





Concise Communication

Changes in intravenous and oral antimicrobial prescriptions during the coronavirus disease 2019 (COVID-19) pandemic: an experience at a tertiary-care center

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Abstract

Antimicrobial use during the coronavirus disease 2019 (COVID-19) pandemic at a tertiary-care center was analyzed using interrupted time-series analysis. Among intravenous antimicrobials, the use of azithromycin and third-generation cephalosporins significantly decreased during the current pandemic. Similarly, the use of oral antimicrobials, including azithromycin and fluoroquinolones, also decreased.

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Since the coronavirus disease 2019 (COVID-19) pandemic began in early 2020, the widespread use of antimicrobial agents, especially in patients with COVID-19, has become an emerging concern. Although concurrent bacterial infections are rare, >50% of patients with COVID-19 receive antimicrobial therapy on admission, presumably because these patients demonstrate pulmonary infiltrates on chest radiograph that are considered to be a symptom of community-acquired pneumonia.¹ Moreover, antimicrobials are also indicated for the treatment of healthcare-associated infections and invasive fungal infections following COVID-19-related pneumonia, especially in patients requiring intensive care.^{2,3}

Although antimicrobial use increased during the COVID-19 pandemic, the rate of use varied widely among healthcare centers, healthcare settings (eg, inpatient or outpatient), antimicrobial classes, and types of formulation (intravenous versus oral).^{4,5} Understanding the general trends in antimicrobial use during the pandemic is crucial because the administration of antimicrobials during this period may have counteracted the efforts of those involved in antimicrobial stewardship programs (ASPs). We investigated how the national government's policies regarding the COVID-19 emergency impacted intravenous and oral antimicrobial use at a tertiary-care center in Japan.

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Methods

This observational study was conducted at Tokyo Metropolitan Tama Medical Center, a 790-bed tertiary-care center in Japan, which accepts only adult patients. We compared intravenous (inpatient) and oral (outpatient) antimicrobial consumption between the prepandemic period (September 2018–February 2020) and the pandemic period (March 2020–August 2021). Both periods were divided by the date of the issuance of the Japanese government's first emergency declaration on March 11, 2020. Intravenous antimicrobial consumption data at the study institution were obtained from electronic medical records and were expressed as days of therapy (DOT) per 1,000 patient days. DOT were measured using facility-wide, monthly, barcode medication administration (BCMA) records. Oral antimicrobial consumption in the outpatient setting was calculated based on the data at the study center and is expressed as the number of prescriptions per 1,000 patient visits.

The trends in intravenous antimicrobial consumption were assessed in selected categories, including overall use, antipseudomonal agent use (ie, total carbapenems, piperacillin–tazobactam, and cefepime), antimicrobial prescriptions for community-acquired infections (eg, third-generation cephalosporins and ampicillin–sulbactam), fluoroquinolones (the total of ciprofloxacin and levofloxacin consumption), ampicillin, vancomycin, and azithromycin. The trends in overall and specific oral antimicrobial use, including amoxicillin, amoxicillin/clavulanate, fluoroquinolones (ie, ciprofloxacin and levofloxacin), trimethoprim–sulfamethoxazole, cephalexin, and azithromycin, were also assessed. Segmented regression in interrupted time-series analysis (ITSA) was used to assess the differences in antimicrobial use between the 2 study periods. The study center has an in-hospital ASP, including

