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Impact of Antibiotic Time-Outs in Multidisciplinary ICU Rounds for Antimicrobial Stewardship Program on Patient Survival: A Controlled Before-and-After Study

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OBJECTIVES: The antimicrobial stewardship program (ASP) is an important quality improvement initiative that is recommended in the ICU. However, the shortage of infectious disease physicians in Japan has led to the need for simpler methods for implementing ASPs. We investigated whether antibiotic time-outs (ATOs) during multidisciplinary rounds as part of an ASP can improve patient survival and reduce the number of days of therapy (DOT) with antibiotics.

DESIGN: Single-center controlled before-and-after study.

SETTING: Medical/surgical ICU in a tertiary university medical center in Tokyo, Japan.

PATIENTS: All patients 16 years old or older admitted consecutively in the ICU between October 2016 and March 2020.

INTERVENTIONS: An intensivist-driven ICU multidisciplinary round was introduced in October 2016, and ATOs with ICU rounds were implemented in June 2018. ATOs were conducted 3, 7, and 14 days after initiation of antibiotics.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was the subdistribution hazard ratio (SHR) of survival to hospital discharge compared between multidisciplinary rounds (phase 1) and ATO during multidisciplinary rounds (phase 2) using the multivariable Fine-Gray model. The secondary outcomes were the SHR of survival to ICU discharge and the trends in the DOT with IV antibiotics per 1,000 patient-days between October 2016 and March 2020 by using interrupted time-series analysis. The number of patients in phases 1 and 2 was 777 and 796, respectively. The group that underwent ATO during multidisciplinary rounds showed a significant increase in the survival to hospital discharge in comparison with the multidisciplinary round-only group (SHR, 1.13; 95% CI, 1.02–1.25); however, the SHR of survival to ICU discharge showed no significant intergroup difference. The DOT with total IV antibiotics decreased after ATO implementation (change in intercept, −178.26; 95% CI, −317.74 to −38.78; change in slope, −7.00; 95% CI, −15.77 to 1.78).

CONCLUSIONS: ATOs during multidisciplinary rounds are associated with improved patient survival and reduced DOT.

KEY WORDS: antibiotic time-out; antimicrobial stewardship program; intensive care unit; multidisciplinary rounds

Excessive exposure to antibiotics has been reported to negatively affect patient outcomes, such as an increase in the occurrence rate of resistant organisms, invasive fungal infections, and mortality (1–3). In the light of the growing threat of antimicrobial resistance due to the inappropriate use of antibiotics, the World Health Organization has recommended

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KEY POINTS

Question: Does an intensivist-driven routine antibiotic time-out (ATO) at 3, 7, and 14 days after initiation of antibiotics during multidisciplinary rounds improve ICU patient outcomes and decrease the number of days of antibiotic therapy (DOT)?

Findings: In this single-center controlled before-and-after study, the subdistribution hazard ratio (SHR) of survival to hospital discharge was higher with ATOs during ICU multidisciplinary rounds than without ATO (SHR, 1.13; 95% CI, 1.02–1.25).

Meaning: Incorporation of ATOs into the multidisciplinary rounds in the ICU allowed the implementation of an antibiotic stewardship program that was effective for reducing the DOT and improving patient outcomes.

the implementation of antimicrobial stewardship programs (ASPs) (4). ASPs are especially important in ICU settings because critically ill patients are more likely to receive long-term broad-spectrum antibiotic treatment and thus have a greater risk of developing multidrug-resistant infections (5). Several review of ICU patients treated with broad-spectrum antibiotics by infectious disease (ID) specialists under an ASP to assess the appropriateness of antibiotic use showed a reduction in the use of broad-spectrum antibiotics, the risk of emergence of multidrug-resistant organisms, and the hospital length of stay (5–8). However, implementation of such ASPs would be challenging for many hospitals in countries like Japan, which have a shortage of ID specialists.

The Centers for Disease Control and Prevention and Infectious Diseases Society of America recommend antibiotic time-outs (ATOs) as a process to evaluate antibiotic use in ASPs (9, 10). ATO is one of the fundamental methods employed by ASPs, and it involves a provider-led reassessment of antibiotic use when the clinical picture is clearer and culture results may be available without the intervention of ID specialist teams. ATOs are considered easy to incorporate into routine care because they are performed by the providers themselves (11). A prescriber-driven ATO at 48 to 72 hours of treatment with paper or electronic medical record ATO tools has been reported to decrease inappropriate antibiotic therapy and days of therapy (DOT) with antibiotics (11–13). Similarly, pharmacist-driven ATO was reported to be associated with more frequent assessments and changes in antibiotic use (14) and was also more effective in reducing the use of vancomycin in comparison with interventions by ID specialists (15).

