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Coronavirus Pandemic

Impact of the COVID-19 pandemic on antibiotic utilization in a tertiary hospital

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Abstract

Introduction: This study aimed to determine the use of antimicrobial drugs during the second year of the coronavirus disease 2019 (COVID-19) pandemic, and evaluate the pandemic's impact on antibiotic use by comparing with the pre-pandemic period.

Methodology: The study was a retrospective point prevalence study. Patients aged ≥ 18 years, who received antibiotics in our hospital between 11 February 2020. and 3 January 2022 were evaluated. The antibiotics were categorized according to the 2021 Access/Watch/Reserve (AWARe) classification. Compliance with recommendations from infectious diseases (ID) physicians, and reasons for inappropriate treatment were evaluated.

Results: Among the hospitalized patients, 323 (36.4%) during the pre-pandemic days (PPD), and 361 (50.1%) during pandemic days (PD), used at least one antimicrobial drug ($p < 0.001$). The most frequently used antibiotics during PPD and PD were piperacillin, tazobactam, and imipenem/meropenem. The use of the "Access" group antibiotics decreased in the PD, while the use of the "Watch" and "Reserve" groups increased ($p = 0.034$). There was 100% (n = 209) compliance with ID consultation in the PPD, and 91.9% (n = 227) in the PD ($p < 0.001$). In the PPD, 64 (19.8%). of the treatments received by inpatients were inappropriate, and during the PD 100 (27.7%) were inappropriate ($p = 0.016$).

Conclusions: The pandemic led to an increase in the overuse and inappropriate use of antimicrobial drugs, particularly in the Watch and Reserve groups, in both COVID-19 and non-COVID-19 clinics. There was a notable transition towards the increased utilization of broad-spectrum antibiotics during the pandemic.

Key words: antibiotics; COVID-19 pandemic; inappropriate drug use.

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Introduction

The global occurrence of the coronavirus disease 2019 (COVID-19) pandemic has resulted in an upsurge in the consumption of antibiotics worldwide. According to reports, during the initial phases of the pandemic, up to 70% of patients with COVID-19 were administered antibiotics [1]. Although numerous studies have indicated a relatively low incidence (< 20%) of bacterial infections as a secondary effect of COVID-19, the necessity for hospitalization and the severity of the disease often dictated the empirical use of antibiotics [2–5]. However, the utilization of antibiotics in non-COVID-19 patients and the pandemic's impact on other hospitalized individuals remain unclear.

The World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines developed the AWARe (Access, Watch, Reserve) classification in 2017, which was further updated in 2021 [6]. This classification serves as a valuable tool for monitoring antibiotic consumption and plays a vital role in promoting antimicrobial stewardship.

In the present study, our primary aim was to comprehensively examine and analyze the distribution patterns of antimicrobial drugs administered across different categories outlined by the AWARe classification. By conducting a comparative analysis, we sought to evaluate and compare the distribution trends of these drugs prior to the emergence of the COVID-19 pandemic and during its second year. This investigation aimed to provide valuable insights into any potential shifts or changes in the utilization of antimicrobial drugs over time, particularly in the context of the pandemic's impact. Ultimately, our objective was to contribute to a deeper understanding of the evolving landscape of antimicrobial consumption

and its implications in both the pre-pandemic and pandemic periods.

Methodology

Study design

Our study was designed as a retrospective point prevalence study and followed the guidelines and recommendations set forth by WHO for such studies on antibiotic use in hospital settings [7].

Setting

The study included patients who were admitted to our hospital at two specific time points: 11 February 2020, prior to the onset of the COVID-19 pandemic (pre-pandemic day; PPD), and 3 January 2022, during the second year of the COVID-19 pandemic (pandemic day; PD).

