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Antibiotic use during the first 6 months of COVID-19 pandemic in Iran: A large-scale multi-centre study

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Abstract

What is known and objective: Although antibiotics are ineffective against viral infections, epidemiological studies have revealed that the COVID-19 pandemic resulted in the overuse of antibiotics and disruption of antimicrobial stewardship programmes. We investigated the pattern of antibiotic use during the first 6 months of the COVID-19 pandemic in Iran.

Methods: A multi-centre retrospective study was designed to investigate the use of 16 broad-spectrum antibiotics in 12 medical centres. The rate of antibiotic use was calculated and reported based on the Defined Daily Dose (DDD) per 100 hospital bed-days. The bacterial co-infection rate was also reported.

Results and discussion: Totally, 43,791 hospitalized COVID-19 patients were recruited in this study. It was found that 121.6 DDD of antibiotics were used per 100 hospital bed-days, which estimated that each patient received approximately 1.21 DDDs of antibiotics every day. However, the bacterial co-infections were detected only in 14.4% of the cases. A direct correlation was observed between the rate of antibiotic use and mortality ($r[142] = 0.237$, $p = 0.004$). The rate of antibiotic

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consumption was not significantly different between the ICU and non-ICU settings ($p = 0.15$).

What is new and conclusion: In this study, widespread antibiotic use was detected in the absence of the confirmed bacterial coinfection in COVID-19 patients. This over-consumption of broad-spectrum antibiotics may be associated with increased mortality in hospitalized COVID-19 patients, which can be an alarming finding.

KEYWORDS
antibiotic, COVID-19, microbial resistance, mortality, SARS-COV-2

1 | INTRODUCTION

In December 2019, the world encountered a new viral infection, COVID-19, which spread rapidly and caused a pandemic.[1] Experiences from the H1N1 influenza pandemic in 2009 that indicated the high rate (34%) of secondary bacterial infections in patients admitted to the intensive care unit (ICU) and the high rate of morbidity and mortality in these patients, led to the empirical antimicrobial treatment in cases with COVID-19 pneumonia in the early days of the pandemic.[2,3] However, a few months later, serious concerns arose about the irrational use of antibiotics and the development of antimicrobial-resistant pathogens, which was a critical issue along with other worldwide consequences of the COVID-19 pandemic.[4–9]

The current multi-centre study was conducted to evaluate the pattern of broad-spectrum antibiotic use in hospitalized COVID-19 patients during the first 6 months of the COVID-19 pandemic in Iran.

2 | MATERIALS AND METHODS

2.1 | Patients and settings

In a multi-centre retrospective study, the antibiotic consumption rate was assessed in the hospitalized patients with COVID-19 during the first 6 months of the pandemic in Iran (February 20 to July 31, 2020, based on the calendar months of the solar year according to the national official data registration).

Twelve tertiary teaching medical centres (MC1–MC12) from seven provinces were included, and the relevant data (number of hospitalized COVID-19 patients, mortality rate, number of bed-days, antibiotic defined daily dose (DDD), and DDD per 100 bed-days) were collected from each centre. The rate of broad-spectrum antibiotic use in hospitalized COVID-19 patients in these MCs was calculated and reported based on DDD for each antibiotic according to the Anatomical Therapeutic Chemical (ATC)/DDD list, which is published by the WHO Collaborating Centre for Drug Statistics Methodology.[10] In the next step, the calculated doses of antibiotics based on DDD were adjusted per 100 bed-days, which is called the antibiotic consumption index (ACI) in this study. To calculate mortality rate, only the deaths that occurred after the first 24 hours of admission were considered.

The study population included all COVID-19 hospitalized patients whose diagnosis was based on either a positive SARS-COV2 PCR of the nasopharyngeal swab or the presence of clinical symptoms and radiological findings consistent with the disease. Cases under 18 years of age, discharged from the emergency room, or discharged or died within 24 h of hospitalization were excluded.

All systemic broad-spectrum antibiotics used for COVID-19 patients in the general wards and ICUs were considered in this study, including colistin, imipenem/cilastatin, meropenem, vancomycin, amikacin, gentamicin, linezolid, clindamycin, cefepime, ceftazidime, cefixime, ceftriaxone, piperacillin/tazobactam, azithromycin, ciprofloxacin, and levofloxacin.

In addition, data on the prevalence of identified bacterial infections (co-infections and/or secondary infections) were collected.

2.2 | Ethical consideration

The study was approved by the Research Ethics Committee of National Institute for Medical Research Development (NIMAD) (Approval number: IR.NIMAD.REC.1399.135).

2.3 | Data collection

The required data (drug name, strength, and dosage forms; antibiotic cost; number of hospital bed-days; mortality rate; and length of hospital stay [LOS]) were obtained from the hospital information system (HIS) and pharmaceutical care unit (PCU) in each MC and recorded in prepared Microsoft Excel software. To standardize the process of data collection and calculation, a pilot study was carried out in MC1. The extracted data were collected in a template format and sent to all centres after the rearrangement of data and calculation. To ensure data collection consistency, the key information, including concepts, calculations, and data entry in the format file was explained to the representatives of the centres through a virtual session. The information was also provided to the centres in the form of a PDF file (Appendix).

