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MAJOR ARTICLE

Antimicrobial Time-Out for Vancomycin by Infectious Disease Physicians Versus Clinical Pharmacists: A Before-After Crossover Trial

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Background. The present study assessed the impact of time-out on vancomycin use and compared the strategy's efficacy when led by pharmacists versus infectious disease (ID) physicians at a tertiary care center.

Methods. Time-out, consisting of a telephone call to inpatient providers and documentation of vancomycin use >72 hours, was performed by ID physicians and clinical pharmacists in the Departments of Medicine and Surgery/Critical Care. Patients in the Department of Medicine were assigned to the clinical pharmacist-led arm, and patients in the Department of Surgery/Critical Care were assigned to the ID physician-led arm in the initial, 6-month phase and were switched in the second, 6-month phase. The primary outcome was the change in weekly days of therapy (DOT) per 1000 patient-days (PD), and vancomycin use was compared using interrupted time-series analysis.

Results. Of 587 patients receiving vancomycin, 132 participated, with 79 and 53 enrolled in the first and second phases, respectively. Overall, vancomycin use decreased, although the difference was statistically nonsignificant (change in slope, −0.25 weekly DOT per 1000 PD; 95% confidence interval [CI], −0.68 to 0.18; $P = .24$). The weekly vancomycin DOT per 1000 PD remained unchanged during phase 1 but decreased significantly in phase 2 (change in slope, −0.49; 95% CI, −0.84 to −0.14; $P = .007$). Antimicrobial use decreased significantly in the surgery/critical care patients in the pharmacist-led arm (change in slope, −0.77; 95% CI, −1.33 to −0.22; $P = .007$).

Conclusions. Vancomycin time-out was moderately effective, and clinical pharmacist-led time-out with surgery/critical care patients substantially reduced vancomycin use.

Keywords. antimicrobial stewardship program; days of therapy; interrupted time-series analysis; time-out; vancomycin.

Antimicrobial stewardship programs (ASPs) are vital for reducing inappropriate antimicrobial consumption, lead to improved patient outcomes [1, 2], and help prevent the emergence of antimicrobial-resistant pathogens, including *Clostridioides difficile* [3–5]. A simple ASP intervention used in real clinical settings consists of reassessing treatment within a certain time frame. The Society for Healthcare Epidemiology of America (SHEA) recommends that prescribers discontinue the use of antimicrobial agents after 72 hours unless patients have clear evidence of an infection requiring antimicrobial therapy [6]. The Centers for Disease Control and Prevention also encourage reassessing the need to continue prescribing antimicrobials as well as the choice of antimicrobial agents if a precise clinical picture and diagnostic information are available [7, 8].

Intravenous vancomycin, a glycopeptide antimicrobial, is the drug of choice for infections caused by Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). It is commonly used in empiric therapy for presumed healthcare-associated infections (HAIs), such as catheter-related bloodstream infections and surgical site infections. Given the significant burden imposed by HAIs, vancomycin is frequently overprescribed at a rate of 20%–70% in acute care settings [9–11].

Antimicrobial "time-out" is considered to be one of the more effective interventions among the various methods available for reducing inappropriate antimicrobial prescriptions in acute care settings because it prompts all clinicians to review antimicrobial use 48–72 hours after initiation [12, 13]. In addition, time-out intervention is less resource-intensive than postprescription review and feedback (PPRF), and its simplicity and feasibility contribute to the sustainability of ASP.

Although both clinical pharmacists and infectious disease (ID) physicians are key providers of ASPs, the difference in the efficacy of antimicrobial time-out led by the respective parties has rarely been investigated [14]. Moreover, there are only a few

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studies assessing the efficacy of the time-out strategy for vancomycin use [12, 15, 16]. The present study aimed to investigate the impact of time-out on vancomycin use and to compare the efficacy of antimicrobial time-out between different types of provider (pharmacist vs ID physician) and patient groups (medicine vs surgery/critical care).

METHODS

Study Setting and Participants

The present study was a before-after trial conducted at Tokyo Metropolitan Tama Medical Center, a 789-bed tertiary care center in Tokyo, Japan. Vancomycin prescriptions in all the wards were surveyed in the preintervention period, during which hospital-wide implementation of the intervention was planned. Physicians were required to enter data on indications into a preorder reporting form contained in electronic medical records (EMRs) when ordering intravenous vancomycin for hospitalized patients. The inpatient population was divided into either a medicine group or a surgery/critical care group; the former included all hospitalized patients in the medical subspecialties, whereas the latter included all hospitalized patients in the surgical subspecialties and intensive care units.

