J Surg Med. 2021;5(2):124-127.
DOI: 10.28982/josam.834535

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Antibiotic consumption in the hospital during COVID-19 pandemic, distribution of bacterial agents and antimicrobial resistance: A single-center study

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Ethics Committee Approval
This study was approved by the Non-invasive Clinical Research Ethics Board of Karabük University (approval number: 2020/242).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 February 19

Abstract

Background/Aim: In recent years, the consumption of broad-spectrum antibiotics used in hospitals and the number of multidrug-resistant pathogens are increasing. Coronavirus disease 2019 (COVID-19) pandemic could also affect consumption of antibiotics used in the treatment of hospital-acquired infections and cause a difference antibiotic resistance rate. There is no study on whether there was a change in this trend during the COVID-19 pandemic in Turkey. Our study was conducted to determine antibiotic consumption, the distribution of bacterial agents in culture samples and changes in their antimicrobial resistance rates in our hospital during the COVID-19 pandemic.
Methods: In this retrospective cohort study, January and February 2020 were defined as the pre-pandemic period (PPP), and March and April, as the pandemic period (PP). The bacterial agents isolated from blood, urine, and respiratory samples and the rates of antibiotic consumption during these periods were compared using statistical methods.
Results: A total of 3,384 samples were analyzed during the PPP and 2,170 samples, during the PP. While the total bacterial agents isolated in PPP was 469, this number was 394 in PP. The isolation of *Escherichia coli, Acinetobacter baumannii* complex was significantly lower in the PP ($P<0.001$; $P=0.008$, respectively). Conversely, the isolation of *Enterococcus* spp. was higher during the PP ($P<0.001$). In the PP, the consumption of piperacillin-tazobactam, teicoplanin, meropenem and fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) were significantly higher ($P<0.001$; $P=0.016$; $P=0.016$; $P=0.02$; $P<0.001$; $P=0.018$, respectively) while that of cefazolin was significantly lower ($P<0.001$). Total antibiotic consumptions during the PPP and PP were 725.8 DDD / 1000 and 811.4 DDD / 1000 inpatient days, respectively ($P=0.002$).
Conclusions: Although bacterial agents isolated in PP were lower, antibiotics consumption was higher. The high positivity rate of *Enterococcus* spp. during the PP suggests that hand hygiene and contact isolation should be strictly observed, as this may be related to the inadequacy of hygiene practices.

Keywords: Covid-19, Culture, Infection, Antibiotic-resistance, Bacteria

How to cite: Hamidi AA, Yılmaz Ş. Antibiotic consumption in the hospital during COVID-19 pandemic and distribution of bacterial agents and antimicrobial resistance: A single-center study. J Surg Med. 2021;5(2):124-127.

Introduction

Antibiotic consumption has been increasing worldwide in recent years. The problem of antimicrobial resistance due to antibiotic consumption is one of the world's current problems that require urgent action. Consumption of carbapenem, polymyxin, and oxazolidinone antibiotics, used in the treatment of hospital-acquired infections caused by multidrug-resistant bacteria, is steadily increasing [1]. In addition, the rate of antimicrobial resistance development in bacteria is high [2, 3].

Coronavirus disease 2019 (COVID-19) appeared in Wuhan, China in December 2019 and caused a pandemic [4]. In Turkey, the first case was detected on March 11, 2020 and the number of cases continued to increase rapidly. On March 17, 2020, health authorities decided to defer elective surgeries, stop non-emergency hospitalizations, and minimize services offered at the outpatient clinics, so that healthcare services could be directed at the COVID-19 pandemic. In our center, which is a tertiary hospital, emergency surgeries and non-COVID-19 patient hospitalizations were continued in a separate department of the hospital while serving as a pandemic hospital.

Consumption of antibiotics used in the treatment of hospital-acquired infections may be affected, and there may be changes in the distribution of bacteria growing in culture and in the rates of antibiotic resistance during the COVID-19 pandemic. The present study was, therefore, conducted to compare antibiotic consumption and the distribution of bacteria growing in culture in our hospital before and during the COVID-19 pandemic.