Patients in the ICU greatly benefit from a multidisciplinary round, and ATOs performed during multidisciplinary rounds can be conducted routinely with minimal effort and synchronized with the patient's clinical needs. We hypothesized that routine ATO during multidisciplinary rounds would reduce antibiotic use and improve patient outcomes. Therefore, the objective of this study was to examine whether the implementation of ATOs with multidisciplinary rounds improved patient survival and reduced the DOT with antibiotics in the ICU.

MATERIALS AND METHODS

Study Setting and Participants

The present study was a controlled before-and-after study conducted between October 2016 and March 2020 in a semi-closed medical and surgical ICU with 12 beds at a tertiary university hospital (Tokyo Medical and Dental University, Tokyo, Japan). In October 2016, we implemented multidisciplinary rounds in the ICU with intensivists, primary physicians, full-time pharmacists, nutritionists, physical therapists, physiatrists, and medical technicians. The intensivists functioned as critical care consultants for all patients in the ICU and comanaged the patients with primary physicians. A dedicated full-time pharmacist was made available in the ICU after October 2016. The intensivists and pharmacists did not possess specialized training in the field of IDs. ID specialists were typically consulted less than once a month at our institution because of their limited availability. The frequency of consultation requests to ID specialists was similar throughout the study period.

All patients consecutively admitted to the ICU during the study period were included in the study. The study period was divided into two parts: the period with only a multidisciplinary round (pre-ATO period; October 2016 to May 2018) and the period with ATOs in addition to multidisciplinary rounds (ATO period; June 2018 to March 2020)

(**Supplemental Fig. 1**, http://links.lww.com/CCX/B121). We compared the survival rates of patients in the last 12 months of the pre-ATO period (phase 1) and the last 12 months of the ATO period (phase 2) to ensure that the analyses were performed when the interventions were well-established and sufficiently functional after implementation. The assessment of survival rates was performed in patients 16 years old or older who were admitted to the ICU during phase 1 or phase 2. We excluded patients who had been hospitalized for greater than 2 years, whose hospitalization overlapped these two phases, and those who were readmitted to the ICU after their initial ICU admission. We also collected monthly DOT data for the pre-ATO period (20 mo) and the ATO period (22 mo) to perform an interrupted time-series analysis including the entire study period, and thereby evaluate the actual changes in DOT since the changes may occur slowly over time after ATO implementation.

This study was approved in accordance with the ethical standards on human experimentation and the Helsinki Declaration of 1975 by the Institutional Review Board of Tokyo Medical and Dental University (Japan) on July 19, 2019 (M2019-055) and registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN ID: UMIN000038633).

Intervention

Prior to October 2016, we reported the use of broad-spectrum antibiotics to the Infection Control Department of our hospital as part of the ASP. The ICU pharmacist adjusted the doses of antibiotics on the basis of renal function and therapeutic drug monitoring during multidisciplinary rounds, which were conducted every morning on weekdays from October 2016. Subsequently, we introduced ATOs for all antibiotics administered to patients in the ICU in June 2018. ATOs targeted all IV antibiotics prescribed to all ICU patients, except those administered for prophylaxis (e.g., surgical site infection prophylaxis). On the basis of the list of antibiotics being administered on days 3, 7, and 14 after antibiotic initiation that was prepared by the ICU pharmacist, the intensivist declared an ATO during multidisciplinary rounds and verbally asked the primary physician three questions: 1) "What is the target of the antibiotic?" 2) "What is the planned duration of antibiotic treatment?" 3) "Is the antibiotic effective for the patient?" The ICU pharmacist logged the answers into the electronic medical records. The purpose of the ATO was to prompt the primary physician to review the results of cultures, assess the clinical course of antibiotic use, and ultimately create the setting for the intensivists and ICU pharmacist to discuss antibiotic usage in each case with the primary physician. ATOs were conducted 5 days a week from Monday to Friday.

Outcome Measurement

The primary outcome was patient survival at hospital discharge in phases 1 and 2. The secondary outcomes were survival at ICU discharge and changes in the monthly DOT, calculated as X days per 1,000 patient-days, for all IV antibiotics, IV antibiotics targeting methicillin-resistant *Staphylococcus aureus* (MRSA), IV antibiotics targeting for *Pseudomonas* species, and IV carbapenems (16). **Supplemental Table 1** (http://links.lww.com/CCX/B121) shows the antibiotics used in this study. Data on outcomes and patient background factors were extracted from the electronic medical records.

