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Research Article

Does the Pandemic Influence Antimicrobial Stewardship? A Historical Control Study before and after Severe Acute Respiratory Syndrome Coronavirus-2 Infection Care in a Teaching Hospital

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ABSTRACT

Background: To see whether the COVID-19 pandemic influenced the 3-year use of parenteral antimicrobials, we attempted a historical control study.

Methods: Materials were the electronic medical record on the use of a total of 33 antimicrobials. We compared Antimicrobial Use Density (AUD, total dose/Defined Daily Dose/patient-day × 100) of Pre-pandemic 1 Year (PreY), the first Pandemic Year (Pan1Y), and the second Pandemic Year (Pan2Y). Our antimicrobial team monitored all in-patients and COVID-19 patients underwent clinical pathways with antivirals.

Results: Results showed that in a total of 20,013 patients (7,534, 6,146, and 6,333 for PreY, Pan1Y, and Pan2Y), sepsis-3 was diagnosed in 152, 132, and 283 patients while *Clostridioides difficile* toxin tests were positive in 17, 5, and 7 patients, respectively. Among patients with COVID-19 (N=622) at a median age of 58 (range, 1-99), 11 (1.8%) died, parenteral antimicrobials were given in 59 patients (9.5%) preceded by bacteriological tests in 48 (81.4%).

Discussion: Comparing before and during the pandemic, parametric analyses showed that the means of total AUD decreased from 16.440 (PreY) to 14.630 (Pan2Y) (P=0.020). Likewise, the means of carbapenems' AUD showed decrease from 0.773 (PreY) to 0.462 (Pan1Y) but increase into 0.777 (Pan2Y) (P=0.001).

The non-parametric comparison between COVID-19 and other wards showed that the medians of AUD in the COVID-19 wards were significantly (P<0.05) less in 22 out of 33 antimicrobials (66.7%) and in the total AUD.

Conclusion: The COVID-19 pandemic stewardship decreased the total AUD and may have contributed to decrease *C. difficile* infection. The burden of sepsis-3 may have fluctuated the carbapenems' use.

Keywords: Antimicrobial use density; Stewardship; Sepsis; COVID-19; *Clostridioides difficile* infection

INTRODUCTION

Nori and others have described "pandemic stewardship" for antimicrobial stewardship amid the COVID-19 (Severe Acute Respiratory Syndrome Coronavirus-2 Infectious Disease-19) pandemic [1,2]. The authors stressed that COVID-19, a viral disease, caused inconsistent use of antimicrobials, which may augment antimicrobial resistance. In Japan, Ono et al. reported that the nationwide surveillance of antimicrobial sales showed reduction after the pandemic, due to awareness for antimicrobial stewardship [3]. They reiterated that indiscriminate use of broad spectrum antimicrobials would lead into drug resistance. To elucidate the pandemic effect on antimicrobial use and subsequent influence on the clinical data, we herein conducted a historical study.

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MATERIALS AND METHODS

Materials were electronic data produced from the format of the medical insurance system or the Diagnostic Procedure and Combination since March 1, 2019 through February 28, 2022. We defined the Pre-pandemic Year (PreY) as March 2019 through February 2020, the first Pandemic Year (Pan1Y) as March 2020 through February 2021, and the second Pandemic Year (Pan2Y) as March 2021 through February 2022. We admitted the first COVID-19 patient on March 3, 2020 and subsequent patients in two dedicated wards for their care using clinical pathways that included antivirals. Non-COVID-19 patients were admitted to remaining eight wards.

Methods of stewardship included intervention at the administration of broad spectrum agents unlocking the electronic order system after confirmation of the blood culture. Weekly audits of antimicrobials by the stewardship team recommended de-escalation or change into susceptible agents, in accordance with the therapeutic guidance for COVID-19 patients by certified infectious diseases specialists. In line with the guideline [4], perioperative prophylactic antimicrobials were mostly cefazolin. On the other hand, patients diagnosed as sepsis-3 [5] underwent bacteriological tests and the administration of broad-spectrum antimicrobials in compliance with the surviving sepsis campaign guideline [5,6]. They were, however, corrected by bacteriological results. Should Extended Spectrum Beta-Lactamase (ESBL)-producing microbes be isolated and susceptible for cefmetazole, for example, we recommended susceptible antimicrobials sparing carbapenems.

