2017	*p* value*	*p* value**
No. of prescriptions of cefdinir	463	458	336	205	153	130	**0.025**	**0.012**
Dosing period (days)								
Mean	7.7	7.0	6.7	6.5	6.3	6.5	0.064	0.158
Median	7	7	7	7	7	7	–	–
Dosages (mg)								
Mean	2205	2050	2060	1950	1890	1930	**0.047**	0.101
Median	2100	2100	2100	2100	2100	2100	–	–
Total no. of prescriptions in the Urology Department (%)	82	84	77	75	63	74	**0.047**	0.114
Total dosages in the Urology Department (%)	88	88	82	78	70	75	**0.025**	**0.019**

**p* value: the Spearman's correlation coefficient by the rank test for comparison between years and each parameter

**We compared the last 3 years (2015–2017) with the first 3 years (2012–2014)

Bold values indicate statistical significance

Results

Antibiotic use

We investigated the number of prescriptions, dosing periods, and amount prescribed for outpatients with NB in the Urology Department. The averages and medians are shown in Table 1. The total number of prescriptions of CFDN significantly decreased from 463 cases to 130 cases over 6 years ($p = 0.012$). The average dosing periods and dosages in each year slightly decreased from 7.7 days to 6.5 days after 2012, but the median of those factors did not change substantially (Table 1). Mean dosages of CFDN significantly decreased from 2205 mg in 2012 to 1930 mg in 2017 ($p = 0.047$). We also found that the proportion of prescription and total dosages significantly decreased from 2012 to 2017 ($p = 0.047$ and $p = 0.025$, respectively).

The average and median of LVFX prescriptions, dosing periods, and amount prescribed for outpatients in the Urology Department and for total hospital outpatients are shown in Table 2. The number of prescriptions of LVFX significantly decreased from 640 cases in 2012 to 171 cases in 2017 in the Urology Department ($p = 0.025$). The total amount of LVFX used for outpatients in 2017 significantly decreased from 2334 g in 2012 to 610 g in 2017 ($p = 0.035$). We also found that the proportion of prescription and total dosages significantly decreased from 2012 to 2017 (both $p = 0.048$) (Table 2).

Antibiotic-resistant bacteria

We investigated the incidence rate of antibiotic-resistant *E. coli*, *K. pneumoniae*, and *P. aeruginosa* from urine culture. ESBL-producing *E. coli* and *K. pneumoniae* were the most commonly detected antibiotic-resistant *Enterobacteriaceae*. Antibiotic-resistant *P. aeruginosa* showed resistance to three or more antibiotics. As seen in Fig. 1, the proportion of ESBL-producing *E. coli* to total *E. coli* slightly, but not significantly, decreased from 26% in 2012 to 24% in 2017 ($p = 0.744$). The incidence of ESBL-producing *K. pneumoniae* showed a remarkable decrease from 25% in 2012 to 7% in 2017 ($p < 0.001$). The incidence of *P. aeruginosa* decreased from 21% in 2012 to 14% in 2017 ($p = 0.193$) (Fig. 1). LVFX-resistant *E. coli* and *K. pneumoniae* were also seen and the changes in these over the 6-year study period are shown in Fig. 2. The incidence of LVFX-resistant *E. coli* significantly decreased from 46% in 2012 to 31% in 2017 ($p = 0.03$). The incidence of LVFX-resistant *K. pneumoniae* decreased from 12% in 2012 to 3% in 2017 ($p = 0.016$) (Fig. 2).

Discussion

ASW programs have been encouraged globally, and the number of related studies has increased over the last decade [11]. In this study, we found a significant reduction in the prescription of third generation cephalosporins and quinolones between 2012 and 2017 due to the implementation of an ASW program, associated with a decrease of ESBL-producing *K. pneumoniae*, antibiotic-resistant *P. aeruginosa*, LVFX-resistant *E. coli*, and LVFX-resistant *K. pneumoniae* in outpatients with NB, where antibiotic exposure was commonly seen in the presence of pyuria or bacteriuria and high risk for UTI [12].

It is important to reduce antibiotic use and thus prevent the emergence of antibiotic-resistant bacteria even in this high-risk population. Our study showed reduced use of antibiotics, especially broad-spectrum third generation cephalosporins, CFDN and fluoroquinolones like LVFX for urological outpatients with NB over the 6 years of the study. We found that the incidence of antibiotic-resistant bacteria

Table 2 Changes in levofloxacin prescriptions in the urological outpatient setting.