Statistical Analyses

The patient groups in phases 1 and 2 were compared using the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. The subdistribution hazard of survival to hospital discharge and ICU discharge between the two groups was compared with the Fine-Gray model, which included all eligible patients and assumed death as a competing event (17). Subdistribution hazard ratios (SHRs) were reported with 95% CIs. Assuming a hospital death rate of 8%, we calculated that a sample of 1,027 patients would provide 80% power to detect an HR of 1.2 to 2 for hospital discharge survival, with a significance level of 0.05. Predictors in the Fine-Gray model included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, whether infection was the primary reason for ICU admission, admission status (scheduled or emergent), surgical status (after surgery or not) (18–20), and immune status (immunocompromised host or not) (21). Immunocompromised hosts were defined as patients with lymphoma, acute myelogenous leukemia, multiple myeloma, or those receiving immunosuppressive therapy with the following agents in the preceding 6 months: immunosuppressive drugs,

chemotherapy, radiotherapy, and steroids (prednisolone equivalent > 0.375 mg/kg/d). APACHE II scores within 24 hours after admission to the ICU were determined retrospectively from electronic medical records for patients admitted to the ICU until March 2018 and prospectively for those admitted from April 2018. We additionally adjusted the subdistribution hazard of survival to hospital discharge using the monthly DOT value for each antibiotic in the month of ICU admission to assess the contribution of DOT to the effects of ATOs on survival to hospital discharge.

The changes in DOT were evaluated using an interrupted time-series analysis with linear regression analysis. We examined the changes in DOT immediately after ATO was introduced (determined by changes in the intercept), and the consistency of the change over the period of the intervention (determined by the slope following the ATO introduction). We used the autoregressive integrated moving average to adjust for autocorrelation from 1 year to the next because of the effects of seasonality. Two-sided p value of less than 0.05 was considered significant. All analyses were performed using R 4.1.0 software for statistical computing (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

RESULTS

Characteristics of Patients

The study enrolled 2,730 patients who were consecutively admitted to the ICU between October 2016 and March 2020, of which 1,199 patients were admitted in the pre-ATO period and 1,386 patients were admitted in the ATO period (**Fig. 1)**. The number of patients in phases 1 and 2 was 777 and 796, respectively. **Table 1** shows the demographic characteristics of patients in each phase. In both phases, 70% of patients underwent elective surgeries, and infection was the primary reason for ICU admission in less than 10% of the patients. The two groups were similar in terms of sex, age, and comorbidities, including the proportion of immunocompromised hosts. The APACHE II score was slightly lower in phase 2, but the median score was 13 in both groups, which also accurately reflected the disease severity of our ICU patients. The survival rate to ICU discharge was 96.8% in phase 1 versus 98.2% in phase 2 (Table 1; $p = 0.07$), and the survival rate to hospital discharge was 92.0% in phase 1 versus 93.7% in phase 2 (Table 1; $p = 0.20$). **Supplemental Table 2** (http://links.lww.com/CCX/B121) shows the demographic characteristics of all patients during the study period. Patient characteristics for the total study period and the last 12 months in each period were similar.

Fine-Gray Model for Survival

Figure 2 shows the cumulative occurrence rate of survival to hospital discharge among patients in phases 1 and 2. Based on multivariable analysis with the Fine-Gray model, ATO (SHR, 1.13; 95% CI, 1.02–1.25; $p = 0.02$) was associated with a better subdistribution hazard of survival to hospital discharge (**Table 2**). Additionally, when we adjusted for the monthly DOT with all IV antibiotics as a crude check of mediation, the SHR decreased from 1.13 (95% CI, 1.02–1.25) to 0.98 (95% CI, 0.82–1.17) (**Supplemental Table 3**, http://links.lww.com/CCX/B121). The SHR results that were additionally adjusted for the DOT with anti-MRSA antibiotics and antipseudomonal antibiotics were similar to the SHRs closer to null (i.e., SHR of 1.0).

For ICU discharge, no significant effect of ATOs was observed on survival based on the cumulative occurrence rate of survival to ICU discharge (**Supplemental Fig. 2**, http://links.lww.com/CCX/B121) and the results of the multivariable analysis (**Supplemental Table 4**, http://links.lww.com/CCX/B121).

Antibiotic Use

The DOT with all IV antibiotics decreased significantly immediately after the implementation of ATO (change in intercept, −178.26; 95% CI, −317.74 to −38.78; $p = 0.02$) and tended to decrease further (change in slope, −7.00; 95% CI, −15.77 to 1.78; $p = 0.13$; **Fig. 3**; **Table 3**). The DOT with antipseudomonal antibiotics and anti-MRSA antibiotics showed similar and significant reductions in both intercept and slope after the introduction of ATOs. The intercept of the DOT with carbapenem did not decrease before and after the implementation of ATO, whereas the slope decreased significantly.

