Antimicrobial time-out for vancomycin by infectious disease physicians vs clinical pharmacists: a before-after crossover trial

Shinya Hasegawa\( ^{1,2} \), Yasuaki Tagashira\( ^{1,2,3} \), Shutaro Murakami\( ^{2,4} \), Yasunori Urayama\( ^{4} \), Akane Takamatsu\( ^{1,2} \), Yuki Nakajima\( ^{1} \), and Hitoshi Honda\( ^{1,2} \)

Shinya Hasegawa, MD

\(^1\) Division of Infectious Diseases and \(^2\) Department of Infection Control
Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan
Email: hase_pokkun@yahoo.co.jp

Yasuaki Tagashira, MD, PhD

\(^1\) Division of Infectious Diseases and \(^2\) Department of Infection Control,
Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan
Email: y.tagashira@gmail.com

\(^3\) Department of Microbiology, Juntendo University Graduate School of Medicine
3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

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Shutaro Murakami, BSP

2 Division of Infection Control, Tokyo Metropolitan Tama Medical Center
2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

Yasunori Urayama, BSP

4 Department of Pharmacy, Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

Email: yasunori.urayama@gmail.com

Akane Takamatsu, MD

1 Division of Infectious Diseases and 2 Department of Infection Control
Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

3 Department of Microbiology, Juntendo University Graduate School of Medicine
3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

Email: chrise.type@gmail.com
Yuki Nakajima, MD

1 Division of Infectious Diseases and 2 Department of Infection Control

Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

Email: apilalum13@gmail.com

Hitoshi Honda, MD, PhD

1 Division of Infectious Diseases and 2 Department of Infection Control

Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

Email: hondah@hotmail.com

This study was performed at Tokyo Metropolitan Tama Medical Center
2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

Corresponding author: Hitoshi Honda, MD, PhD

Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan

Tel: (+81) 42-323-5111

Fax: (+81) 42-323-9209

Email: hondah@hotmail.com
Key points: 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 physicians. Vancomycin time-out was moderately effective, and pharmacist-led time-out with surgery/critical care patients substantially reduced vancomycin use.
Abstract

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 ID physician-led arm, and patients in the Department of Surgery/Critical Care were assigned to the clinical pharmacist-led arm in the initial, six-month phase and were switched in the second, six-month phase. The primary outcome was the change in weekly days of therapy (DOT) per 1,000 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 non-significant (change in slope, −0.25 weekly DOT per 1,000 PD; 95% confidence interval, −0.68 to 0.18, p = 0.24). The weekly vancomycin DOT per 1,000 PD remained unchanged during phase 1 but decreased significantly in phase 2 (change in slope, −0.49; −0.84 to −0.14, p = 0.007). Antimicrobial use decreased significantly in the surgery/critical care patients in the pharmacist-led arm (change in slope, −0.77; −1.33 to −0.22, p = 0.007).
Conclusions

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

Key words: vancomycin, time-out, antimicrobial stewardship program, days of therapy, interrupted time-series analysis
Background

Antibiotic stewardship programs (ASP) 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 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]. Additionally, time-out intervention is less resource-intensive than post-prescription 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 ASP, 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 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 versus 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 pre-intervention period, during which hospital-wide implementation of the intervention was planned. Physicians were required to enter data on indications into a pre-order reporting form contained in electronic medical records (EMR) 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 while 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 was involved no direct interaction with patients, and 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 (e.g., surgical antimicrobial prophylaxis) without any clear discontinuation date.

**Interventions**

The time-out intervention was implemented from October 2018 to October 2019. For the first six 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 one month was then instituted. For the remaining six 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 three ID physicians. All telephone call providers underwent a standardized education session on how to perform time-out telephone calls in the pre-intervention period to minimize inter-operator variability in the quality of the calls. A time-out telephone call was made by 35 pharmacists and 3 ID physicians while two core clinical pharmacists and 3 ID physicians performed post time-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 therapy (DOT) per 1,000 patient days (PD) on a weekly basis. Vancomycin consumption data prior to the study period were collected to evaluate the general trends in vancomycin use.