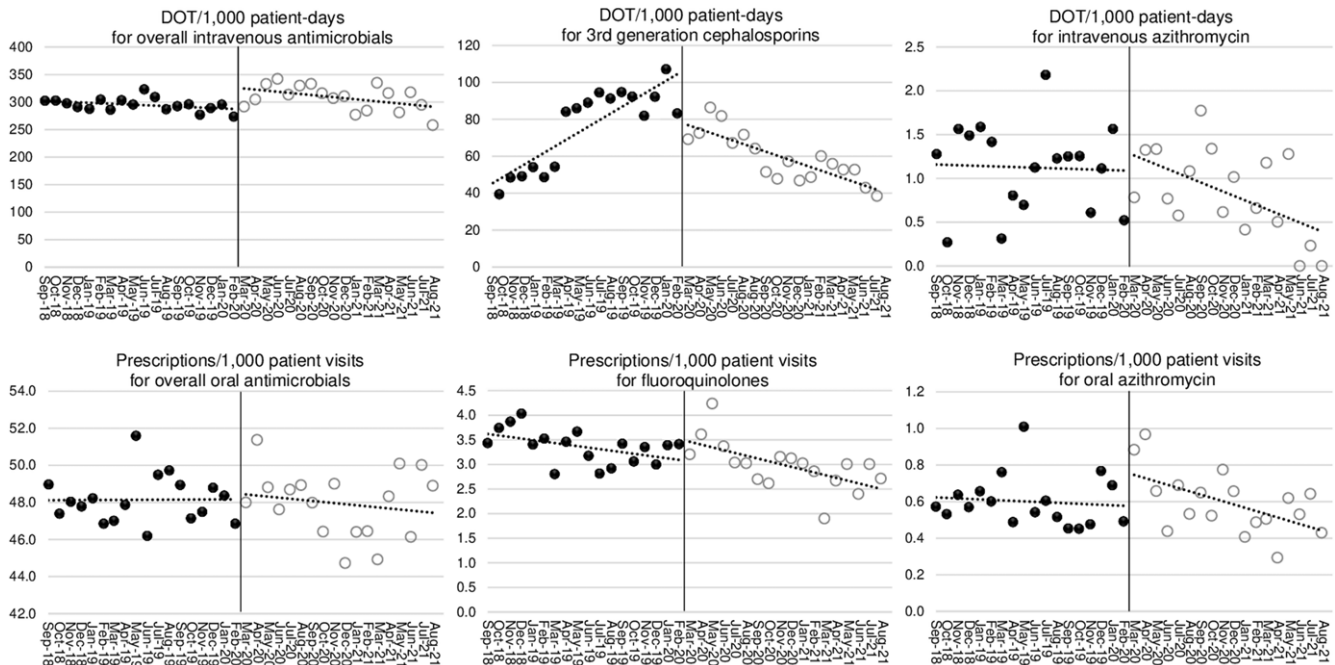


Fig. 1. Changes in intravenous (inpatient) and oral (outpatient) antimicrobial use during the prepandemic and pandemic periods. Intravenous antimicrobials (overall, third-generation cephalosporins, and azithromycin) and oral antimicrobials (overall, fluoroquinolones, and azithromycin). Note. DOT, days of therapy.

postprescription review and feedback for broad-spectrum antimicrobials and a preauthorization protocol for vancomycin use. The present study was approved by the Institutional Review Board of Tokyo Metropolitan Tama Medical Center (approval no. 3-136).

Results

Figure 1 shows the changes in intravenous (inpatient) and oral (outpatient) antimicrobial use before and during the pandemic. The ITSA revealed an immediate increase in overall intravenous antimicrobial use (+37.9 DOT per 1,000 patient days; $P < .001$ for change in level) following the emergency declaration in Japan, but the change in the slope of overall antimicrobial use significantly decreased (from -0.851 to -1.094 DOT per 1,000 PD; $P = .040$ for change in trend), particularly for third-generation cephalosporins and azithromycin (Table 1).

Overall use of oral antimicrobial agents did not change significantly between the 2 periods in either level or trend, but the use of certain antimicrobials, such as azithromycin and fluoroquinolones, significantly decreased during the pandemic period for azithromycin from -0.003 to -0.015 prescriptions per 1,000 patient visits, a change of -0.018 (95% CI, -0.030 to -0.005 ; $P = .006$ for change in trend), and fluoroquinolones decreased from -0.031 to -0.025 prescriptions per 1,000 patient visits, a change of -0.056 (95% CI, -0.088 to -0.025 ; $P = .001$ for change in trend).

Discussion

Studies addressing the impact of COVID-19 on ASPs have increased, and our understanding of trends in hospital antimicrobial use during the pandemic have become essential to maintaining the efficacy of hospital antimicrobial stewardship.^{3,6} Antimicrobial use in the inpatient setting decreased despite a peak in the overall use of antimicrobials immediately after the emergency

declaration. This trend was particularly significant in third-generation cephalosporins and azithromycin. Moreover, among oral antimicrobials, azithromycin and fluoroquinolone use immediately increased in the early period of the pandemic before decreasing significantly.