Participants

The inclusion criteria were patients aged ≥ 18 years and who received a minimum of one antimicrobial agent. Patients who were already admitted to the hospital on or before 08:00 AM. on the specified days were included, while those hospitalized after 08:00 AM. on the specified days were excluded. Antimicrobial treatments that were recommended on or before 08:00 A.M. were included, while any modifications or additions made to the treatment after 08:00 A.M. were not considered for inclusion in the study.

Data collection

The data were retrieved through the patient files and the electronic system in the hospital. The gender, age, wards where they were followed-up, COVID-19 infection status, length of stay in the hospital, and antimicrobial medications were recorded. The wards were categorized as medical wards (internal medicine, neurology, dermatology, cardiology etc.), surgical wards (general surgery, cardiothoracic surgery, neurosurgery, otolaryngology, obstetrics and gynecology, orthopedics etc.), intensive care unit (ICU), COVID-19 clinics/ICUs, and the wards with high risk for infectious diseases (hematology, oncology, bone marrow transplant unit, burn unit, infectious diseases clinic).

Antimicrobial agents included

Oral and parenteral antimicrobial agents were included in the study; topical and ophthalmic antimicrobial agents were not included. The name of the antimicrobial agents used, route of administration, dose and duration of use, and reasons of modification, if any, were recorded. Due to the intermittent shortages of imipenem and meropenem in the hospital formulary in the pandemic period, the two antibiotics were recorded together as a single block.

Stratification of antimicrobial treatment

Antimicrobial treatment was categorized as empirical in the absence of culture data or targeted initiation if it was based on culture results. Antimicrobial agents given for prophylaxis without infection were also recorded. Antibiotics were categorized according to the 2021 update of the AWARe classification developed by the WHO Expert Committee on the Selection and Use of Essential Medicines [6]. This classification system involves the division of antibiotics into three distinct groups: Access, Watch, and Reserve. The classification takes into consideration the impact of different antibiotics and antibiotic classes on antimicrobial resistance, highlighting the importance of their appropriate and responsible use.

a) The "Access" group denotes antibiotics that are the recommended choice for the 25 most common infections. These antibiotics should be readily available, affordable, and of assured quality.

b) The "Watch" group comprises the majority of the "highest-priority critically important antimicrobials". These antibiotics are recommended for specific and limited indications only.

c) The "Reserve" group consists of antibiotics designated for use as a last resort when all other antibiotics have proven ineffective.

d) Drugs such as antiviral, antifungal, and anti-tuberculosis are not included in the three groups mentioned and are in the unclassified group.

Infectious diseases (ID) consultations

Our patients were attended to by ID physicians who had extensive expertise of over 20 years in the field of ID.

Rationale of treatment

The study included recording the adherence to ID consultant's recommendations, documenting cases of inappropriate treatments, and capturing the reasons behind them. The appropriateness of antibiotic therapy was assessed by a team of ID physicians based on current guidelines [8–14].

Table1. Demographic characteristics of patients who received antimicrobial agents on the study dates.

	PPD 11 February 2020	PD 3 January 2022	*p**
Demographic features			
Age in years, median (IQR)	60 (40–71)	60 (40–73)	0.66
Gender (Female/Male)	140/183	152/209	0.74
Length of hospital stay, day, median (IQR)	6 (3–14)	8 (3–16.5)	0.014
Duration of antimicrobial use, day, median (IQR)	4 (2–8)	4 (1.25–9)	0.013

*Chi-Square and Mann Whitney-U test is used. PD: pandemic day; PPD: pre-pandemic day.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS; IBM; Chicago, IL) version 23 software package. Distribution of continuous data was described by median and interquartile ranges (IQR) and categorical data by number and percentage. The conformity of continuous variables to normal distribution was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for two-group comparisons of continuous variables, and the Kruskal-Wallis test was used for multi-group comparisons. The Chi square test was used to compare categorical variables between groups. The level of statistical significance was accepted as $p < 0.05$.

Ethics approval

Our study was approved by the ethics committee of our hospital, ensuring compliance with ethical standards and guidelines. (Dated 16.12.2022, with reference number 46418926 and decision number 2022/02-37).