**Outcomes**

The primary outcomes were the change in weekly DOT per 1,000 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 (i.e., ID physicians vs clinical pharmacists), and different patient populations (i.e., 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 χ2 test for categorical variables. An interrupted time-series analysis (ITSA) was applied to assess changes in DOT per 1,000 PD by comparing ID physician-led and pharmacist-led time-out across the two study
periods. The ITSA had 26 data points during each stage of the pre-intervention 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 seven-day interval, then standardized to 1,000 PD (DOT per 1,000 PD) using the total PD for all hospital admissions. All analyses were performed using Stata software version 15.2 (StataCorp, College Station, Texas) 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 one 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 the proportion of surgeries performed during index hospitalization (31.0% and 14.4%, p = 0.047) and the
history of chemotherapy (14.3% and 52.2%, p < 0.001) 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, 8).

**Vancomycin use**

The DOT slope describes trends in long-term efficacy in each phase while a change in intercept represents a change in the period immediately following intervention implementation [18]. Total vancomycin consumption at the study institution during the first six months of the pre-intervention period was constant over time (slope of +0.06 weekly DOT per 1,000 PD; 95% confidence interval, −0.36 to 0.47) but began to decrease after the start of the intervention despite the change being statistically non-significant (change in intercept: +4.48; −0.75 to 9.71, p = 0.09; change in slope: −0.25 weekly DOT per 1,000 PD; −0.68 to 0.18, p = 0.24) (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 1,000 PD remained unchanged after the implementation of time-out (slope of −0.02; weekly DOT per 1,000 PD: −0.21 to 0.17) but thereafter showed a significantly decreasing trend during the subsequent phase (change in intercept: +2.18; −3.71 to 8.07; p = 0.46; change in slope: −0.49; weekly DOT per 1,000 PD: −0.84 to −0.14; p = 0.007). 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; −1.85 to 14.76; p = 0.13; change in slope: −0.77; weekly DOT per 1,000 PD: −1.33 to −0.22; p = 0.007) 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 pre-intervention and 12.9% the intervention periods, \( p = 0.52 \)) or the median length of stay (38 days in the pre-intervention period and 35 days in the intervention period, \( p = 0.17 \)) between the pre-intervention 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 appeared 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 versus 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 “ostearticular 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 two arms occurred unexpectedly, since 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 two 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 modestly 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 pre-intervention 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 ASP [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 a 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 ASP, 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, though the washout period would ideally make the intervention periods independent of each other, it is possible that the first intervention period primed the physicians for the second intervention period in a carry-over 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, as 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, as the antimicrobial prescribers might have begun to suspect that the information provided by our ASP team was for study purposes [45].

**Conclusion**

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.
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Authors’ contributions.

Literature search: S. H., Y. T.

Data collection: S. H., Y. T., S. M., Y.U., Y. N.

Study design: Y. T., S. M., H. H.

Data analysis: S. H., Y. T.

Manuscript preparation: S. H.

Critical review of the manuscript for important intellectual content: S. H., Y. T., S. M., Y.U., A. T., Y. N., H. H.

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Potential conflicts of interest.

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

[1] Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003;24(9):699-706.

[2] Peter Davey, Charis A Marwick, Claire L Scott, et al. Interventions to Improve Antibiotic Prescribing Practices for Hospital Inpatients. *Cochrane Database Syst Rev* 2017;2(2):CD003543.

[3] Leah M Feazel, Ashish Malhotra, Eli N Perencevich, Peter Kaboli, Daniel J Diekema, Marin L Schweizer. Effect of Antibiotic Stewardship Programmes on Clostridium Difficile Incidence: A Systematic Review and Meta-Analysis. *J Antimicrob Chemother* 2014;69(7):1748-54.

[4] Anurag N Malani, Patrick G Richards, Shikha Kapila, Michael H Otto, Jennifer Czerwinski, Bonita Singal. Clinical and Economic Outcomes From a Community Hospital’s Antimicrobial Stewardship Program. *Am J Infect Control* 2013;41(2):145-8.

[5] Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016; 62:1197–202

[6] Morgan DJ, Croft LD, Deloney V, et al. Choosing Wisely in Healthcare Epidemiology and Antimicrobial Stewardship. *Infect Control Hosp Epidemiol* 2016;37(7):755-60.

[7] Don’t continue antibiotics beyond 72 hours in hospitalized patients unless patient has clear evidence of infection. Choosing Wisely website. [http://www.choosingwisely.org/clinician-lists/shea-antibiotics-in-hospitalized-patients](http://www.choosingwisely.org/clinician-lists/shea-antibiotics-in-hospitalized-patients). Published 2015. Accessed August 21, 2020.