RESULTS

We studied following parenteral antimicrobials. By categories, penicillins included benzylpenicillin, ampicillin, piperacillin, ampicillin/sulbactam, and piperacillin/tazobactam; the first generation cephalosporin was cefazolin; the second generation cephalosporin represented cefotiam; the third generation cephalosporins were cefotaxime, ceftazidime, ceftriaxone, and cefoperazone/sulbactam; the fourth generation cephalosporin was cefepime; oxacephems/cephamycins were flomoxef and cefmetazole; carbapenems were meropenem and imipenem/cilastatin; glycopeptides were teicoplanin and vancomycin; oxazolidine was linezolid; arbekacin represented arbekacin; daptomycin was for daptomycin; quinolones included ciprofloxacin and levofloxacin; aminoglycosides were amikacin, gentamycin, dibekacin, and streptomycin; tetracyclines included tigecycline and minocycline; lincomycin represented clindamycin; macrolide was azithromycin; sulfamethoxazole/trimethoprim was for the same; and metronidazole represented metronidazole.

For the index of the stewardship, Antimicrobial Use Density (AUD) was defined as:

(Total dose)/(Defined Daily Dose)/(patient-day) × 100

where the Defined Daily Dose was described by the World Health Organization [7]. We collected parenteral monthly AUDs as semi-automated data by the Japan Surveillance for Infection Prevention and Healthcare Epidemiology System (J-SIPHE). To use the data of our institute alone, we obtained written consent from the headquarter.

These AUD data underwent the Kolmogorov-Smirnov tests for the normal distribution, which led into parametric or non-parametric tests for multiple comparisons using analysis of variance with the Bonferroni correction or Kruskal-Wallis tests, respectively. For computation, we used software SPSS Statistics Version 27 (IBM Japan Inc., Tokyo, Japan).

Outcomes were measured twofold. 1) The primary purpose was AUD comparison over the years and between the COVID-19 wards and non-COVID-19 wards. 2) Secondly, clinical and bacteriological events were documented. As indices of antimicrobial stewardship, we studied the data on ESBL-producing microbes and the *Clostridioides difficile* toxin tests. For COVID-19 patients, we recorded antivirals, all-cause in-hospital mortality, and antimicrobials with their preceding culture tests.

A total of 20,013 patients were subjected (Table 1). Annually, operations were performed constantly but sepsis-3 was diagnosed with a peak in Pan2Y. In patients with COVID-19 (N=622) at a median age of 58 (range, 1-99), 11 (1.8%) died. No patients were positive for *C. difficile* toxin. Parenteral antimicrobials were given in 59 patients (9.5%), which were preceded by microbial tests in 48 (81.4%) or computed tomography to confirm additional aspiration pneumonia. A total of 619 patients (99.5%) underwent clinical pathways that included antivirals, such as favipiravir (N=15, 2.3%), remdesivir (N=205, 33.0%), casirivimab/imdevimab (N=102,

Table 1: Annual trend of clinical profiles, including operations, sepsis-3, Extended Spectrum Beta-Lactamase (ESBL)-producing microbes, and *Clostridioides difficile* toxin-positive patients in the Pre-pandemic Year (PreY), the first Pandemic Year (Pan1Y), and the second Pandemic Year (Pan2Y).

	PreY	Pan1Y	Pan2Y	Total
Patients	7,534	6,146	6,333	20,013
Operations	6,816	5,577	5,772	18,165
	(90.5%)	(90.7%)	(91.1%)	
Sepsis-3	152	132	283	567
	(2.0%)	(2.2%)	(4.5%)	
Patients with ESBL-producing microbes	125	100	102	327
	(1.66%)	(1.63%)	(1.61%)	
C. difficile toxin-positive patients	17	5	7	29
	(0.22%)	(0.08%)	(0.11%)	

16.4%) [8], and sotrovimab (N=105, 16.9%).