DISCUSSION

Our study found that in comparison with ICU patients who underwent multidisciplinary rounds alone, those who underwent antibiotic stewardship with ATO during multidisciplinary rounds showed a significantly

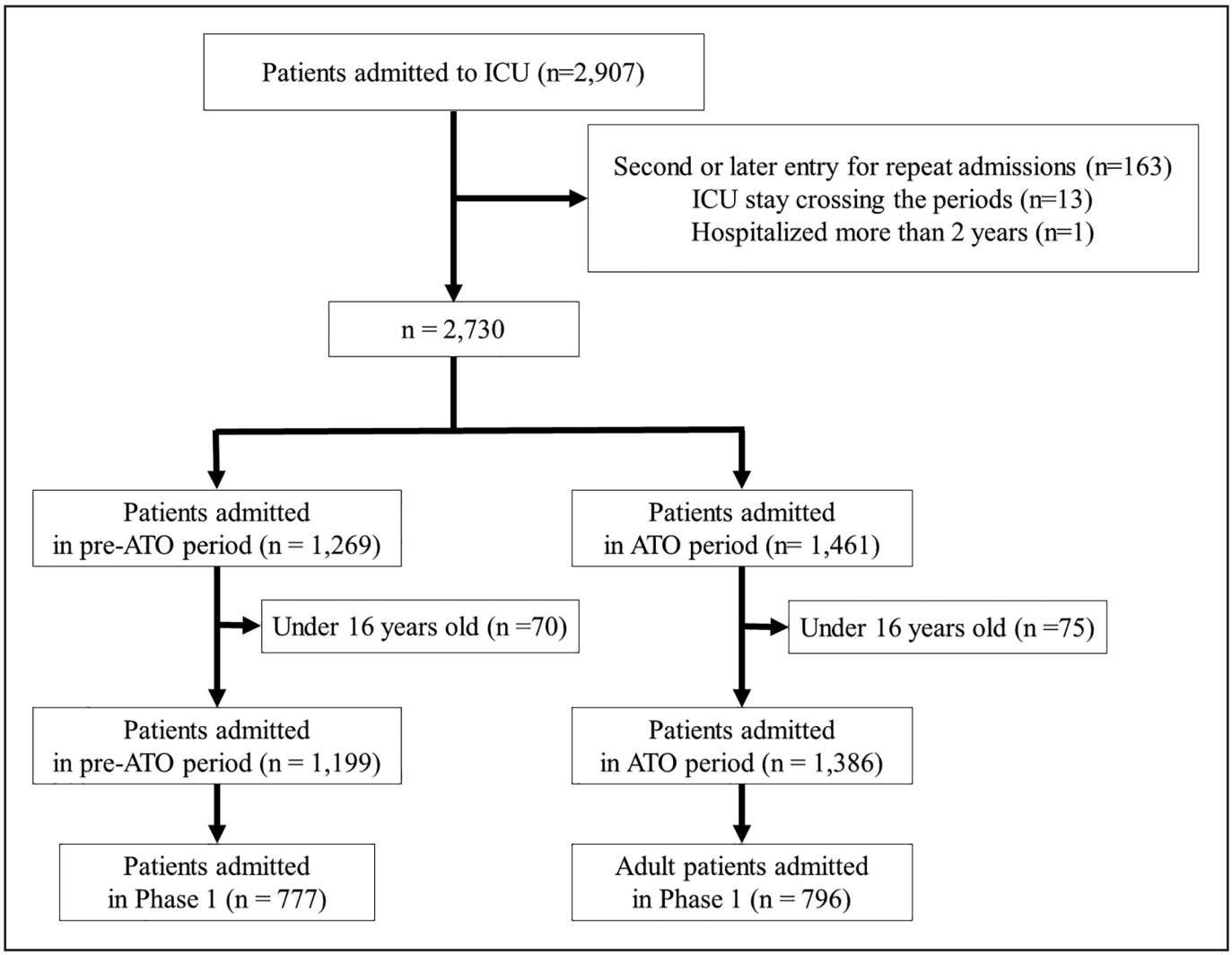

Figure 1. Patient flow chart. ATO = antibiotic time-out.

higher survival hospital discharge subdistribution hazard, which suggested a shorter adjusted length of hospital stay (22). Additionally, the DOT with all IV antibiotics, anti-MRSA antibiotics, antipseudomonal antibiotics, and carbapenems decreased after the implementation of ATOs.