[8] Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. *Clin Infect Dis* 2014;59 Suppl 3:S97-100.
[9] Junior MS, Correa L, Marra AR, Camargo LF, Pereira CA. Analysis of vancomycin use and associated risk factors in a university teaching hospital: a prospective cohort study. *BMC infectious diseases* 2007;7:88.

[10] Kim NH, Koo HL, Choe PG, et al. Inappropriate continued empirical vancomycin use in a hospital with a high prevalence of methicillin-resistant Staphylococcus aureus. *Antimicrob Agents Chemother* 2015;59(2):811-7.

[11] Snyder GM, Patel PR, Kallen AJ, Strom JA, Tucker JK, D'Agata EM. Antimicrobial use in outpatient hemodialysis units. *Infect Control Hosp Epidemiol* 2013;34(4):349-57.

[12] Graber CJ, Jones MM, Glassman PA, et al. Taking an Antibiotic Time-out: Utilization and Usability of a Self-Stewardship Time-out Program for Renewal of Vancomycin and Piperacillin-Tazobactam. *Hosp Pharm* 2015;50(11):1011-24.

[13] Pardo J, Klinker KP, Borgert SJ, Trikha G, Rand KH, Ramphal R. Time to positivity of blood cultures supports antibiotic de-escalation at 48 hours. *Ann Pharmacother* 2014;48(1):33-40.

[14] Li Z, Cheng B, Zhang K, et al. Pharmacist-driven antimicrobial stewardship in intensive care units in East China: A multicenter prospective cohort study. *Am J Infect Control* 2017;45(9):983-9.

[15] Lee TC, Frenette C, Jayaraman D, Green L, Pilote L. Antibiotic self-stewardship: trainee-led structured antibiotic time-outs to improve antimicrobial use. *Ann Intern Med* 2014;161(10 Suppl):S53-8.

[16] Kayihura Manigaba, Samuel J Borgert, Kenneth P Klinker, Kartikeya Cherabuddi, Veena Venugopalan. SCAN: A novel approach for vancomycin time-out. *Infect Control Hosp Epidemiol* 2018;39(12):1501-3.
[17] Honda H, Murakami S, Tagashira Y, et al. Efficacy of a Postprescription Review of Broad-Spectrum Antimicrobial Agents With Feedback: A 4-Year Experience of Antimicrobial Stewardship at a Tertiary Care Center. *Open Forum Infect Dis* 2018;5(12):ofy314.

[18] Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *The State Journal* 2015;15:480-500.

[19] Wickens HJ, Farrell S, Ashiru-Oredope DA, Jacklin A, Holmes A. Antimicrobial Stewardship Group of Department of Health Advisory Committee on Antimicrobial Resistance and Health Care Associated Infections (ASG-ARHAI). The increasing role of pharmacists in antimicrobial stewardship in English hospitals. *J Antimicrob Chemother* 2013;68(11):2675-81.

[20] Cappelletty D, Jacobs D. Evaluating the impact of a pharmacist's absence from an antimicrobial stewardship team. *Am J Health Syst Pharm* 2013;70(12):1065-9.

[21] Leah Molloy, Eric McGrath, Ronald Thomas, Keith S Kaye, Michael J Rybak. Acceptance of Pharmacist-Driven Antimicrobial Stewardship Recommendations With Differing Levels of Physician Involvement in a Children’s Hospital. *Clin Pediatr (Phila)* 2017;56(8):744-51.

[22] C Dustin Waters. Pharmacist-driven Antimicrobial Stewardship Program in an Institution Without Infectious Diseases Physician Support. *Am J Health Syst Pharm* 2015;72(6):466-8.

[23] Pedro Mas-Morey, Alfonso Ballesteros-Fernández, Elisabet Sanmartin-Mestre, Marta Valle. Impact of Clinical Pharmacist Intervention on Antimicrobial Use in a Small 164-bed Hospital. *Eur J Hosp Pharm* 2018;25(e1):e46-e51.

[24] Gross R, Morgan AS, Kinky DE, Weiner M, Gibson GA, Fishman NO. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis* 2001;33(3):289-95.
[25] Conan MacDougall, Ron E Polk. Antimicrobial Stewardship Programs in Health Care Systems. *Clin Microbiol Rev* 2005; 18(4): 638–56.

[26] Donald F Storey, Perry G Pate, Autumn Tt Nguyen, Fung Chang. Implementation of an Antimicrobial Stewardship Program on the Medical-Surgical Service of a 100-bed Community Hospital. *Antimicrob Resist Infect Control* 2012;1(1):32.