Although a previous study demonstrated increased use of antimicrobials in patients with COVID-19 requiring hospitalization during the pandemic,^{7,8} these findings have some unique implications. We observed a decrease in the use of ceftriaxone and azithromycin, which were treatment options for community-acquired pneumonia (CAP) related to COVID-19. Whereas immediate changes in antimicrobial use were solely associated with the emergency declaration, changes in the trend of antimicrobial use may have been further influenced by in-house polymerase chain reaction (PCR) testing, changes in the COVID-19 incidence, and increased experience in treating the disease, which may have led the treating physicians to refrain from administering empiric antimicrobial therapy at admission. Moreover, despite an increase in the number of severe COVID-19 cases, the use of broad-spectrum antimicrobials (eg, carbapenems) and the use of vancomycin remained relatively stable during both periods presumably because of the pre-existing ASP at the study center.

In the outpatient setting, both azithromycin and fluoroquinolone prescriptions temporarily increased at the outset of the pandemic before falling. Notably, azithromycin and fluoroquinolones are the most commonly prescribed oral antimicrobials in Japan, mainly for community-acquired infections, including pneumonia.⁹ In addition to the effect of the emergency declaration, the reduction in prescriptions may be associated with a decrease in the number of medical visits for conditions unrelated to COVID-19, as seen in the United States under lockdown conditions.⁵ The Japanese government issued at least 4 “stay-at-home orders,” which may have led to the observed decrease in hospital visits.¹⁰ Moreover, physicians’ prescribing behaviors may have gradually normalized over time with increasing understanding of COVID-19

Table 1. Changes in Intravenous and Oral Antimicrobial Use During the Study Period Using Interrupted Time-Series Analysis

Variable	Days of Therapy per 1,000 Patient Days per Month (Intravenous Antimicrobials)							
	Baseline Prepandemic Trend (95% CI)	P Value	Trend During Pandemic (95% CI)	P Value	Change in Level (95% CI)	P Value	Change in Trend (95% CI)	P Value
All intravenous antimicrobials	−0.851 (−1.569 to −0.133)	.022	−1.094 (−3.339 to 1.151)	.329	37.900 (20.164 to 55.635)	<.001	−1.944 (−3.793 to −0.095)	.040
Three antipseudomonal agents	−0.314 (−0.797 to 0.169)	.194	0.261 (−0.792 to 1.315)	.616	3.198 (−9.733 to 16.130)	.618	−0.053 (−0.997 to 0.891)	.910
Vancomycin	−0.275 (−0.591 to 0.042)	.087	0.054 (−0.323 to 0.432)	.772	2.829 (−2.268 to 7.927)	.267	−0.221 (−0.430 to −0.011)	.039
Third-generation cephalosporins	3.555 (2.587 to 4.524)	<.001	−5.608 (−6.929 to −4.287)	<.001	−31.218 (−45.262 to −17.173)	<.001	−2.052 (−2.811 to −1.293)	<.001
Ampicillin/sulbactam	−0.583 (−2.121 to 0.955)	.446	1.067 (−1.271 to 3.404)	.360	4.814 (−17.839 to 27.468)	.668	0.483 (−0.989 to 1.956)	.509
Ampicillin	−0.070 (−0.375 to 0.235)	.644	0.025 (−0.348 to 0.397)	.894	0.488 (−3.374 to 4.349)	.799	−0.045 (−0.222 to 0.131)	.604
Azithromycin	−0.004 (−0.031 to 0.023)	.758	−0.047 (−0.093 to −0.0004)	.048	0.175 (−0.201 to 0.551)	.350	−0.051 (−0.084 to −0.018)	.004
Fluoroquinolones	−0.072 (−0.211 to 0.067)	.302	0.055 (−0.114 to 0.223)	.514	0.481 (−1.558 to 2.520)	.634	−0.017 (−0.113 to 0.079)	.722
Number of prescriptions per 1,000 patient visits per month (oral antimicrobials)								
All oral antimicrobials	0.003 (−0.063 to 0.070)	.923	−0.061 (−0.232 to 0.111)	.475	0.255 (−1.648 to 2.158)	.787	−0.058 (−0.229 to 0.114)	.499
Amoxicillin	−0.009 (−0.054 to 0.037)	.704	0.032 (−0.060 to 0.124)	.481	−0.886 (−1.835 to 0.063)	.066	0.024 (−0.056 to 0.103)	.548
Amoxicillin/clavulanate	0.050 (0.007 to 0.093)	.023	−0.071 (−0.122 to −0.019)	.009	−0.193 (−0.752 to 0.365)	.486	−0.021 (−0.053 to 0.011)	.200
Azithromycin	−0.003 (−0.010 to 0.005)	.477	−0.015 (−0.031 to 0.0004)	.055	0.171 (0.031 to 0.310)	.018	−0.018 (−0.030 to −0.005)	.006
Fluoroquinolones	−0.031 (−0.056 to −0.006)	.017	−0.025 (−0.069 to 0.019)	.252	0.398 (0.031 to 0.766)	.035	−0.056 (−0.088 to −0.025)	.001
Trimethoprim-sulfamethoxazole	0.003 (−0.021 to 0.028)	.771	−0.011 (−0.151 to 0.130)	.880	0.991 (−0.593 to 2.574)	.212	−0.007 (−0.136 to 0.122)	.912
Cephalexin	0.135 (0.082 to 0.188)	<.001	−0.127 (−0.216 to −0.038)	.007	0.051 (−0.921 to 1.023)	.915	0.008 (−0.055 to 0.071)	.802