Patient Consent Statement

Patient consent was waived because the present study involved no direct interaction with patients, and it was mainly associated with quality-improvement intervention introduced at the hospital level with negligible risk of harming patients. The institutional review board at Tokyo Metropolitan Tama Medical Center approved this study.

Eligibility Criteria

All hospitalized patients who received vancomycin for more than 72 hours were eligible. Patients were excluded if they met any of the following criteria: age younger than 18 years, beta-lactam allergy, diagnosis of an infection caused by Gram-positive organisms (pathogens against which vancomycin is considered to be a first-line agent), and vancomycin administration for prophylaxis (eg, surgical antimicrobial prophylaxis) without any clear discontinuation date.

Interventions

The time-out intervention was implemented from October 2018 to October 2019. For the first 6 months of the study (phase 1), the patients in the medicine group and the surgery/critical care group were assigned to a clinical pharmacist-led time-out arm and an ID physician-led time-out arm, respectively. A washout period of 1 month was then instituted. For the remaining 6 months (phase 2), the patients were assigned to the alternate time-out arm (Figure 1). The clinical pharmacists tracked patients who continued receiving vancomycin beyond 72 hours. Time-out consisted of a telephone call to the inpatient providers and documentation of the indications in the electronic medical records (EMRs) by 35 clinical pharmacists and 3 ID physicians. All telephone call providers underwent a standardized education session on how to perform time-out telephone calls in the preintervention period to minimize interoperator variability in the quality of the calls. A time-out telephone call was made by 35 pharmacists and 3 ID physicians, whereas 2 core clinical pharmacists and 3 ID physicians performed posttime-out follow up, EMR documentation, and data collection. These 3 ID physicians were equally allocated to the call shift (including patient types and patients' ward). The documented data consisted of information on vancomycin use (intravenous vancomycin use longer than 72 hours, confirmation of culture results, and a request to reconsider the need to continue intravenous vancomycin) (Supplementary Table 1). Vancomycin time-out providers were directed not to recommend either continuation or discontinuation of use. Regarding the ASP activities at the study institution, although PPRF for broad-spectrum antimicrobial agents (carbapenems and piperacillin/tazobactam) was instituted in 2014, no new ASP interventions other than vancomycin time-out were implemented in the inpatient setting during the study period [17].

Measurements

Data on the patient characteristics, EMR documentation of indications for vancomycin use, disease severity metrics, the date of the initial and last vancomycin doses, and clinical and laboratory characteristics related to vancomycin administration were collected. Vancomycin use was expressed as days of

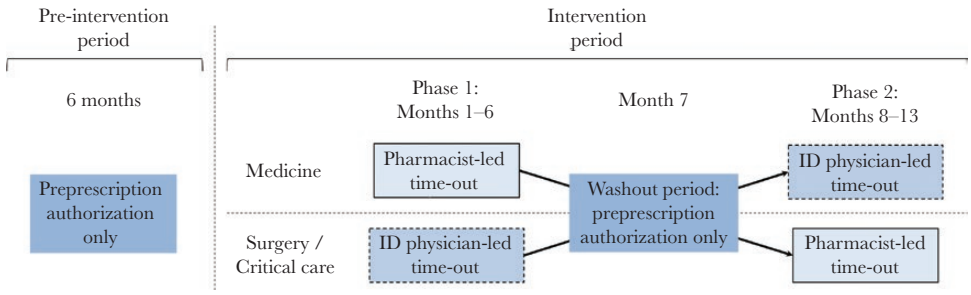

Figure 1. Study design comparing vancomycin use between the medicine group and surgery/critical care group in each phase. ID, infectious diseases.

therapy (DOT) per 1000 patient-days (PD) on a weekly basis. Vancomycin consumption data before the study period were collected to evaluate the general trends in vancomycin use.

Outcomes

The primary outcomes were the change in weekly DOT per 1000 PD per week for vancomycin use between phases 1 and 2 of the intervention, the difference in vancomycin use rates between the different time-out providers (ie, ID physicians vs clinical pharmacists), and different patient populations (ie, medicine patients vs surgery/critical care patients). The secondary outcomes were the proportion of vancomycin discontinuations within 72 hours, average vancomycin use, the median length of stay, and in-hospital mortality before and after the time-out intervention.