Years	2012	2013	2014	2015	2016	2017	*p* value*	*p* value**
No. of prescriptions of levofloxacin	640	506	320	286	196	171	**0.025**	0.072
Dosing period (days)								
Mean	7.35	7.44	7.16	7.24	7.13	7.16	0.092	0.213
Median	7	7	7	7	7	7	–	–
Dosages (mg)								
Mean	3645	3665	3560	3620	3560	3565	**0.025**	0.347
Median	3500	3500	3500	3500	3500	3500	–	–
Total LVFX (g)	2334	1852	1141	1036	669	610	**0.035**	0.074
Total no. of prescriptions in Urology Department (%)	92	93	88	91	81	75	**0.048**	0.243
Total dosages in Urology Department (%)	92	93	88	90	71	60	**0.048**	0.192

**p* value: the Spearman's correlation coefficient by the rank test for comparison between years and each parameter

**We compare the last 3 years (2015–2017) with the first 3 years (2012–2014)

Bold values indicate statistical significance

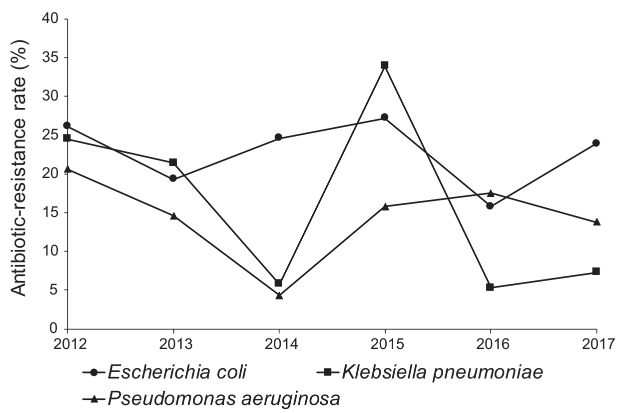

Fig. 1 Antibiotic resistance rate of *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. The proportion of extended-spectrum β-lactamase-producing *E. coli* and *Klebsiella* versus total *E. coli* and *K. pneumoniae* is shown. Antibiotic-resistant *P. aeruginosa* showed resistance to three or more antibiotics.

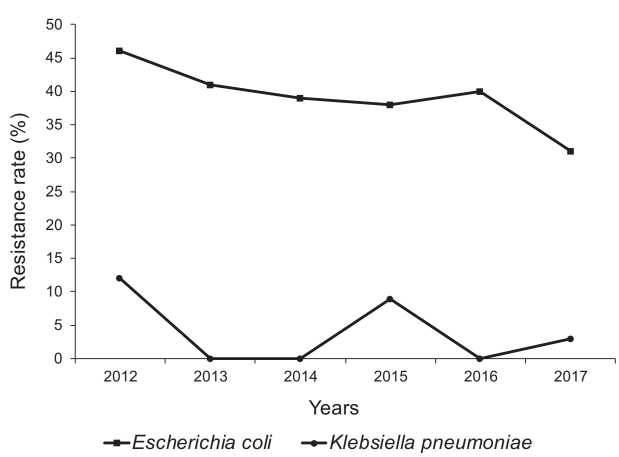

Fig. 2 Quinolone resistance rate of *E. coli* and *K. pneumoniae*. The proportion of quinolone-resistant *E. coli* and *K. pneumoniae* is shown.

in urine cultures did not increase. The decrease in CFDN and LVFX prescriptions seems to have been one of the key factors, since the dosing periods and median amount of CFDN and LVFX for each patient did not show a dramatic change or decrease from 2012 to 2017.

De-escalation of antibiotics and switching to narrower-spectrum coverage is one modality by which ASW programs can help us to avoid unnecessary use of broad-spectrum antibiotics [13]. Carbo et al. showed that ASW programs including prescription review and feedback, restricted formularies, guideline development, and education significantly shortened the duration of antibiotic therapy and improved clinical outcomes of inpatients and outpatients [14]. Hicks et al. found that comprehensive oversight of outpatient antibiotic prescriptions was an essential strategy for reducing the spread of antibiotic resistance and a critical step in identifying where appropriate-use interventions can have the most impact [15]. In the present study, we found that dosing periods for CFDN and LVFX were slightly shortened and total consumption was reduced to achieve de-escalation over the study period. The prescribed amounts of CFDN and LVFX decreased after 2012, while the amount of ST and cefaclor tended to increase over the study period (data not shown), indicated that ASW stewardship led to less use of broad-spectrum and more focused use of narrower-spectrum antibiotics, decreasing the chance of emergence of antibiotic-resistant strains. The use of narrow-spectrum antibiotics such as ST or first generation cephalosporin was reported to yield low antibiotic resistance rates in outpatients with UTI [16], supporting our results.