TABLE 1 Total antibiotic consumption, length of hospital stay, and rate of mortality during the first 6 months of COVID-19 pandemic in each 12 included MCs in total and by ward and ICU

Medical centres	Setting	Total ACI per month						ACI median (IQR)	LOS median (IQR) (day)	Rate of mortality median (IQR) (%)
		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6			
MC1	Ward	293.9	86.7	115.9	100.1	85.5	67.0	93.4 (80.9–160.4	5.27 (4.8–5.8)	8.24 (3.2–10.76)
	ICU	103.4	155.8	582.6	865.4	123.3	187.0	171.4 (118.3–653.3)	10.74 (8.2–12.1)	54.43 (41.46–62.78)
	Total	162.9	117.0	239.5	249.3	97.8	107.8	139.9 (105.3–241.9)	6.07 (5.9–7.3)	19.18 (13.13–21.91)
MC2	Ward	120.5	280.2	120.4	185.8	130.8	153.2	142 (120.5–209.4)	18.15 (11.3–28.75)	8.2 (6.9–10.38)
	ICU	190.3	260.1	175.5	566.6	397.8	460.7	329 (186.6–487.2)	5.7 (3.3–19.4)	35.6 (30.42–53.35)
	Total	130.8	277.3	132.3	228.8	169.7	182.5	176.1 (131.9–240.9)	13.64 (8.9–23.7)	17.6 (14.09–20.33)
MC3	Ward	624.2	12.1	25.5	84.4	19.0	17.2	22.2 (15.9–219.4)	3.53 (3–3.9)	4.24 (2.89–5.5)
	ICU	83.2	59.1	107.0	138.8	48.9	71.8	77.5 (56.5–115)	5.04 (4.6–5.7)	29.5 (26.75–31.24)
	Total	193.7	46.7	87.5	126.5	41.0	59.3	73.4 (45.3–143.3)	4.5 (4.25–4.9)	21.38 (19.46–22.9)
MC4	Ward	197.7	158.4	78.8	13.6	79.8	46.0	79.3 (37.9–168.2)	4.4 (3.75–5.45)	1.25 (0.45–1.85)
	ICU	56.2	9.0	21.5	12.4	60.9	23.0	22.2 (11.5–57.4)	6.6 (5.7–7.3)	19 (10.25–20.12)
	Total	169.7	123.1	62.4	13.1	76.3	39.2	69.3 (32.7–134.7)	4.85 (4–5.6)	3.45 (2.77–5.98)
MC5	Ward	620.2	405.0	474.5	428.0	400.4	512.7	451.2 (403.8–539.6)	4.2 (4–4.7)	4.15 (3.17–8.17)
	ICU	378.3	357.6	395.8	410.7	447.9	452.8	403.2 (373.1–449.1)	5.9 (5.15–6.4)	34 (31.5–37)
	Total	448.8	375.9	427.2	418.0	426.7	479.4	427 (407.5–456.4)	5.2 (4.9–5.35)	19.6 (18–23.3)
MC6	Ward	123.1	49.1	123.1	70.5	40.0	33.7	59.8 (38.4–123.1)	4.45 (3.8–5)	1.85 (0.85–2.75)
	ICU	130.0	106.1	94.6	106.7	86.7	68.6	100.3 (82.1–112.5)	6.55 (4.6–7.65)	50.9 (45.7–56.5)
	Total	124.2	61.0	116.1	78.7	68.7	41.4	73.7 (56.1–118.1)	4.76 (3.9–5.9)	9.7 (8.7–16.9)
MC7	Ward	86.3	128.0	255.3	65.3	249.1	178.6	153.3 (81.1–250.6)	5.4 (4.85–6.6)	9.4 (5.9–20.7)
	ICU	229.9	48.9	123.2	146.5	174.4	147.3	146.9 (104.6–188.2)	6.05 (5–7.4)	48.85 (44.4–51.85)
	Total	110.9	107.0	211.4	98.9	233.0	170.5	140.7 (104.9–216.8)	5.42 (5.1–6.5)	23.9 (13.5–28.5)
MC8	Ward	209.4	83.0	71.7	72.3	79.5	77.3	78.4 (72.2–114.6)	5.25 (4–7)	2.4 (1.4–10.35)
	ICU	174.4	68.6	129.0	102.2	89.5	71.5	95.9 (70.8–140.3)	7.35 (7–8)	53.9 (44.75–61.1)
	Total	205.3	80.6	83.8	78.2	80.8	76.3	80.7 (77.7–114.2)	5.4 (4.4–6.9)	10.7 (6.5–17.1)
MC9	Ward	133.8	162.7	86.1	27.1	192.7	135.1	134.5 (74.1–170.2)	7 (5.9–12.1)	3 (1.4–4.1)
	ICU	31.9	345.5	161.9	40.8	695.6	516.5	253.7 (38.6–561.3)	7 (6–9)	62.5 (46.75–69.5)
	Total	113.0	220.8	112.2	32.4	300.5	213.5	163.2 (92.2–240.7)	6.98 (6.3–9.9)	17.9 (14.2–26.9)
MC10	Ward	161.4	248.3	68.6	29.4	41.0	60.6	64.6 (38.1–183.1)	2.9 (2.5–3.4)	3.4 (2–4.5)
	ICU	0.0	144.6	112.1	82.9	95.6	87.2	91.4 (62.2–120.2)	7.65 (4.6–9.1)	14.1 (6.5–24.7)
	Total	161.5	222.0	80.8	34.8	63.8	68.8	74.8 (56.5–176.6)	3.44 (2.9–4.1)	4.5 (3–6.3)
MC11	Ward	86.8	44.5	73.8	74.1	106.2	110.0	80.5 (66.5–107.1)	3.65 (3.15–4.1)	1.4 (0.4–2.75)
	ICU	155.0	93.9	126.0	101.2	108.2	130.2	117.1 (99.4–136.4)	4.85 (3.1–6.15)	18 (8.5–24.4)