Statistical Analyses

The groups were compared using the *t* test for continuous variables and the χ^2 test for categorical variables. An interrupted time-series analysis (ITSA) was applied to assess changes in DOT per 1000 PD by comparing ID physician-led and pharmacist-led time-out across the 2 study periods. The ITSA had 26 data points during each stage of the preintervention period and phases 1 and 2 of the intervention period at weekly intervals. Days of therapy with intravenous vancomycin per patient were calculated and summarized for each 7-day interval, then standardized to 1000 PD (DOT per 1000 PD) using the total PD for all hospital admissions. All analyses were performed using Stata software version 15.2 (StataCorp, College Station, TX) and R 3.6.3 software for statistical computing (https://www.r-project.org/).

RESULTS

Characteristics of Patients

Among the 587 patients who received vancomycin during the intervention period (309 [52.6%] in phase 1 and 278 [47.4%] in phase 2), vancomycin was indicated in 132 (22.5%) patients (Supplementary Figure). Of these patients, 79 (59.8%) and 53 (40.2%) were in phase 1 and phase 2, respectively. Table 1 shows the demographic characteristics and background of the patients. The median Charlson comorbidity index and the quick sequential organ failure assessment score (qSOFA) at the initiation of vancomycin therapy were almost identical across both study periods as were the clinical characteristics and laboratory findings at time-out (Table 1 and Supplementary Table 2). Among the time-out-eligible patients, oral anti-MRSA agents, including trimethoprim/sulfamethoxazole, clindamycin, and linezolid, were prescribed after time-out implementation only in 1 patient in phase 1, and no oral anti-MRSA agents were prescribed in phase 2. The number of patients in whom vancomycin was discontinued within 72 hours after time-out in phases 1 and 2 was 47 (59.5%) and 35 (66.0%), respectively (Supplementary Table 3). Supplementary Tables 4 and 5 compare the characteristics of the medicine and surgery/critical care groups and the ID physician- and pharmacist-led arms, respectively. Most of the patient characteristics were generally similar between the departments and time-out providers, except for the proportion of surgeries performed during index hospitalization (31.0% and 14.4%, $P = .047$) and the history of chemotherapy (14.3% and 52.2%, $P < .001$) between the surgery/critical care and medicine groups, due to the reasons for hospitalization per group. The indications for vancomycin use did not differ significantly between the phases (Supplementary Table 6), although the proportion of indications for vancomycin differed between the ID physician and pharmacist-led arms for "sepsis not otherwise specified" and "osteoarticular infection" and between the medicine and surgery/critical care group for "febrile neutropenia" (Supplementary Tables 7 and 8).

Vancomycin Use

The DOT slope describes trends in long-term efficacy in each phase, whereas a change in intercept represents a change in the period immediately after intervention implementation [18]. Total vancomycin consumption at the study institution during the first 6 months of the preintervention period was constant over time (slope of +0.06 weekly DOT per 1000 PD; 95% confidence interval [CI], −0.36 to 0.47) but began to decrease after the start of the intervention despite the change being statistically nonsignificant (change in intercept: +4.48, 95% CI = −0.75 to 9.71, $P = .09$; change in slope: −0.25 weekly DOT per 1000 PD, 95% CI = −0.68 to 0.18, $P = .24$) (Figure 2). Figure 3 shows the changes in the monthly use of vancomycin among all hospital wards between phases 1 and 2 of the intervention period. Vancomycin DOT per 1000 PD remained unchanged after the implementation of time-out (slope of −0.02: weekly DOT per 1000 PD, 95% CI = −0.21 to 0.17) but thereafter showed a significantly decreasing trend during the subsequent phase (change in intercept: +2.18, 95% CI = −3.71 to 8.07, $P = .46$; change in slope: −0.49, weekly DOT per 1000 PD, 95% CI = −0.84 to −0.14, $P = .007$). For the surgery/critical care patients, the clinical pharmacist-led time-out appeared to be more effective in reducing vancomycin use than the ID physician-led time-out (change in intercept: +6.46, 95% CI = −1.85 to 14.76, $P = .13$; change in slope: −0.77, weekly DOT per 1000 PD, 95% CI = −1.33 to −0.22, $P = .007$), although vancomycin use in the medicine group did not change significantly between the ID physician- and clinical pharmacist-led time-out phases (Figure 4).