Materials and methods

Our hospital, a tertiary university hospital, allocated 80% of its capacity for COVID-19 patients during the pandemic and 20% for emergency surgeries and emergency patient hospitalization. The hospital has 465 adult hospital beds and 52 adult intensive care beds. Non-COVID-19 patients were monitored in two separate services and a ten-bed intensive care unit while COVID-19 patients were followed up in eight services and in four ten-bed intensive care units. In the present study, blood, urine, bronchoalveolar lavage (BAL), sputum, and endotracheal aspirate (ETA) cultures analyzed in our hospital's microbiology laboratory between January 1, 2020 and April 30, 2020 were retrospectively evaluated. To prevent duplication, one sample from the same patient was included in the study according to urine, blood and respiratory samples. In this retrospective cohort study, the period between January 1 and February 29 was considered as the pre-COVID-19 pandemic period (PPP) while March 1 and April 30 was considered as the pandemic period (PP). Blood cultures were incubated for seven days in the automated blood culture system BACTEC FX 40 (Becton Dickinson, USA). The samples with growth signals were inoculated in 5% sheep blood agar, eosin methylene blue (EMB) agar, and chocolate agar and incubated at 37°C for 24–48 hours. Urine samples were inoculated in 5% sheep blood agar and EMB agar while BAL, sputum, and ETA samples were inoculated in 5% sheep blood agar, EMB agar, and chocolate agar and incubated at 37°C for 24–48 hours. Conventional methods and the Phoenix™ (Becton Diagnostics, USA) fully automated system were used to identify microorganisms with observed growth in their media. Antimicrobial susceptibility of active microorganisms was determined using Kirby–Bauer disk diffusion method, E-test (bioMérieux, France), and the Phoenix (Becton Diagnostics, USA) fully automated system, according to the European Committee on Antimicrobial Susceptibility Testing criteria. Carbapenem resistance in the group of *Enterobacteriaceae*, and vancomycin and teicoplanin resistance in the isolates of *Enterococcus* spp. were confirmed using the E-test stripes with gradient test method.

Bacteria that could be the causative agents of infection were classified as *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus* spp., and *Escherichia coli*. The strains of *Enterobacter* spp., *Serratia marcescens, Proteus* spp., and *Citrobacter* spp. were also classified as other gram-negative bacteria.

The amounts of antibiotics consumed were determined retrospectively at the hospital pharmacy between January 1 and April 30. Antibiotic consumption was calculated using the anatomical therapeutic chemical/defined daily dose (ATC/DDD) per 1000 inpatient days method determined by the World Health Organization. The amounts of antibiotics consumed and the antibiotic groups were compared between the PPP and PP.

Statistical analysis

Statistical Package for Social Sciences (SPSS) 15.0 (SPSS Inc.; Chicago, IL, USA) Windows program was used for statistical analysis of the data. Descriptive statistics were presented as mean, standard deviation, median, and minimum and maximum values, while chi-square test was used for categorical variables and Student's *t*-test was used for variables with normal distribution. Mann–Whitney U test was performed on continuous variables with non-normal distribution.

Results

During the two months before the COVID-19 pandemic, the total number of cultures requested at our hospital was 3,384, while this number dropped to 2,170 during the pandemic. The number of blood, urine and respiratory cultures requested during the PPP was 1051, 2174 and 159, respectively, which dropped to 956,1106 and 108, respectively, during PP. Among the cultures of blood, urine, and respiration (ETA, BAL, and sputum) samples studied, the most requested was urine culture, and the most frequently isolated agent was *E. coli* (Table 1). The positivity rates in different types of culture samples during the PPP and PP were also examined. In urine and blood cultures, the positivity rate of the causative agents during the PP was significantly higher than in the PPP ($P<0.001$; $P=0.012$ respectively). However, there was no significant difference between the PPP and PP in terms of the positivity rate of the causative agents in the respiratory samples (Table 2).

Table 1: Distribution of causative bacteria in urine, respiratory and blood cultures before and during COVID-19 pandemic periods (n)

Sample type	Date	*Escherichia coli*	*Klebsiella spp.*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii* complex	Other gram negative bacteria	*Staphylococcus aureus*	*Enterococcus spp.*	Total culture
		The numbers of isolated agents							
Urine	PPP*	206	55	16	-	25	-	27	2174
	PP**	135	44	8	-	15	-	41	1106
ETA-BAL-SPUTUM	PPP	2	16	12	14	6	5	-	159
	PP	4	10	17	4	2	5	-	108
Blood	PPP	14	17	6	5	7	12	24	1051
	PP	6	40	1	5	4	16	37	956
Total	PPP	222	88	34	19	38	17	51	3384
	PP	145	94	26	9	21	21	78	2170

*: Pre-pandemic period, **: Pandemic period

Table 2: Comparison of the numbers of causative agents in pre-pandemic and pandemic periods according to the sample types

Sample type	Pre-pandemic period (%)		Pandemic period (%)		*P*-value
	Positive	Negative	Positive	Negative	
Blood culture	8.1	91.9	11.4	88.6	0.012
ETA-BAL-SPUTUM culture	34.6	65.4	38.9	61.1	0.474
Urine culture	15.1	84.9	22.0	78.0	<0.001

The isolation of *E. coli*, *Acinetobacter baumannii* complex, and other gram-negative bacilli were significantly lower in the PP than in the PPP ($P<0.001$; $P=0.008$; $P=0.002$, respectively). However, *Enterococcus* spp. isolation rate was significantly higher during the PP than in the PPP ($P<0.001$). In other causative agents, there was no significant difference in terms of the isolation rates in both periods ($P>0.05$). Although there was a decrease in extended spectrum beta lactamases and carbapenem resistance in gram-negative bacteria, methicillin resistance in staphylococci, and vancomycin resistance in enterococci in the PP, there was no statistically significant difference between both periods ($P>0.05$) (Table 3).