The goal of ASPs is to not only improve the quality of antibiotic use but also improve patient outcomes (9, 23). To evaluate the effect of the ASP in this study, we measured processes such as changes in antibiotic use and outcomes associated with these changes. Although the DOT as a process measure has been reported to decrease in prior studies, the effectiveness of ATOs in reducing mortality has not been determined (11–15). In this study, the difference in the hospital discharge rate was almost negligible (phase 1, 92.0%; phase 2, 93.7%) and not significant with the chi-square model. The length of hospital stay (24 d vs 23 d) also did not demonstrate a significant difference. However, the Fine-Gray model showed a significant improvement in the survival subdistribution hazard because the Fine-Gray model is a survival analysis accounting for a competing event, and it was adjusted with multivariable analysis, which explained the differences in results. In the Fine-Gray model, SHR greater than 1 suggested that the adjusted survival hospital discharge rate increased at any point for the surviving patients who had remained hospitalized, which meant a shorter adjusted length of hospital stay for the surviving discharged patients (17, 22). We believe that the results of the Fine-Gray model are important because the analysis includes multiple variables, and the potential impact of improved outcomes with ATO in critically ill patients will be relevant.

We evaluated the SHR of survival to hospital discharge by using DOT values to assess whether ATO was the reason for the improved outcomes. We found

TABLE 1.
Patient Characteristics in Phases 1 and 2

Characteristics	Phase 1 (*n* = 777)	Phase 2 (*n* = 796)	*p*
Sex, *n* (%)			
Male	493 (63.4)	496 (62.3)	0.68
Female	284 (36.6)	300 (37.7)	
Age, yr, median (IQR)	68 (4–75)	68 (55–75)	0.52
Admission status			
Scheduled	529 (68.1)	562 (70.6)	0.30
Emergent	248 (31.9)	234 (29.4)	
Operation, *n* (%)	589 (75.8)	637 (80.0)	0.05
Comorbidity, *n* (%)			
Immunocompromised host[a]	108 (13.9)	90 (11.3)	0.13
Cancer metastasis	36 (4.6)	32 (4.0)	0.62
Chronic kidney disease on dialysis	35 (4.5)	29 (3.6)	0.44
Chronic lung failure (home oxygen therapy)	13 (1.7)	5 (0.6)	0.06
Chronic liver failure or cirrhosis	10 (1.3)	8 (1.0)	0.64
Chronic heart failure (New York Heart Association IV)	3 (0.4)	3 (0.4)	1.00
Infection as primary reason for ICU admission, *n* (%)	75 (9.7)	71 (8.9)	0.66
Infectious focus, *n* (%)			-
Pneumonia	18	20	
Respiratory except pneumonia	2	3	
Cardiovascular infection	20	15	
Abdomen	15	14	
Urinary tract	4	5	
Bone and soft tissue	8	5	
CNS	2	5	
Catheter-related blood stream infection	1	1	
Others	5	3	
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	13 (10–17)	13 (9–17)	0.05
Ventilator use within 24 hr of ICU admission, *n* (%)	332 (42.7)	358 (45.0)	0.39
Vasopressor[b] use within 24 hr of ICU admission, *n* (%)	266 (34.2)	273 (34.3)	1.00
Survival to ICU discharge, *n* (%)	752 (96.8)	782 (98.2)	0.07
ICU length of stay, d, median (IQR)	2 (2–4)	2 (2–5)	0.06
Survival to hospital discharge, *n* (%)	715 (92.0)	746 (93.7)	0.20
Hospital length of stay, d, median (IQR)	24 (15–45)	23 (14–39)	0.06

IQR = interquartile range.

[a]Immunocompromised hosts included patients with lymphoma, acute myelogenous leukemia, multiple myeloma, or a history of any of the following immunosuppressive therapies in the preceding 6 mo: immunosuppressive drugs, chemotherapy, radiotherapy, and steroid treatment (prednisolone equivalent > 0.375 mg/kg/d).