Secondary Outcomes

Supplementary Table 3 summarizes the secondary outcomes, including the proportion of patients in each department per phase. There was no statistical difference in in-hospital mortality (16.7% in the preintervention and 12.9% the

Table 1. Baseline Characteristics of Patients per Phase[a]

Characteristics	First Phase (n = 79)	Second Phase (n = 53)	*P* Value
Age, years	69 [62–80]	67 [56–76]	.06
Male gender	42 (53.2)	28 (52.8)	>.99
Residential Status Before Admission			
Home	64 (81.0)	46 (86.8)	Ref.
Nursing home or long-term care facility	5 (6.3)	2 (3.8)	.74
Chronic care hospital	1 (1.3)	3 (5.7)	.39
Acute care hospital	9 (11.4)	2 (3.8)	.18
Healthcare exposure within 30 days	73 (92.4)	46 (86.8)	.45
History of hospitalization within 90 days	36 (45.6)	26 (49.1)	.83
Comorbidities/Past Medical History			
Smoking status, ever	22 (27.8)	25 (47.2)	.04
Current alcohol use	19 (24.1)	10 (18.9)	.62
Diabetes mellitus	13 (16.5)	15 (28.3)	.16
Chronic liver disease	7 (8.9)	5 (9.4)	>.99
End-stage renal disease requiring hemodialysis	5 (6.3)	7 (13.2)	.30
Chronic heart failure	10 (12.7)	14 (26.4)	.08
Acute coronary syndrome	7 (8.9)	7 (13.2)	.61
Peripheral arterial disease	3 (3.8)	1 (1.9)	.91
COPD	8 (10.1)	4 (7.5)	.84
Peptic ulcer disease	2 (2.5)	5 (9.4)	.18
Cerebrovascular disease	4 (5.1)	5 (9.4)	.53
Hemiplegia	2 (2.5)	0 (0.0)	N/A
Dementia	6 (7.6)	3 (5.7)	.94
Hypertension	23 (29.1)	12 (22.6)	.53
Connective tissue disease	8 (10.1)	3 (5.7)	.56
Active malignancy	38 (48.1)	27 (50.9)	.89
HIV	0 (0.0)	2 (3.8)	N/A
History of chemotherapy within 28 days	31 (39.2)	22 (41.5)	.94
History of steroid use within 28 days	28 (35.4)	26 (49.1)	.17
Charlson comorbidity index score	2 (1–3)	2 (1–3)	.26
Any antimicrobial allergy	6 (7.6)	7 (13.2)	.45
Penicillin	3 (3.8)	5 (9.4)	
Cephalosporin	0 (0.0)	1 (1.9)	
Quinolone	2 (2.5)	0 (0.0)	
Sulfa	1 (1.3)	1 (1.9)	
Surgery performed before time-out during index hospitalization	6 (7.6)	20 (37.7)	<.001
ID consultations during index hospitalization	11 (13.9)	10 (18.9)	.60

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses; ID, infectious diseases; N/A, not applicable.

[a]Data are expressed as a No. (%) or the median [interquartile range].

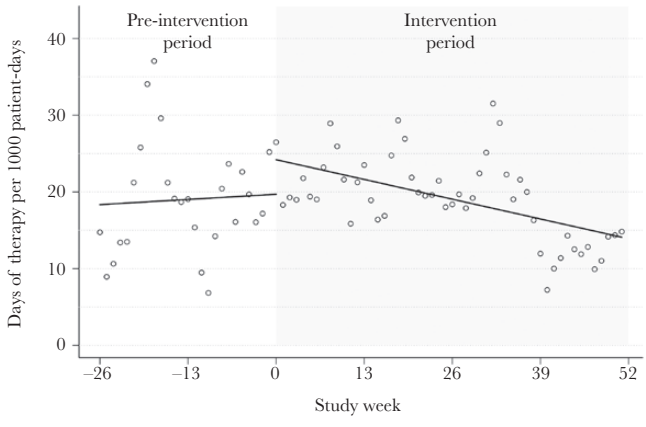

Figure 2. Time-series analysis comparing weekly days of vancomycin therapy per 1000 patient-days in all hospital wards between the preintervention period and the intervention period.

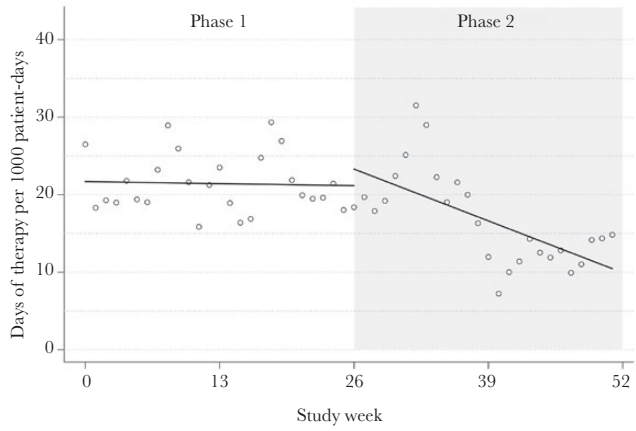

Figure 3. Time-series analysis comparing weekly days of vancomycin therapy per 1000 patient-days in all hospital wards during the intervention period.