As for outcome 1) comparing AUDs over the years, we used the parametric analyses because 14 out of the 18 hospital-wide AUDs (77.8%) met the normal distribution. The means of the first generation cephalosporins decreased from PreY to Pan2Y (P=0.001) as well as from Pan1Y to Pan2Y (P=0.015).

The means of carbapenems' AUD decreased from PreY to Pan1Y (P=0.001) but increased from Pan1Y to Pan2Y (P=0.001). The means of the total AUD decreased from PreY to Pan2Y (P=0.020) (Table 2).

To compare COVID-19 wards and others, we used non-parametric Kruskal-Wallis tests because all AUDs were out of the normal distribution. Thus, the median AUDs in the COVID-19 wards were significantly (P<0.050) less in 22 out of 34 antimicrobials (64.7%) (Table 3).

Table 2: Analysis of Variance (ANOVA) for Antimicrobial Use Density (AUD, (total dose)/(Defined Daily Dose)/(patient-day) × 100) comparing the Pre-pandemic Year (PreY) and the first and the second Pandemic Years (Pan1Y and Pan2Y, respectively). The Kolmogorov-Smirnov test showing the data fit for the normal distribution, we use mean values.

Year	PreY		Pan1Y		Pan2Y		ANOVA	Bonferroni correction
Categories	Mean	SEM	Mean	SEM	Mean	SEM	P	PreY vs. Pan1Y PreY vs. Pan2Y Pan1Y vs. Pan2Y
Penicillins	2.882	0.952	3.065	0.694	2.645	0.38	0.364	
1-Cephalosporins	4.759	0.569	4.531	0.518	3.896	0.462	0.001*	0.871 0.001* 0.015*
2-Cephalosporins	0.136	0.09	0.102	0.041	0.133	0.05	0.369	
3-Cephalosporins	3.19	0.963	2.996	0.492	2.645	0.463	0.154	
4-Cephalosporins	0.17	0.153	0.178	0.073	0.151	0.208	0.908	
Oxacephems/ cephamycins	1.636	0.363	1.417	0.357	1.424	0.27	0.203	
Carbapenems	0.773	0.147	0.462	0.202	0.777	0.233	<0.001*	0.001* 1.000 0.001*
Glycopeptides	0.588	0.216	0.691	0.408	0.78	0.247	0.309	
Oxazolidines	0.117	0.096	0.174	0.161	0.189	0.169	0.452	
Arbekacin	0.004	0.012	0.008	0.029	0	0	0.534	
Daptomycin	0.136	0.144	0.113	0.135	0.094	0.089	0.715	
Quinolones	0.872	0.365	0.817	0.299	0.905	0.348	0.814	
Aminoglycosides	0.175	0.091	0.217	0.157	0.165	0.107	0.549	
Tetracyclines	0.11	0.106	0.147	0.09	0.126	0.115	0.686	
Lincomycin	0.517	0.262	0.563	0.197	0.535	0.27	0.901	
Macrolides	0.025	0.046	0.009	0.023	0.006	0.022	0.327	
Sulfamethoxazole/ trimethoprim	0.001	0.005	0.034	0.059	0	0.001	0.034*	0.078 1.000 0.061
Metronidazole	0.347	0.225	0.257	0.128	0.156	0.143	0.033*	0.605 0.029 0.474
Total	16.44	2.157	15.78	1.099	14.63	1.058	0.022*	0.898 0.020 0.220

Note: *statistical significance; SEM: Standard Error of the Mean; Cephalosporins:1-, 2-, 3-, and 4-, the first, second, third, and fourth generations; Bonferroni correction, comparisons.