[27] James M Bartlett, Patricia L Siola. Implementation and First-Year Results of an Antimicrobial Stewardship Program at a Community Hospital. *Am J Health Syst Pharm* 2014;71(11):943-9.

[28] Svetlana Sadyrbaeva-Dolgova, Pilar Aznarte-Padial, Alberto Jimenez-Morales, Manuela Expósito-Ruiz, Miguel Ángel Calleja-Hernández, Carmen Hidalgo-Tenorio. Pharmacist Recommendations for Carbapenem De-Escalation in Urinary Tract Infection Within an Antimicrobial Stewardship Program. *J Infect Public Health* 2020;13(4):558-63.

[29] Massimo Sartelli, Therese M Duane, Fausto Catena, et al. Antimicrobial Stewardship: A Call to Action for Surgeons. *Surg Infect (Larchmt)* 2016;17(6):625-31.

[30] Charani E, Ahmad R, Rawson TM, Castro-Sanchèz E, Tarrant C, Holmes AH. The Differences in Antibiotic Decision-making Between Acute Surgical and Acute Medical Teams: An Ethnographic Study of Culture and Team Dynamics. *Clin Infect Dis* 2019;69(1):12-20.

[31] Brad Spellberg. The New Antibiotic Mantra-"Shorter Is Better". *JAMA Intern Med* 2016;176(9):1254-5.

[32] Ho-Kwong Li, Ines Rombach, Rhea Zambellas, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *N Engl J Med* 2019;380(5):425-36.

[33] Catherine J Mathews, Vivienne C Weston, Adrian Jones, Max Field, Gerald Coakley. Bacterial septic arthritis in adults. *Lancet* 2010;375(9717):846-55.
[34] Miguel A Sanz, Javier López, Juan J Lahuerta, et al. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin for initial antibiotic therapy in haematology patients with febrile neutropenia: results of an open, randomized, multicentre trial. J Antimicrob Chemother 2002;50(1):79-88.

[35] José Molina, Germán Peñalva, María V Gil-Navarro, et al. Long-Term Impact of an Educational Antimicrobial Stewardship Program on Hospital-Acquired Candidemia and Multidrug-Resistant Bloodstream Infections: A Quasi-Experimental Study of Interrupted Time-Series Analysis. Clin Infect Dis 2017;65(12):1992-9.

[36] Trevor C Van Schooneveld, Mark E Rupp, R Jenifer Cavaleiri, Elizabeth Lyden, Kiri Rolek. Cluster randomized trial of an antibiotic time-out led by a team-based pharmacist. Infect Control Hosp Epidemiol 2020;41(11):1266-71.

[37] Céline Pulcini, Inge C Gyssens. How to educate prescribers in antimicrobial stewardship practices. Virulence 2013;4(2):192-202.

[38] Scott Fridkin, James Baggs, Ryan Fagan, et al. Vital Signs: Improving Antibiotic Use Among Hospitalized Patients. MMWR Morb Mortal Wkly Rep 2014;63(9):194-200.

[39] Peter Zarb, Brice Amadeo, Arno Muller, et al. Identification of Targets for Quality Improvement in Antimicrobial Prescribing: The Web-Based ESAC Point Prevalence Survey 2009. J Antimicrob Chemother 2011;66(2):443-9.

[40] Daniella Meeker, Jeffrey A Linder, Craig R Fox, et al. Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial. JAMA 2016;315(6):562-70.
[41] Edina Avdic, Lisa A Cushinotto, Andrew H Hughes, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis* 2012;54(11):1581-7.

[42] Elizabeth S Dodds Ashley, Keith S Kaye, Daryl D DePestel, Elizabeth D Hermsen. Antimicrobial Stewardship: Philosophy Versus Practice. *Clin Infect Dis* 2014;59 Suppl 3:S112-21.

[43] Pranita D Tamma, Alison Holmes, Elizabeth Dodds Ashley. Antimicrobial Stewardship: Another Focus for Patient Safety? *Curr Opin Infect Dis* 2014;27(4):348-55.

[44] Philip Sedgwick. Bias in randomised controlled trials: comparison of crossover group and parallel group designs. *BMJ* 2015;351:h4283.