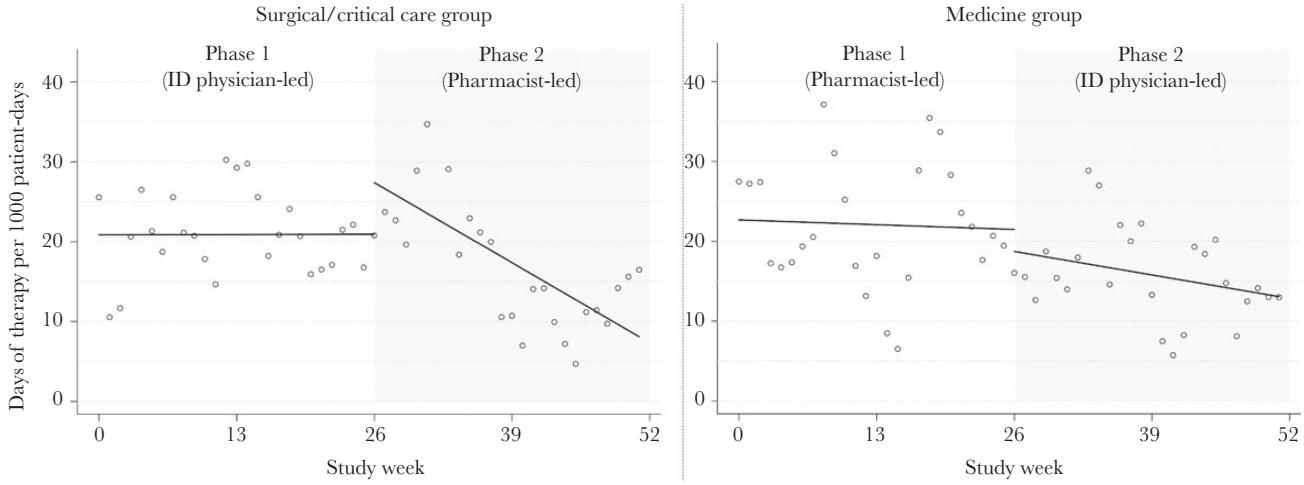

Figure 4. Time-series analysis comparing weekly days of vancomycin therapy per 1000 patient-days in the surgery/critical care group and medicine group during the intervention period. ID, infectious diseases.

intervention periods, $P = .52$) or the median length of stay (38 days in the preintervention period and 35 days in the intervention period, $P = .17$) between the preintervention and intervention periods.

DISCUSSION

The highlight of the present study was our successful demonstration of the difference in the effectiveness of an antimicrobial time-out between types of provider (pharmacy versus ID physician) and between different patient groups (medicine vs surgery/critical care). In the present study, vancomycin use declined moderately during the vancomycin time-out intervention period, especially in the second phase. No significant adverse outcomes related to the intervention were observed during the study period, and the importance of pharmacist-led time-out for the surgical team was demonstrated. Moreover, the crossover design with a washout period enabled the risk of residual antimicrobial effects to be minimized via communication with the ASP providers in the first phase. Considering the ease and safety of its implementation, time-out is a highly feasible strategy for preventing vancomycin overuse, especially in time- and resource-constrained situations.

The present study found that the clinical pharmacist-led time-out in the surgery/critical care department seemed to be more effective in terms of reducing vancomycin use. This finding underscores clinical pharmacists' competence in ASP. Previous studies also demonstrated that pharmacists had a substantial influence on ASP, for example, by lowering in-hospital mortality, reducing the emergence of multidrug-resistant pathogens, optimizing antimicrobial use, and reducing the cost of care [19–24]. Pharmacists have an important role in processing medication orders as experts in the hospital formulary [25], and a high acceptance rate of pharmacists' recommendations by attending physicians has repeatedly been shown in studies done in the United States and Europe [23–28], suggesting that pharmacists in Japan are likely to enjoy a similar level of confidence.