Results

Overall antibiotic usage

A total of 887 adult patients were hospitalized in our hospital on PPD, with 323 of them (36.4%) receiving antimicrobial agents. There were 720 adult patients on PD, out of which 102 were admitted to the COVID-19 clinic or COVID-19 ICU. Among the PD patients, 361 (50.1%) received at least one antimicrobial drug. Detailed information regarding the demographic characteristics, length of stay, and antibiotic usage of the patients are summarized in Table 1.

In comparison to PPD, the rate of antimicrobial drug use was higher on PD, accompanied by longer mean lengths of stay, durations of antimicrobial use, and higher rate of parenteral antibiotic use ($p < 0.001$, $p = 0.014$, $p = 0.013$, and $p < 0.001$, respectively). Furthermore, it was observed that the rate of empirical revision increased on PD due to clinical unresponsiveness ($p = 0.003$) (Table 2).

Table 2. Antimicrobial usage of patients on study dates.

	PPD 11 February 2020		PD 3 January 2022		*p**
	n	%	n	%	
Hospitalized patients					
Non-COVID-19 clinics	887	100	618	85.8	
COVID-19 clinic/ICU	-	-	102	14.2	
Patients receiving antimicrobial agents					
Non-COVID-19 clinics	323	36.4	314	50.8	
COVID-19 clinic/ICU	-	-	47	46	
Total	323	36.4	361	50.1	< 0.001
Monotherapy	191	59.1	224	62	0.43
Combined therapy	132	40.9	137	38	
Route of administration					
Oral	160	31.8	108	19.4	< 0.001
Parenteral	343	68.2	449	80.6	
Clinics					
Medical clinics	117	23.3	80	14.4	
Surgical clinics	168	33.4	201	36,1	
High-risk clinics	138	27.4	94	16.9	< 0.001
ICUs	80	15.9	11	19.9	
COVID-19 clinic and ICU	-	-	71	12.7	
Antibiotic modification					
No modification	383	76.1	376	68	
Empirical revision after clinical non-response	53	10.5	98	17.6	
Targeted revision after culture result	56	11.1	63	11.3	0.003
Transition from prophylaxis to treatment	7	1.4	4	0.7	
Switching to oral therapy	2	0.4	7	1.3	
Allergy/adverse effect	2	0.4	6	1.1	

*Chi square test was used.COVID-19: coronavirus disease 2019; ICU: intensive care unit; PD: pandemic day; PPD: pre-pandemic day.

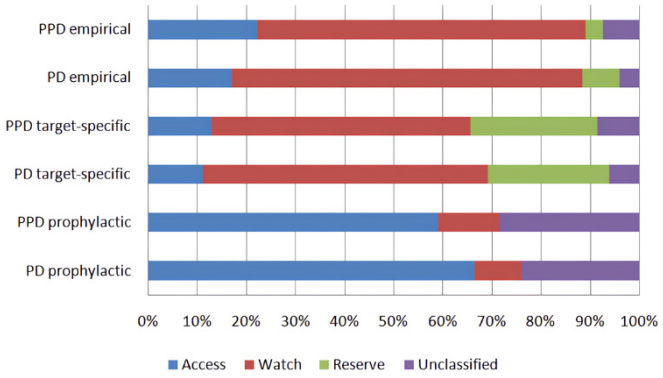
Stratification according to AWARe classification

In terms of the AWARe classification, when categorizing the antimicrobials used on both the PPD and PD, it was found that on PPD, 170 antimicrobials (33.8%) belonged to the "Access" group, 231 (45.9%) belonged to the "Watch" group, 27 (5.4%) were categorized as "Reserve,", and 75 (14.9%) were in the unclassified group. On the other hand, on PD, 162 antimicrobials (29.1%) were in the "Access" group, 297 (53.3%) were in the "Watch" group, 45 (8.1%) were categorized as "Reserve,", and 53 (9.5%) were in the unclassified group. A statistically significant difference was observed, indicating a decrease in the usage of antibiotics in the "Access" group and an increase in the "Watch" and "Reserve" groups ($p = 0.034$). A detailed breakdown of initiation of antibiotherapy according to the AWARe classification is presented in Table 3. Additionally, considering the usage patterns, there was a decrease in empirical use in the "Access" group, while an increase was observed in the "Watch" and "Reserve" groups (Figure 1).