Table 3: Non-parametric analysis for Antimicrobial Use Density (AUD, (total dose)/(Defined Daily Dose)/(patient-day) × 100) comparing COVID-19 wards (N=2) and non-COVID-19 wards (N=8) during the pandemic two years. The Kolmogorov-Smirnov test showing the data not fit for the normal distribution, we use mean values.

		Non-COVID-19 Wards			COVID-19 Wards			
Categories	Antimicrobials	Median	Minimum	Maximum	Median	Minimum	Maximum	P
Penicillins	Benzylpenicillin	0	0	16.24	0	0	0	0.388
	Ampicillin	0	0	3.90	0	0	0	<0.001*
	Piperacillin	0	0	0.44	0	0	0	0.087
	Ampicillin/ sulbactam	1.66	0	15.39	0	0	33.33	0.049*
	Piperacillin/ tazobactm	0	0	8.30	0	0	9.52	0.008*
1-Cephalosporins	Cefazolin	2.08	0	29.31	0	0	1.91	<0.001*
2-Cephalosporins	Cefotiam	0	0	0.92	0	0	0	<0.001*
3-Cephalosporins	Cefotaxime	0	0	2.31	0	0	0	0.007*
	Ceftazidime	0	0	4.83	0	0	2.58	0.001*
	Ceftriaxone	1.28	0	14.65	0	0	20.00	0.108
	Cefoperazone/ sulbactam	0	0	3.33	0	0	1.01	<0.001*
4-Cephalosporins	Cefepime	0	0	13.33	0	0	0	0.002*
Oxacephems/ cephamycins	Flomoxef	0	0	6.51	0	0	0	0.029*
	Cefmetazole	1.32	0	11.00	0	0	3.45	<0.001*
	Imipenem/ cilastatin	0	0	2.44	0	0	0	0.222
Glycopeptides	Teicoplanin	0	0	1.10	0	0	0	0.388
	Vancomycin	0.37	0	27.55	0	0	3.64	<0.001*
Oxazolidines	Linezolid	0	0	5.92	0	0	0	0.005*
Arbekacin	Arbekacin	0	0	0.65	0	0	0	0.349
Daptomycin	Daptomycin	0	0	4.97	0	0	0	0.044*
Quinolones	Ciprofloxacin	0	0	11.10	0	0	7.50	0.013*
	Levofloxacin	0.36	0	13.30	0	0	4.02	<0.001*
Aminoglycosides	Amikacin	0	0	3.73	0	0	0	0.029*
	Gentamycin	0	0	2.09	0	0	0	0.087
	Dibekacin	0	0	0.97	0	0	0	0.039*
	Streptomycin	0	0	0.35	0	0	0	0.349
Tetracyclines	Tigecycline	0	0	0.44	0	0	0	0.722
	Minocycline	0	0	6.59	0	0	1.53	0.007*
Lincomycin	Clindamycin	0.24	0	6.56	0	0	0.48	0.007*
Macrolides	Azithromycin	0	0	0.54	0	0	0	0.969
Sulfamethoxazole/ trimethoprim	Sulfamethoxazole/ Trimethoprim	0	0	2.66	0	0	0	0.717
Metronidazole	Metronidazole	0	0	5.38	0	0	0	0.006*
Total		16.15	0	89.63	0	0	65.08	<0.001*

Note: *statistical significance; Cephalosporins: 1-, 2-, 3-, and 4-, the first, second, third, and fourth generations.

For outcome 2) ESBL-producing microbes were isolated constantly but patients positive for *C. difficile* toxin decreased in Pan1Y and Pan2Y (Table 1).

DISCUSSION

Our study revealed that the means of AUD for the first generation cephalosporins decreased from the pre-pandemic year to the pandemic years, as did the numbers of operative cases. This was most likely derived from the decrease in perioperative prophylactic antimicrobials due to the citizen's reluctance to visit hospitals during the pandemic. A similar observational study during the pandemic was reported by Gu and others [9].