There are arguments both for and against ASP for surgeons, including matters pertaining to education [29]. One of the considerable difficulties of ASP implementation for surgeons is the limited time spent by surgeons in hospital wards; surgeons may not have enough time to inform their colleagues about the antimicrobial management of their patients [30]. In the present study, differences in the effectiveness of an antimicrobial time-out between types of provider (pharmacy vs ID physician) and between different patient groups (medicine vs surgery/critical care) might be explained by the difference in the patient characteristics between the groups. As shown in Supplementary Tables 7 and 8, the proportion of indications for vancomycin for sepsis not otherwise specified and osteoarticular infection was significantly smaller in the pharmacist-led arm as was the proportion of indications for vancomycin for febrile neutropenia in the surgery/critical care group. The different proportion of the indications for vancomycin between 2 arms occurred unexpectedly, because patients were allocated to each arm on the basis of the phase without random assignment to each arm (Figure 1). These patient populations typically receive a longer duration of treatment with antimicrobials, including vancomycin, according to previous studies [31–34]. Because of the difference in the type of patient in the 2 groups, vancomycin prescription in the surgery/critical care group in the pharmacist-led intervention arm might easily be modified by intervention.

A moderate reduction in vancomycin use was observed throughout the intervention period, and the decreasing slope was statistically greater in phase 2 than in phase 1. Previous studies demonstrated that the efficacy of ASP during the implementation period was able to be sustained or was more apparent in the later phase of the intervention [5, 35].

Although the current study revealed that time-out only modesty impacted the intravenous vancomycin prescription rate, additional considerations when implementing time-out may further strengthen its efficacy. A previous study demonstrated that the efficacy of pharmacist-led time-out was augmented by a more informative approach, such as providing culture results and allergy information to inpatient providers at time-out intervention. [16]. Another study showed that a team-based, pharmacist-led, time-out strategy using an algorithm potentially promotes oral antimicrobial use [36]. Exploring more effective time-out strategies for antimicrobial use is needed to bolster the efficacy of time-out.

During the study period, patients' clinical outcomes, including in-hospital mortality and length of hospitalization, were similar in the preintervention and intervention periods, indicating that discontinuation of vancomycin after time-out intervention did not endanger the patients. Discontinuation of unnecessary antimicrobial use, one of the significant aims of ASPs [5], occurred at a rate of 62% in the present study (Supplementary Table 3). Although the intention of prescribers is to provide optimal therapy to the patients under their care [37], more than one third of antimicrobial prescriptions are considered inappropriate according to evidence-based guidelines [38, 39]. In previous studies, several interventions aimed at modifying prescribing behavior did not correlate with any significant, critical, adverse outcomes [40, 41]. Patient safety is always the highest priority and is the foremost concern in ASPs, including time-out as well. Limiting inappropriate antimicrobial use is a quality initiative paralleling effort in other areas, such as the effort to reduce the incidence of HAI [42, 43].

The present study has several limitations. First, as a single-center study, the sample size was small and the results might therefore not be generalizable to other institutions. The median length of stay was relatively long in the present study (Supplementary Table 3), and hence practice pattern including vancomycin use at the study institution could be different from that at institutions in other high-income countries. Moreover, this study was not a randomized controlled trial and was unable to control for unmeasured confounding variables. However, the crossover design with washout periods minimized potential confounding factors, especially in phase 2. Second, although the washout period would ideally make the intervention periods independent of each another, it is possible that the first intervention period primed the physicians for the second intervention period in a carryover effect [44]. Third, the prescribers' reasons for rejecting time-out as an outcome, which might provide important data on the strategy, were unable to be ascertained. Fourth, changes in the physicians at the study institution during the study period potentially affected the overall results of the present study, because changes in prescribing patterns after time-out intervention may be dependent on the physicians' prescribing behaviors. Last, the possibility of the Hawthorne effect was unable to be excluded, because the antimicrobial prescribers might have begun to suspect that the information provided by our ASP team was for study purposes [45].

CONCLUSIONS

Vancomycin time-out was moderately effective in reducing vancomycin use and caused no hazardous outcomes at the study institution, and clinical pharmacist-led time-out for surgery/critical care patients substantially reduced vancomycin use. These findings are likely due to the composition of the surgery team and empowerment of the pharmacists to lead the intervention. Although our study suggested that time is required to change vancomycin prescribing behaviors, vancomycin time-out has the potential to be a practical strategy for optimizing use of this antimicrobial agent in inpatient settings, especially if it is led by clinical pharmacists.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Figure. Selection of participants for enrollment.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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