Antimicrobial selection

Piperacillin tazobactam emerged as the most frequently utilized antibiotic on both PD and PPD, with 57 patients (11.3%) on PPD and 70 patients (12.6%) on PD receiving this medication. Following closely, meropenem/imipenem was the second most commonly prescribed antibiotic, with 42 patients (8.3%) on PPD and 52 patients (9.3%) on PD. Notably, ceftriaxone was the third most frequently used antibiotic on PPD, administered to 29 patients (5.8%), while fluoroquinolones took the third spot on PD, given to 45 patients (8.1%). The utilization of antibiotics in various clinics based on the AWARe classification is detailed in Table 4.

Figure 1. Distribution of antibiotics according to initiation type in AWARe classification.



AWARe: Access, Watch, Reserve; PD: pandemic day; PPD: pre-pandemic day.

Compliance with ID consultations

On PPD, 209 patients (64.7%) were consulted by an ID physician, and the compliance rate with the consultation recommendations reached 100%. In contrast, on PD, 247 patients (68.4%) received consultations from ID physicians, and the compliance rate with the consultation recommendations was 91.9% (n = 227; $p < 0.001$).

Inappropriate antimicrobial treatment

Upon evaluating the appropriateness of antibiotherapy on PPD and PD, it was found that 64 patients (19.8%) on PPD and 100 patients (27.7%) on PD were receiving inappropriate treatment. This

Table 3. Distribution of antibiotics used in treatment on the study dates according to the AWARe classification.

Date	Type of therapy	Access		Watch		Reserve		Total		*p**
		n	%	n	%	n	%	n	%	
PPD	Empirical	57	18.9	172	57	9	3	238	78.8	
	Target-specific	9	3	37	12.3	18	6	64	21.2	
PD	Empirical	56	14.2	236	60.1	25	6.4	317	80.7	
	Target-specific	9	2.3	47	12	20	5.1	76	19.3	
Total	PPD	66	21.9	209	69.2	27	8.9	302	100	
	PD	65	16.5	283	72	45	11.5	393	100	0.034

*Chi square test was used.AWARe: Access, Watch, Reserve; PD: pandemic day; PPD: pre-pandemic day.

Table 4. The most common use of antibiotics in clinics according to AWARe classification on the pre-pandemic and the pandemic day.

Date		Medical clinics	Surgical clinics	High risk clinics	ICU	COVID-19 clinic/ICU
PPD	Access	Amoxicilin clavulanate	Ampicilin sulbactam	Ampicilin sulbactam	Amikacin	-
	Watch	Piperacilin Tazobactam	Piperacilin tazobactam	Piperacilin Tazobactam	Piperacilin Tazobactam	-
	Reserve	Tigecycline	Linezolid	Linezolid	Linezolid	-
PD	Access	Ampicillin sulbactam	Ampicillin sulbactam	Metronidazole	Amikacin	-
	Watch	Ceftriaxone	Ceftriaxone	Piperacillin Tazobactam	Carbapenem	Fluoroquinolone
	Reserve	Daptomycin/Linezolid	Tigecycline/Linezolid	-	Tigecycline	Linezolid

COVID-19: coronavirus disease 2019; ICU: intensive care unit; PD: pandemic day; PPD: pre-pandemic day.

indicated an increase in the rate of inappropriate treatment on PD compared to the PPD ($p = 0.016$). The most prevalent reason for inappropriateness on both days was the prolonged duration of antibiotic use ($p = 0.2$) (Table 5).