Despite the emergence of COVID-19, however, our antimicrobial stewardship facilitated reducing carbapenems' AUD from PreY to Pan1Y. Their subsequent increase from Pan1Y to Pan2Y, on the contrary, may reflect the increased number of sepsis-3 patients necessitating broad-spectrum antimicrobials based upon the Early Goal Directed Therapy [5].

During Pan1Y and Pan2Y, we observed decreased numbers kept for ESBL-producing microbes and for the patients with *C. difficile* infection. These may have resulted from reducing AUDs of overall antimicrobials as described by Granata and others during the pandemic [10].

On the mortality of COVID-19 as of February 28, 2022 or the end of our study period, the domestic surveillance Ministry of Health and Welfare reported the cumulative numbers of deaths and "case-patients were requiring inpatient care" were 23,625 and 703,137, respectively [11]. The nationwide mortality thus being 3.4%, ours at 1.8% was low despite lowered AUDs in COVID-19 wards. Likewise, Chan et al. described that, during the pandemic, reduction in broad-spectrum antibiotic use in intensive care unit did not increase mortality [12].

Nori et al. reported "outpatient pandemic stewardship" for outpatient administration of neutralizing antibody agents [2]. The domestic ministry of health, however, had regulated that these agents be given in-hospital setting. Our in-hospital stewardship prioritized the early administration of antivirals using clinical pathways for COVID-19, peruse, viral infection. Likewise, Bartlett and others reiterated that clinical pathways for COVID-19 patients would augment antimicrobial stewardship [13]. At the emergence of COVID-19, the main difficulty in the pandemic stewardship resided in previously unknown pathophysiology in the care of patients.

No guidelines having been available initially, the fear of co-infection with bacterial pneumonia may have led into overuse of antimicrobials. Prior to the pandemic, however, the diagnostic stewardship did maintain the antimicrobial principle based on the bacteriological diagnosis. After the onset of COVID-19 as well, Rubin and others stressed to add imaging diagnosis to differentiate from superimposed infection [14].

The limitation of our study includes being a retrospective study in a single institute. A multi-institutional studies before and after the emergence of COVID-19 may be possible using, for example, the big data from J-SIPHE. Secondly, frequently revised guidelines on the use of steroids may have created historical biases on the administration of prophylactic antimicrobials. Thirdly, the time course of AUDs may fluctuate seasonally or by the climate change. Theoretically, therefore, time series analyses may provide better insights into perennial trend of AUDs.

CONCLUSION

Comparing before and during the pandemic, parametric analyses showed that the means of total AUD decreased from 16.440 (PreY) to 14.630 (Pan2Y) (P=0.020). Likewise, the means of carbapenems' AUD showed decrease from 0.773 (PreY) to 0.462 (Pan1Y) but increase into 0.777 (Pan2Y) (P=0.001). The non-parametric comparison between COVID-19 and other wards showed that the medians of AUD in the COVID-19 wards were significantly (P<0.05) less in 22 out of 33 antimicrobials (66.7%) and in the total AUD.

The COVID-19 pandemic stewardship decreased the total AUD and may have contributed to decrease *C. difficile* infection. The burden of sepsis-3 may have fluctuated the carbapenems' use.

CONFLICT OF INTEREST

The first author had Conflict of Interest (COI) with FUJIFILM Toyama Chemical Co., Ltd., Japan for the clinical trial of favipiravir. Other authors have no financial support or benefits if any from commercial sources for the work reported in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

DECLARATIONS

Ethics approval and consent to participate

The institution's Ethics Committee approved the current study with the reference number 2022SCHEC-005. Thereby, the need for informed consent was waived in accordance with the Chapter 5, Part 12, B) Research not involving invasiveness, b) Research not involving intervention of the Ethical Guideline from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Authors' contributions

Contributor JY was responsible for the organization and coordination of the study. TK conducted microbiological tests. AM supervised the infection control. MT was the senior investigator responsible for the data analysis. All the authors contributed to the writing of the final manuscript.

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