[45] Yanes AF, McElroy LM, Abecassis ZA, Holl J, Woods D, Ladner DP. Observation for assessment of clinician performance: a narrative review. *BMJ Qual Saf* 2016;25(1):46-55.
Table 1. Baseline characteristics of patients per phase

|                              | First phase (n = 79) | Second phase (n = 53) | P value |
|------------------------------|----------------------|-----------------------|---------|
| Age, years                   | 69 [62–80]           | 67 [56–76]            | 0.06    |
| Male gender                  | 42 (53.2)            | 28 (52.8)             | >0.99   |
| Residential status prior to admission |                      |                       |         |
| Home                         | 64 (81.0)            | 46 (86.8)             | Ref.    |
| Nursing home or long-term care facility | 5 (6.3)      | 2 (3.8)               | 0.74    |
| Chronic care hospital        | 1 (1.3)              | 3 (5.7)               | 0.39    |
| Acute care hospital          | 9 (11.4)             | 2 (3.8)               | 0.18    |
| Healthcare exposure within 30 days | 73 (92.4)       | 46 (86.8)             | 0.45    |
| History of hospitalization within 90 days | 36 (45.6) | 26 (49.1)             | 0.83    |
| Co-morbidities/past medical history |                      |                       |         |
| Smoking status, ever         | 22 (27.8)            | 25 (47.2)             | 0.04    |
| Current alcohol use          | 19 (24.1)            | 10 (18.9)             | 0.62    |
| Diabetes mellitus            | 13 (16.5)            | 15 (28.3)             | 0.16    |
| Chronic liver disease        | 7 (8.9)              | 5 (9.4)               | >0.99   |
| End-stage renal disease requiring hemodialysis | 5 (6.3) | 7 (13.2)              | 0.30    |
| Chronic heart failure        | 10 (12.7)            | 14 (26.4)             | 0.08    |
| Acute coronary syndrome      | 7 (8.9)              | 7 (13.2)              | 0.61    |
| Peripheral arterial disease  | 3 (3.8)              | 1 (1.9)               | 0.91    |
| COPD                         | 8 (10.1)             | 4 (7.5)               | 0.84    |
| Peptic ulcer disease         | 2 (2.5)              | 5 (9.4)               | 0.18    |
| Cerebrovascular disease      | 4 (5.1)              | 5 (9.4)               | 0.53    |
| Hemiplegia                   | 2 (2.5)              | 0 (0.0)               | N/A     |
| Dementia                     | 6 (7.6)              | 3 (5.7)               | 0.94    |
| Hypertension                 | 23 (29.1)            | 12 (22.6)             | 0.53    |
| Connective tissue disease    | 8 (10.1)             | 3 (5.7)               | 0.56    |
| Active malignancy            | 38 (48.1)            | 27 (50.9)             | 0.89    |
| HIV                          | 0 (0.0)              | 2 (3.8)               | N/A     |
| History of chemotherapy within 28 days | 31 (39.2) | 22 (41.5)             | 0.94    |
| History of steroid use within 28 days | 28 (35.4) | 26 (49.1)             | 0.17    |
Charlson comorbidity index score  & 2 [1–3]  & 2 [1–3]  & 0.26  
Any antimicrobial allergy  & 6 (7.6)  & 7 (13.2)  & 0.45  
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 prior to time-out during index hospitalization  & 6 (7.6)  & 20 (37.7)  & <0.001  
ID consultations during index hospitalization  & 11 (13.9)  & 10 (18.9)  & 0.60  

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

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses; ID, infectious diseases; ASP, antimicrobial stewardship program
Figure Legends

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

Figure 2. Time-series analysis comparing weekly days of vancomycin therapy per 1,000 patient-days in all hospital wards between the pre-intervention period and the intervention period.

Figure 3. Time-series analysis comparing weekly days of vancomycin therapy per 1,000 patient-days in all hospital wards during the intervention period.

Figure 4. Time-series analysis comparing weekly days of vancomycin therapy per 1,000 patient-days in the surgery/critical care group and medicine group during the intervention period.
Figure 1

Pre-intervention period

6 months

Preprescription authorization only

Intervention period

Phase 1: Months 1–6

Medicine
Pharmacist-led time-out

Surgery / Critical care
ID physician-led time-out

Washout period: preprescription authorization only

Month 7

Phase 2: Months 8–13

ID physician-led time-out

Pharmacist-led time-out
Figure 4

Surgical/critical care group

Phase 1 (ID physician-led)

Phase 2 (Pharmacist-led)

Days of therapy per 1,000 patient-days

0 13 26 39 52
Study week

Medicine group

Phase 1 (Pharmacist-led)

Phase 2 (ID physician-led)

0 13 25 39 52
Study week