Discussion

The advent of the COVID-19 pandemic had an immediate and severe impact on the society and the healthcare system, disrupting antimicrobial management programs and leading to excessive antibiotic consumption [15–17]. In our study, we observed a significant surge in the rate of antimicrobial drug use during PD compared to PPD, particularly in ICUs. Notably, a previous point prevalence study conducted in our hospital in 2012 did not demonstrate a substantial increase in antibiotic use over an eight-year period prior to the pandemic [18]. However, with the onset of the pandemic, a significant rise in antimicrobial consumption was observed across both COVID-19 and non-COVID-19 clinics. These findings align with existing literature, which consistently reports an increase in antibiotic consumption associated with the pandemic [19–21].

In our study, we found that half of the COVID-19 patients were prescribed antibiotics. This aligns with a meta-analysis conducted by Langford *et al*., which evaluated antibiotic use in COVID-19 patients during the first six months of the pandemic and reported a prevalence rate of 74.6% [1]. Similarly, Şencan *et al.* conducted a multicenter point prevalence study in Turkey during the early stages of the pandemic, revealing that three-fourths of hospitalized COVID-19 patients were receiving antibiotics [5]. These findings lead us to conclude that antibiotic use decreased in the later stages of the pandemic compared to the initial phases. However, despite the relatively low rates of bacterial infections ranging from 1.2% to 7% among COVID-19 patients, the high rates of antibiotic usage indicate inappropriate and excessive use [22,23].

In our study, the ranking of the most commonly used antibiotics differed between the PPD and the second year of the pandemic. In the PPD, piperacillin-tazobactam, imipenem/meropenem, and ceftriaxone were the top three antibiotics. However, in the second year of the pandemic, piperacillin-tazobactam, imipenem/meropenem, and levofloxacin took the lead. The International Infectious Diseases – International Research Initiative (ID-IRI) study also supported the prevalence of piperacillin-tazobactam as the most frequently used antibiotic during the pandemic period [24]. Interestingly, the increase in the use of quinolones was observed mainly in Turkey in this study. In line with these findings, our study also revealed the frequent use of quinolones during the pandemic period, with an increase in the usage of fluoroquinolones, consistent with findings from other studies [25,26]. The shift towards levofloxacin was likely influenced by its broad spectrum of coverage for pulmonary infections [10].

Between 2005 and 2013, various studies conducted in multiple centers across our country revealed that the most frequently utilized antibiotics were first and third-generation cephalosporins and ampicillin-sulbactam [27–30]. Additionally, a point prevalence survey conducted in 2012 and reported that cephalosporins and quinolones were the most commonly prescribed antibiotics [18]. Over time, there has been an observed increase in the utilization of piperacillin-tazobactam and carbapenems in our hospital prior to the pandemic, and this trend has persisted during the pandemic period.

Our study found a decrease in the utilization of antibiotics categorized under the "Access" group, but a notable increase in the usage of antibiotics from the "Watch" and "Reserve" groups, according to the AWARe classification system. WHO introduced this classification in the 2017 Essential Medicines Model List to promote optimal antibiotic management and usage. WHO recommended that 60% of community-level antibiotics use should fall under the "Access" group [31,32]. In the PPD, the initiation of "Reserve" group antibiotics was primarily based on culture results.

Table 5. Consultation and inappropriate treatment status in the pre-pandemic and the pandemic days.

	PPD		PD		*p**
	11 February 2020		3 January 2022		
	n	%	n	%	
Presence of consultation	209	64.7	247	68.4	0.3
Compliance rate with consultation	209	100	227	91.9	<0.001
Inappropriate treatment	64	19.8	100	27.7	0.016
Causes of inappropriate treatment					
Prolonged duration	45	70.3	55	55	0.2
Inappropriate dose	0	0	4	4	
Different antibiotics use	3	4.7	5	5	
Extra added antibiotics	3	4.7	10	10	
Use without indication	13	20.3	26	26	

Chi square test was used.PD: pandemic day; PPD: pre-pandemic day.