[b]Vasopressors included adrenaline, noradrenaline, dopamine, and dobutamine.

that the SHR decreased and approached null with the DOT for all IV antibiotics, anti-MRSA IV antibiotics, and antipseudomonal IV antibiotics. These results suggest that a reduction in the DOT may function as a

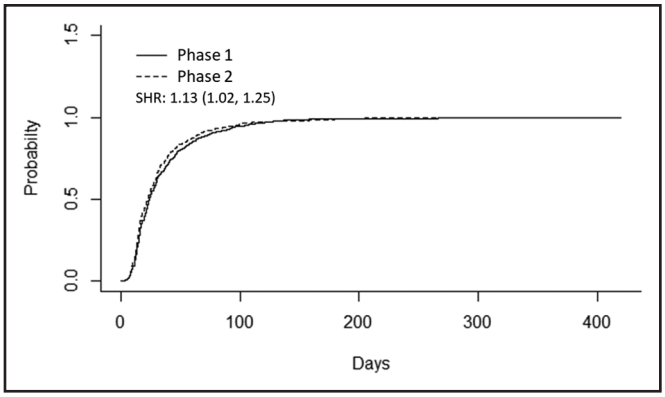

Figure 2. Cumulative survival to hospital discharge. Phase 1 refers to the last 12 mo of the period in which only multidisciplinary rounds were conducted. Phase 2 refers to the last 12 mo of the period in which both multidisciplinary rounds and antibiotic time-outs were conducted. SHR = subdistribution hazard ratio.

positive mediating factor between ATO and patient survival to hospital discharge. Although the DOT value could be confounded by the proportion of patients with infection as the primary reason for ICU admission and patient severity in the ICU, we did not consider these factors to have a significant impact on the DOT because the patient proportion and median APACHE II score were similar across groups. One of the potential mechanisms for improving patient outcomes by decreasing the DOT might be the prevention of adverse events. Drug-related adverse events have been reported to occur in greater than 15% of hospitalized patients, and antibiotics are one of the most common causative drugs (24, 25). Adverse events related to antibiotics and pneumonia are associated with prolonged hospitalization (26). However, the occurrence rate of the longitudinal development of resistance and antibiotic-specific adverse events was not examined and should be explored in future studies.

There was no significant difference in the SHR for survival to ICU discharge. We considered that this may have occurred because the majority of patients were admitted to the ICU for postoperative care after elective surgery; therefore, bed utilization was controlled due to limited ICU capacity, and their ICU length of stay was typically less than 24 hours.

We believe that the difference in our outcome in comparison with prior studies can be explained by the differences in the way we conducted the ATO. First, we conducted a series of repeated ATOs on days 3, 7, and 14 after the initiation of each antibiotic. The

TABLE 2.
Fine-Gray Model for Survival to Hospital Discharge

Intervention	SHR With Univariable Model (95% CI)	*p*	SHR With Multivariable Model[a] (95% CI)	*p*
Time-out	1.13 (1.02–1.25)	0.02	1.13 (1.02–1.25)	0.02

SHR = subdistribution hazard ratio.
[a]Adjusted for sex, age, admission status, operation, Acute Physiology and Chronic Health Evaluation II score, immunocompromised hosts, and infection.

appropriate timing for ATO remains unclear. In most reports, ATOs were conducted 48–72 hours after the initiation of antibiotic therapy (11–14). Even with empiric antibiotic therapy administered according to guidelines, the proportion of patients with identified pathogens who were treated with effective antibiotics was 81%, and 85% when the guidelines were not followed (27). This corresponds to the time when culture results typically become available, and the clinical course can be assessed to determine whether antibiotic therapy is effective. We believe that ATOs conducted consecutively during the initial phase of antibiotic treatment on days 3 and 7 promote timely consultations with ID specialists when clinical symptoms do not improve with empiric antibiotic therapy and provide an opportunity for appropriate interventions, especially in patients with resistant organisms. In the face of the shortage of ID specialists in Japan, our method effectively used the platform afforded by multidisciplinary rounds to identify patients who may benefit further from recommendations from an ID specialist. Furthermore, ATOs on days 7 and 14 may prevent prolonged inappropriate antibiotic use. However, it was difficult to ascertain whether the reduction in DOT resulted from de-escalation or a reduced treatment duration.

Second, our intervention did not rely on computer prompts, dashboards, and other technological assets but rather was incorporated as a routine step into existing routine practice with quick face-to-face intensivist-driven interactions between providers and other ICU disciplines. One of the essential elements of the ASP in the ICU is leadership (5), and multidisciplinary rounds are good routine platforms for intensivists to demonstrate leadership. In addition, Weiss et al (28)