Note. CI, confidence interval; CAP, community-acquired pneumonia.

pathology and the low incidence of bacterial coinfections on admission.

This study had several limitations. As a single-center, observational study, its findings might not represent antimicrobial practices in Japanese hospitals. Although we tried to investigate the impact of the national policy implementation on our antimicrobial practice, ITSA might not enable precise assessment of the impact of the emergency declarations on antimicrobial use because the trend in antimicrobial use might have been affected by various changes occurring during the pandemic.

In conclusion, the use of intravenous and oral antimicrobial agents changed significantly during the pandemic. Although the use of certain antimicrobials, both in their intravenous and oral formulations, for community-acquired infections decreased at the study institution, ASP could have been improved during this period given the lower incidence of bacterial coinfections in patients with COVID-19.

Previous studies have demonstrated the potentially negative impact of the COVID-19 pandemic on hospital antimicrobial stewardship. Therefore, revamping current ASP strategies by incorporating rapid diagnostics and monitoring antimicrobial prescribing practices, especially in patients with COVID-19, is warranted to maintain the efficacy of antimicrobial stewardship in the healthcare setting.

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References

1. Russell CD, Fairfield CJ, Drake TM, *et al*. Coinfections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multi-centre, prospective cohort study. *Lancet Microbe* 2021;2:e354–e365.
2. Koehler P, Bassetti M, Chakrabarti A, *et al*. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2021;21:e149–e162.
3. Ansari S, Hays JP, Kemp A, *et al*. The potential impact of the COVID-19 pandemic on global antimicrobial and biocide resistance: an AMR Insights global perspective. *JAC Antimicrob Resist* 2021;3:dlab038.
4. Rose AN, Baggs J, Wolford H, *et al*. Trends in antibiotic use in United States hospitals during the coronavirus disease 2019 pandemic. *Open Forum Infect Dis* 2021;8:ofab236.
5. King LM, Lovegrove MC, Shehab N, *et al*. Trends in US outpatient antibiotic prescriptions during the coronavirus disease 2019 pandemic. *Clin Infect Dis* 2021;73:e652–e660.
6. Pierce J, Stevens MP. COVID-19 and antimicrobial stewardship: lessons learned, best practices, and future implications. *Int J Infect Dis* 2021;113:103–108.
7. Winders HR, Bailey P, Kohn J, *et al*. Change in antimicrobial use during COVID-19 pandemic in South Carolina hospitals: a multicenter observational cohort study. *Int J Antimicrob Agents* 2021:106453.
8. Vaughn VM, Gandhi TN, Petty LA, *et al*. Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with coronavirus disease 2019 (COVID-19): a multihospital cohort study. *Clin Infect Dis* 2021;72:e533–e541.
9. Muraki Y, Yagi T, Tsuji Y, *et al*. Japanese antimicrobial consumption surveillance: first report on oral and parenteral antimicrobial consumption in Japan (2009–2013). *J Glob Antimicrob Resist* 2016;7:19–23.
10. Osawa I, Goto T, Asami Y, *et al*. Physician visits and medication prescriptions for major chronic diseases during the COVID-19 pandemic in Japan: retrospective cohort study. *BMJ Open* 2021;11:e050938.