However, in the PD, there was a more significant increase in the empirical use of these antibiotics. In our center, due to rising carbapenem resistance rates and the lack of standardized methods for tigecycline, fosfomycin, and colistin susceptibility testing; the empirical use of antibiotics from the "Reserve" group became necessary. Despite the high rates of resistance, it is important to limit the use of these antibiotics for non-critical patient groups and base their usage on culture results whenever possible. Rational use of antibiotics should be prioritized, and inappropriate use should be avoided [33,34].

On both the PPD and PD, approximately two-thirds of patients receiving antibiotic treatment were referred to ID physicians. However, a significant decrease in compliance with ID consultation recommendations was observed after the onset of the pandemic. Numerous studies have emphasized the critical importance of ID physician consultations in the clinical management of patients [35]. Despite the increased workload of ID physicians during the pandemic, the consultation service was maintained at a similar level as in the previous period. However, compliance with treatment recommendations experienced a significant decline within the hospital. Consequently, there was a notable increase in the rate of inappropriate treatment. A meta-analysis encompassing point prevalence studies conducted in our country between 2004 and 2020 revealed that the median rate of inappropriate treatment was 36% [36]. Moreover, in our hospital, the rate of inappropriate treatment in 2012 was documented as 44.3% [18]. Although there was initially a decrease in the rate of inappropriate treatment before the pandemic, it steadily increased with the advent of the pandemic.

Despite the absence of comprehensive evidence-based data on antimicrobial resistance (AMR), the impact of the COVID-19 pandemic and excessive antibiotic consumption on AMR remains unclear [37]. Some studies have reported an increase in infections caused by multi-drug resistant (MDR) microorganisms [38,39], while others have found no significant rise in infections caused by MDR bacteria or fungi [23]. AMR poses a significant threat to global public health [40]. Although our study's specific contribution to the trend of AMR is uncertain, it is evident that antibiotic consumption has increased during the COVID-19 pandemic both in our country and worldwide. The undesirable consequences of this surge in antibiotic use are likely to contribute to the existing AMR problem.

A limitation of this study is that it represents a specific point in time rather than an extended period, due to its nature as a point prevalence study. However, the fact that the study was conducted in the same reference hospital, comparing antibiotic consumption before and during the pandemic, clearly highlights the impact of the pandemic on antibiotic usage.

Conclusions

Our study findings shed light on an alarming trend, indicating a concerning increase in the rate of inappropriate treatment, coupled with a decline in compliance with ID consultation recommendations. This highlights a critical issue that warrants immediate attention and underscores the importance of emphasizing the significance of adhering to ID consultants' recommendations in effectively managing patients. Accordingly, the observed decrease in compliance with ID consultation recommendations is a cause for concern, as these consultations play a vital role in ensuring appropriate and targeted antimicrobial therapy. Collaborating with ID specialists is crucial for optimizing patient outcomes, preventing the development of AMR, and promoting effective infection control practices. In addition, it is crucial to acknowledge the significant impact of the COVID-19 crisis, which may have disrupted the implementation of strategies aimed at combating AMR. Therefore, it is more important than ever to recognize and emphasize the essential role of antimicrobial stewardship programs. These programs play a pivotal role in mitigating unnecessary antibiotic use, preventing the emergence and spread of AMR, and preserving the efficacy of available antibiotics. To address the escalating issue of inappropriate treatment and the subsequent potential for AMR, a comprehensive and multidisciplinary approach is required. This includes fostering collaboration between healthcare providers, implementing robust antimicrobial stewardship initiatives, promoting education and awareness regarding appropriate antibiotic use, and adopting evidence-based guidelines for antimicrobial therapy.

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