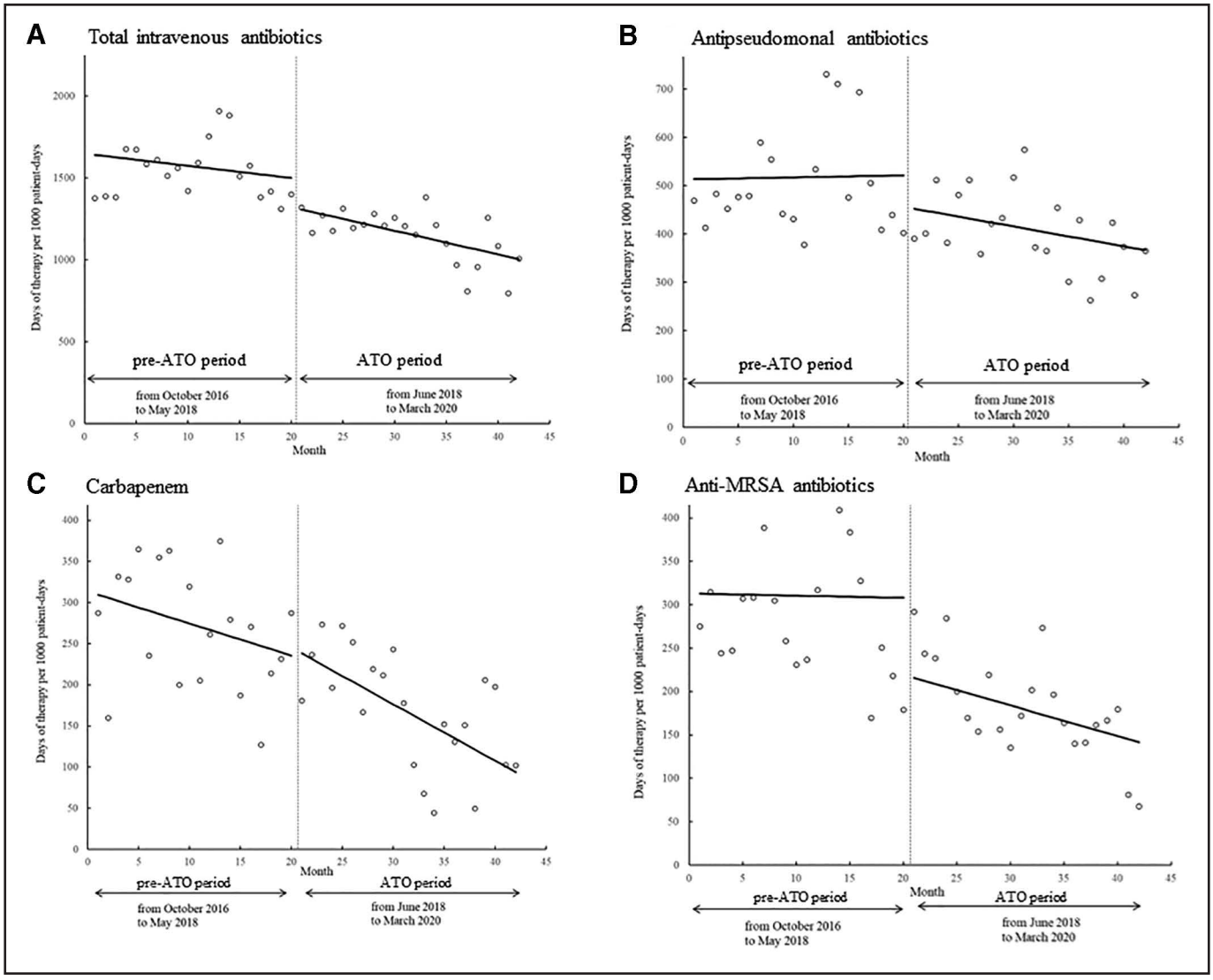

Figure 3. Comparison of the days of therapy with antibiotics between the pre-antibiotic time-out (ATO) and ATO periods. The *dots* show the monthly days of therapy (DOT) per 1,000 patient-days in the ICU. The *lines* show the regression curve predicted by the interrupted time-series analysis. The pre-ATO period was the period during which only multidisciplinary rounds were conducted. The ATO period was the period in which both multidisciplinary rounds and ATOs were conducted. **A**, DOT with total IV antibiotics. **B**, DOT with antipseudomonal antibiotics, including tazobactam/piperacillin, ceftazidime, cefepime, cefozopran, meropenem, doripenem, imipenem, ciprofloxacin, levofloxacin, and pazufloxacin. **C**, DOT with carbapenems, including meropenem, doripenem, and imipenem. **D**, DOT with anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, including vancomycin, teicoplanin, linezolid, and daptomycin.