In our hospital, 5941 (18330 patient days) and 3144 (11789 patient days) patients were hospitalized during the PPP and PP, respectively. When assessed according to the defined daily dose per 1000 inpatient days (DDD/1000 inpatient days), the total consumption of antibiotics was 725.8 DDD/1000 inpatient days in the PPP, and 811.4 DDD/1000 inpatient days during the PP ($P=0.002$). The amount of antibiotics consumed showed that the consumption of cefazolin and colistin was lower ($P<0.001$; $P=0.034$), while meropenem, piperacillin-tazobactam, teicoplanin, and fluroquinolone (ciprofloxacin, levofloxacin, and moxifloxacin) consumption was significantly higher ($P<0.001$; $P=0.016$; $P=0.016$; $P=0.02$; $P<0.001$; $P=0.018$, respectively) in the PP. The consumption of other antibiotics was similar in the two periods. The most consumed antibiotics in our hospital during the period covered in the present study were ceftriaxone, cefazolin, and meropenem (Table 4).

Table 3: Comparison of isolated bacteria and resistance rate in pre-pandemic and pandemic periods

Bacteria and resistance rate*	Pre-pandemic period	Pandemic period	*P*-value
Escherichia coli (n)	222	145	<0.001
- **ESBL (%)	40.5	35.2	
- Carbapenem resistance (%)	7.2	6.2	
Klebsiella spp. (n)	88	94	0.893
- ESBL (%)	68.2	64.9	
- Carbapenem resistance (%)	23.9	18.1	
Pseudomonas aeruginosa (n)	34	26	0.144
- Carbapenem resistance (%)	47.1	34.6	
Acinetobacter baumannii complex (n)	19	9	0.008
- Carbapenem resistance (%)	100	100	
Staphylococcus aureus (n)	17	21	0.359
- Methicillin resistance	17.6	14.3	
Enterococcus spp. (n)	51	78	<0.001
- Vancomycin resistance	2.0	1.3	
Other gram negative bacteria (n)	38	21	0.002
Total	469	394	<0.001

*: There was no significant difference between the two periods in terms of resistance rates, **: Extended spectrum beta-lactamases

Table 4: Antibiotic consumption in pre-pandemic and pandemic periods

Antibiotic lists	Pre-pandemic period *DDD/1000 inpatient-days	Pandemic period DDD/1000 inpatient-days	*P*-value
Colistin	11.7	5.4	**0.034
Imipenem	7.3	6.5	0.695
Ertapenem	6.6	10.4	0.303
Meropenem	65.1	86.4	0.016
Ceftriaxone	199.6	224.6	0.086
Ceftazidime	4.1	3.7	0.690
Cefazolin	148.7	101.9	**<0.001
Ampicillin sulbactam	50.7	43.4	0.243
Piperacillin tazobactam	35.5	63.6	<0.001
Vancomycin	36.5	35.6	0.869
Teicoplanin	5.2	11.6	0.016
Tigecycline	6.7	4.0	0.201
Intravenous Fosfomycin	5.7	6.0	0.657
Ciprofloxacin	33.5	49.1	0.02
Levofloxacin	25.6	53.7	<0.001
Moxifloxacin	43.6	60.0	0.018
Clarithromycin	33.8	34.3	0.863
Amikacin	9.0	11.6	0.355

*DDD: Defined daily dose, ** Significantly lower in the pandemic period

Discussion

In this study, although the number of cultures requested at our hospital laboratory were lower during the PP, the rate of the causative agents isolated in blood and urine cultures were significantly higher. The positivity rate of blood culture varies from 5%–10% in the literature. Positivity rate decreases as a result of performing blood cultures from inappropriate patients at inappropriate times and in non-sterile conditions. Additionally, false positives are also detected as a result of contaminations [5-7]. In our study, the positivity rate in blood culture in the PP (11.4%) was significantly higher compared to that of the PPP (8.1%). When performing blood culture during the PP, paying more attention to sterile conditions and obtaining cultures when really needed can be effective in identifying correct rates. We believe that the increase in the positivity rates of urine culture was because the majority of outpatient clinics were closed in the PP and the samples were usually requested for inpatients.