The total amount of LVFX used for outpatients gradually decreased until 2016, but slightly increased from 2016 to 2017. In contrast, LVFX use in the Urology Department continuously decreased from 2012 to 2017. If this pattern of use spreads to other departments, such as internal medicine which also regularly prescribes antibiotics, it might lead to a decreasing chance of emergent antibiotic-resistant strains in the whole hospital.

Several studies have correlated the establishment of ASW programs with lower antimicrobial therapy costs. Fukuda et al. prospectively monitored ASW management of meropenem, ciprofloxacin, and amikacin for 251 cases in a hospital with 465 beds over 2 years [17]. They showed that antimicrobial therapy costs significantly decreased by 26% after an ASW program was instituted. They also found that consumption of aminoglycosides decreased by 80% and the detection rate of methicillin-resistant *staphylococcus aureus* decreased by 48%. In this study, ASW reduced almost 80% of the CFDN cost and 90% of the LVFX cost in the Urology Department over the 6-year observation period. The Urology Department showed the greatest cost reduction in this study (data not shown).

Regarding antibiotic-resistant bacteria, the total incidence of antibiotic-resistant bacteria tended to decrease from 2012 to 2016, but slightly increased in 2017. In particular, we had an outbreak caused by ESBL-producing *K. pneumoniae* in an inpatient ward [18]. The increased incidence of antibiotic-resistant *K. pneumoniae* in outpatients was possibly affected by this outbreak. In addition, urine culture was done for discharged patients carrying antibiotic-resistant bacteria as outpatients after the outbreak was controlled. The main purpose of ASW programs is to inhibit or prevent the emergence of antibiotic-resistant bacterial infections. Many other studies have shown that ASW intervention reduced antibiotic use and improved patient outcomes, resulting in lowered incidence of antibiotic resistance [19]. Our results did not show a significant change (decrease) of antibiotic-resistant bacteria and further follow-up needs to be performed for definitive evaluation.

ASW programs have spread to many health care institutions [11]. We suggest that ASW should be done in cooperation with an ICT and linked hospital staff to carry out the following: (1) Early monitoring and intervention in treatments for infectious diseases after the initiation of antibiotic treatment and/or detection of positive blood culture. (2) Approval for intended antibiotic use in cooperation with the Pharmaceutical Department. (3) Management of appropriate antibiotic use to monitor dosing and duration along with therapeutic effects after initiation of antibiotic therapy. When necessary, the ASW can send feedback to the doctors in charge regarding the appropriate use of antibiotics. (4) The ASW can order microbiological tests required for early diagnosis, and educate the staffs to collect appropriate specimens. (5) The ASW can monitor the incidence of antibiotic-resistant bacteria in the whole hospital. (6) The ASW can educate medical staff to promote ASW activities using antibiograms and local data. (7) The ASW should have a meeting round once a week if possible.

We would like to emphasize the limitations of this study. First, this study is retrospective and was carried out in one institution. We have missed a longitudinal cohort study consisting of a group exposed to the risk factor (in this case treatment with the extended-spectrum antibiotics) and another control not exposed to this risk factor. Other variables influencing on bacterial resistance such as a previous history of UTI, previous exposure to antibiotics, gender, ASIA impairment scale, history of urological manipulation, presence of urinary catheters, patient histories, and inpatient status was not investigated. Second, patient history and outcome data by treatment were not assessed. Third, the cost issue was not assessed in this study because some antibiotics were changed to generic brands while other new antibiotics were introduced, complicating the possibility of relevant calculation. Fourth, we did not verify the relationship between the use of extended-spectrum antibiotic and bacterial resistance by mechanistic studies. Further prospective multicenter studies need to be performed to draw definitive conclusions. Our study was not designed to address these limitations, but to conduct a retrospective study to assess the effectiveness of our ASW program in terms of NB patients and antibiotic-resistant bacterial strains.