reported that for reducing empiric antibiotic use, in-person ATOs were superior to ATOs using a checklist via electronic medical records. Furthermore, due to the implementation of ATOs under the ICU leadership, we were able to provide consistent antibiotic stewardship in the ICU. Accordingly, the DOT data points during the pre-ATO period were more variable than those in the ATO period and demonstrated inconsistency with antibiotic use. A previous study reported that 30% to 60% of antibiotics prescribed in the ICU are inappropriately broad or narrow (29) and that inappropriate empiric therapy could lead to worse patient outcomes, including mortality (24, 30–32). ATOs prompt physicians to refer to the culture results and facilitate quick constructive discussions during multidisciplinary rounds and tailoring of antibiotics to the patient's clinical needs. As a result, the ATOs in our ICU provided instantaneous feedback and practical bedside decision-making with immediate implementation of ASP with our ICU team. We believe that our method demonstrated that intensivist-led interventions are high-impact interventions that can be implemented globally in areas without technological privileges and with limited access to ID specialists for consultations. Because of the shortage

TABLE 3.
Parameters Estimated From the Interrupted Time-Series Analysis for Changes in Days of Therapy

Parameter	Coefficient (95% CI)	*p*
Total IV antibiotics		
Slope in the pre-ATO period	−7.45 (−15.95 to 1.04)	0.09
Change in intercept	−178.26 (−317.74 to −38.78)	0.02
Change in slope	−7.00 (−15.77 to 1.78)	0.13
Antipseudomonal antibiotics		
Slope in the pre-ATO period	0.43 (−2.84 to 3.71)	0.80
Change in intercept	−65.06 (−118.31 to −11.82)	0.02
Change in slope	−4.51 (−7.64 to −1.39)	< 0.01
Carbapenems		
Slope in the pre-ATO period	−3.89 (−6.36 to −1.43)	< 0.01
Change in intercept	9.29 (−31.18 to 49.76)	0.66
Change in slope	−2.98 (−5.38 to −0.58)	0.02
Anti-methicillin-resistant *Staphylococcus aureus* antibiotics		
Slope in the pre-ATO period	−0.25 (−2.75 to 2.26)	0.85
Change in intercept	−88.86 (−129.34 to −48.39)	< 0.01
Change in slope	−3.28 (−5.90 to −0.66)	0.02

ATO = antibiotic time-out.

of intensivists and ID specialists in Japan, some hospitals may have no ID specialists but intensivists, while others may have ID specialists but no intensivists. Our method is effective in hospitals facing the former scenario. While ATOs are a preliminary step in ASPs, we believe that our ATO methodology can be immediately implemented in other hospitals.

This study had several limitations. First, this was a single-center, nonrandomized controlled before-and-after study; therefore, inferring the impact of the ATO intervention on mortality may not be an optimal approach due to potential bias and limitations of the study design. Many of our patients were admitted to the ICU for elective surgeries, and their disease severity was mild-to-moderate. Therefore, the generalizability of our results must be treated with caution. Further multicenter studies are warranted to replicate our findings. Second, only a small proportion of the patients (10%) had infection as the primary reason for ICU admission. Although we cannot determine whether this factor would have lessened the effect of our ATO, it is an important consideration while interpreting our results. However, in addition to these patients, our study also included patients who acquired infection during ICU admission, and we found that ATOs resulted in significant patient outcomes and reductions in DOT. Third, although we believe that antimicrobial treatment was changed due to ATO-affected patient outcomes, we could not ascertain the exact details. Future studies investigating the adverse effects of antibiotics and monitoring set clinical improvement parameters with and without ATOs may be useful to further confirm and understand the effects of ATOs on patient outcomes. Fourth, we did not include data for oral antibiotics; therefore, we were unable to assess the impact of de-escalation of oral antibiotics as part of ASP in our study. However, oral medications were rarely used to treat infections in ICU. Furthermore, our study did not include factors such as nutritional status (18), withholding or withdrawal of treatment due to palliative care (33), procalcitonin, and other biomarkers in the multivariate analysis. Specifically, procalcitonin has been used in ASPs to guide antibiotic use, and its effect on antibiotic management should be explored in future studies. Finally, the implementation of ATOs may have encouraged ICU staff and pharmacists to take an interest in IDs, which may have produced a treatment bias in addition to the ATO itself. Our study could not quantify this treatment bias with ATOs, and treatment bias in this situation may itself be considered as an inherent part of the positive treatment effect.

CONCLUSIONS

In conclusion, intensivist-driven ATOs during multidisciplinary rounds reduced the DOT with antibiotics, including anti-MRSA antibiotics, antipseudomonal antibiotics, and carbapenems, which may have influenced patient outcomes. Incorporation of ATOs into daily multidisciplinary rounds had a high impact on

ASPs led by intensivists without requiring the use of specific equipment.

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