The present study shows that *A. baumannii* strains, which are important nosocomial agents during the PPP, was significantly lower in the PP. *A. baumannii* is a gram-negative coccobacilli that cause a wide range of hospital-acquired infections in the respiratory tract, urinary system, soft tissues, and wounds. The most important infections caused by *A. baumannii* are ventilator-associated pneumonia and catheter-related bloodstream infection, which have high mortality rates. It has an important role among the causative agents of multidrug-resistant hospital-acquired infections in Turkey [8-10]. While the positivity rate of this bacterium reduced in our hospital during the PP, it was observed that the positivity rate of *K. pneumoniae*, another causative agent of nosocomial infection, insignificantly increased. There was a significant decrease in the detection of *E. coli*, which is probably because it is the most common causative agent of community-acquired urinary tract infections and that most outpatient clinics were closed.

Another agent with a significant increase in positivity in the PP compared to the PPP was enterococci. Enterococci cause bloodstream and urinary tract infections that often develop in hospital settings, and these bacteria have recently gained increasing importance due to vancomycin resistance [11-13]. In our study, *S. aureus*, one of the other important gram-positive bacteria, also increased, albeit insignificantly, in positivity. In order to limit the spread of gram-positive infections within hospitals, healthcare workers have to comply with the preventive measures of hand hygiene and isolation. In addition, the use of some antiseptics, such as chlorhexidine bath, has been found useful in patient care [14, 15]. We believe that healthcare workers used gloves more often than usual and reduced hand hygiene compliance during the PP. We also believe that using double-layered gloves complicates the hand hygiene compliance. Considering that 80% of the cases hospitalized during the PP were COVID-19, it was thought that 80% of the reproductive agents could indicate secondary bacterial infections developed in COVID-19 cases. Likewise, 80% of the antibiotics consumed in the hospital during the PP may be due to the secondary bacterial infections. In a multicenter study conducted in Turkey, antibiotic consumption was 674.5 DDD/1000 inpatient-days in hospitalized patients [16]. In another multicenter study in Switzerland, antibiotic consumption in hospitalized patients was 46.1 - 54.0 DDD / 100 patient bed-days [17]. In our study, the total consumption of antibiotics was 725.8 DDD/1000 inpatient-days in the PPP, and 811.4 DDD/1000 inpatient-days in the PP. Our data was similar to Turkey-wide data. Teicoplanin and piperacillin-tazobactam used against gram-positive bacteria were consumed in greater quantities during the PP, which we believe may also be associated with increased positivity rate of *Enterococcus* spp. and *S. aureus*. In addition, fluoroquinolone consumption increased during the PP in our hospital. Clinical and radiological findings of patients with SARS, Hantavirus, and other viral pneumonia are similar to atypical pneumonia [18]. Hospitalization and monitoring of atypical pneumonia cases with suspected COVID-19 by administering fluoroquinolones therapy during the PP may be an important reason for this finding. The use of antibiotics is the primary factor in the development of bacterial resistance. Common and extensive use of antibiotics leads to the selection of multidrug-resistant bacteria [19, 20]. In study previously conducted by Guclu et al. [16] it was found that at least one antibiotic was used in one of every two patients hospitalized. Additionally, in the said study, carbapenems, cephalosporins, and quinolones were the most used antibiotics in hospitals. Similarly, the consumption of meropenem, cefazolin and ceftriaxone were highest in the present study. The consumption of cefazolin was significantly lower during the PP. Cefazolin is mostly used as a surgical prophylaxis. Since routine surgery was not performed in PP, cefazolin consumption was low in this period. Also, colistin, which is used in *Acinetobacter* infections, is lower in PP because *Acinetobacter* spp. was lower in the same period. Although insignificant, there was a reduction of the resistance rates in gram-negative bacteria during the PP.

One of the limitations of our study is its monocentric design that covers only a brief period i.e., the months in which the pandemic was highly intense in our province. The other limitation is the lack of enough clinical and demographic features about patients. In fact, it has not been determined how much of the evaluated cultures and consumed antibiotics belonged to COVID-19 patients.

Conclusions

The present study showed that the positivity rates of *A. baumannii* and *E. coli* was lower in the blood, urinary, and respiratory tract cultures while *Enterococcus* spp. was significantly higher during the PP. Since the increase of enterococci, which are among the gram-positive bacteria, may be associated with non-adherence to hand hygiene, it is necessary to pay more attention to hand hygiene during the PP. We believe that the increasing detection of causative agents in contrast to the decreasing number of urine and blood culture positivity rates may be associated with unnecessary culture requests during the PPP. Another important result of the study was the high consumption of fluoroquinolones, piperacillin tazobactam, meropenem and teicoplanin in PP compared to PPP. Although fewer pathogens were detected in the PP compared to the PPP, the total antibiotic consumption was higher. This indicates the excess of secondary bacterial infection in COVID-19 cases or the habit of physicians to use antibiotics. This issue needs to be clarified with further and multi-center studies.

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