In conclusion, we showed that the use of CFDN and LVFX decreased for outpatients with NB in our Urology Department from 2012 to 2017. At the same time, the incidence of antibiotic-resistant bacteria from urine cultures did not significantly increase. Even though no direct correlation was shown, the results are consistent with the fact that the decrease in the use of CFDN and LVFX in urological outpatients contributed to the decrease in the incidence of antibiotic-resistant and ESBL-producing bacteria. Although a prospective controlled study is necessary to confirm this hypothesis.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author contributions KK: drafting the paper, analysis and implementation of data; KS: study design and drafting the paper; MN: study design and data collection; NT: data collection; NY: data collection; and MF: paper drafting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers/animals were followed during the course of this research.

References

1. Thorpe KE, Joski P, Johnston KJ. Antibiotic-resistant infection treatment costs have doubled since 2002, now exceeding $2 billion annually. Health Aff. 2018;37:662–9.
2. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:847–56.
3. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect. 2014;69:216–25.
4. Moriyama Y, Ishikane M, Hayakawa K, Yamamoto K, Akazawa T, Sugiki Y, et al. Comparison of knowledge to antimicrobial stewardship institution policies targeting *Staphylococcus aureus* bacteremia and candidemia between medical doctors and pharmacists in an academic teaching hospital in Japan. J Infect Chemother. 2019;25:396–9.
5. Lee CR, Cho IH, Jeong BC, Lee SH. Strategies to minimize antibiotic resistance. Int J Environ Res Public Health. 2013;10:4274–305.
6. Bonkat G, Pickard R, Bartoletti R, Cai T, Bruyère F, Geerlings SE, et al. EAU guideline urological infection. Catheter associated UTI. 2018. p. 22. https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-Infections-2018-large-text.pdf.
7. Kimura T, Uda A, Sakaue T, Yamashita K, Nishioka T, Nishimura S, et al. Long-term efficacy of comprehensive multidisciplinary antibiotic stewardship programs centered on weekly prospective audit and feedback. Infection. 2018;46:215–24.
8. Shigemura K, Kitagawa K, Osawa K, Yamamichi F, Tokimatsu I, Nomi M, et al. Comparison of antibiotics use, urinary tract infection (UTI)-causative bacteria and their antibiotic susceptibilities among 4 hospitals with different backgrounds and regions in Japan. J Chemother. 2018;30:31–6.
9. Jarlier V, Nicolas MH, Fournier G, Philippon A. Extended broad-spectrum bet alactamases conferring transferable resistance to newer bet alactam agents in Enterobacteriaceae: hospital prevalence and susceptibility patterns. Rev Infect Dis. 1988;10:867–78.
10. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268–81.
11. Dyar OJ, Huttner B, Schouten J, Pulcini C. ESGAP (ESCMID Study Group for Antimicrobial stewardship). What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793–8.
12. Takaba K, Shigemura K, Osawa K, Nomi M, Fujisawa M, Arakawa S. Emergence of extended-spectrum β-lactamase-producing *Escherichia coli* in catheter-associated urinary tract infection in neurogenic bladder patients. Am J Infect Control. 2014;42:e29–31.
13. Timsit JF, Harbarth S, Carlet J. De-escalation as a potential way of reducing antibiotic use and antimicrobial resistance in ICU. Intensive Care Med. 2014;40:1580–82.
14. Carbo JF, Ruh CA, Kurtzhalts KE, Ott MC, Sellick JA, Mergenhagen KA. Male veterans with complicated urinary tract infections: influence of a patient-centered antimicrobial stewardship program. Am J Infect Control. 2016;44:1549–53.
15. Hicks LA, Bartoces MG, Roberts RM, Suda KJ, Hunkler RJ, Taylor TH Jr, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis. 2015;60:1308–16.
16. Edlin RS, Shapiro DJ, Hersh AL, Copp HL. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. J Urol. 2013;190:222–7.
17. Fukuda T, Watanabe H, Ido S, Shiragami M. Contribution of antimicrobial stewardship programs to reduction of antimicrobial therapy costs in community hospital with 429 beds—before-after comparative two-year trial in Japan. J Pharm Policy Pract. 2014;7:10.
18. Ikeda Y, Shigemura K, Nomi M, Tabata C, Kitagawa K, Arakawa S, et al. Infection control following an outbreak of extended-spectrum bet alactamase-producing *Klebsiella pneumoniae* isolated from catheter-associated urinary tract infection. Jpn J Infect Dis. 2018;71:158–61.
19. Kinnear CL, Patel TS, Young CL, Marshall V, Newton DW, Read AF, et al. Impact of an antimicrobial stewardship intervention on within and between patient daptomycin resistance evolution in vancomycin-resistant *Enterococcus faecium*. Antimicrob Agents Chemother. 2019;63:e01800−8.