(Continues)

TABLE 1 (Continued)

Medical centres	Setting	Total ACI per month						ACI median (IQR)	LOS median (IQR) (day)	Rate of mortality median (IQR) (%)
		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6			
	Total	100.8	64.8	79.7	77.7	106.5	113.5	90.3 (74.5–108.2)	3.8 (3.5–4.35)	3.2 (1.6–7.7)
MC12	Ward	49.7	47.8	8.0	83.1	64.3	33.9	48.7 (27.4–69)	5.05 (3.8–5.48)	1.7 (1.35–1.9)
	ICU	115.3	112.2	7.9	326.6	150.4	90.3	113.8 (69.7–194.4)	9.65 (6.7–11.3)	62.44 (45.5–66.5)
	Total	63.7	57.7	7.9	134.2	75.3	41.8	60.7 (33.4–90)	5.62 (4.1–5.8)	6.2 (5.7–8.6)

Note: ACI Ward; median (IQR): 86.2 (61.5–162.37). ACI ICU; median (IQR): 119.3 (82.96–189.46). Total ACI; median (ICU + Ward) (IQR): 106.8 (68.59–177.84). LOS in ward; median (IQR): 4.65 (3.9–5.6). LOS in ICU; median (IQR): 6.55 (5.3–7.9). Total LOS (ICU + Ward); median (IQR): 5.6 (4.2–7). Rate of mortality in ward; median (IQR): 3.2 (1.7–6.1). Rate of mortality in ICU; median (IQR): 36.7 (26.1–54.1). Total Rate of mortality (ICU + Ward); median (IQR): 10.7 (3.1–36.8). ACI: Antibiotic consumption index (DDD per 100 bed-days); MC: Medical centre; LOS: Length of hospital stay; and IQR: Interquartile range (Q1–Q3).

A support committee was formed to answer the questions and solve the problems that data collectors might encounter.

2.4 | Outcome measurement

First, the pattern of antibiotic use was investigated in 12 MCs. The most prescribed antibiotics and the MCs with higher rates of antibiotic consumption were also identified. Secondly, the correlations between antibiotic use, mortality rate, and the length of hospital stay were evaluated for each centre and compared. Thirdly, the rate of positive bacterial cultures in each centre was explored during that period. Finally, the total cost of antibiotic consumption was calculated.

2.5 | Statistical analysis

Data analysis was conducted using the SPSS statistics software (Version 26.0. IBM Corp. Armonk, NY, USA). The Kolmogorov–Smirnov test was performed to evaluate the normality of distribution. Antibiotic use, LOS, and rate of mortality across the MCs were summarized by median and interquartile range (IQR, lower quartile-upper quartile). To compare the antibiotic consumption (ACI) among 12 MCs, the Kruskal-Wallis test was used. The linear correlations between ACI, the rate of mortality, and the LOS were investigated by the Pearson correlation coefficient. The Mann–Whitney *U* test was applied to compare the median use of antibiotic, LOS, and rate of mortality between ICUs and Wards. $p < 0.05$ was considered as statistically significant in all tests.

3 | RESULTS

3.1 | Pattern of antibiotic use

Totally, 43,791 patients were recruited from the 12 MCs. Table 1 provides the results obtained from the preliminary analysis of antibiotic consumption based on DDDs and ACIs. The summary statistics for the rate of antibiotic use, LOS, and the rate of mortality are also presented. The total and median antibiotic consumption in the 12 included MCs during the 6-month study period were 121.63 ACI (301339.89 DDDs per 247,743 bed-days) and 106.8 ACI (IQR: 68.59–177.84), respectively. The median use of antibiotic in the ICU and ward were 119.3 ACI (IQR: 82.96–189.46) and 86.2 ACI (IQR: 61.5–162.37), respectively, the difference between which was not statistically significant ($p = 0.15$). A significant difference was observed between the median use of antibiotics among the 12 included MCs ($H^{11} = 43.4$, $p = 0.0001$). Figure 1 presents an overview of the antibiotic consumption among 12 MCs. As shown in Figure 1A, MC5, MC2, MC1, and MC 9 represented the highest rates of total antibiotic consumption, respectively.

Figure 2 shows the antibiotic consumption over the 6-month study period in 12 MCs by month. The median use of antibiotics in

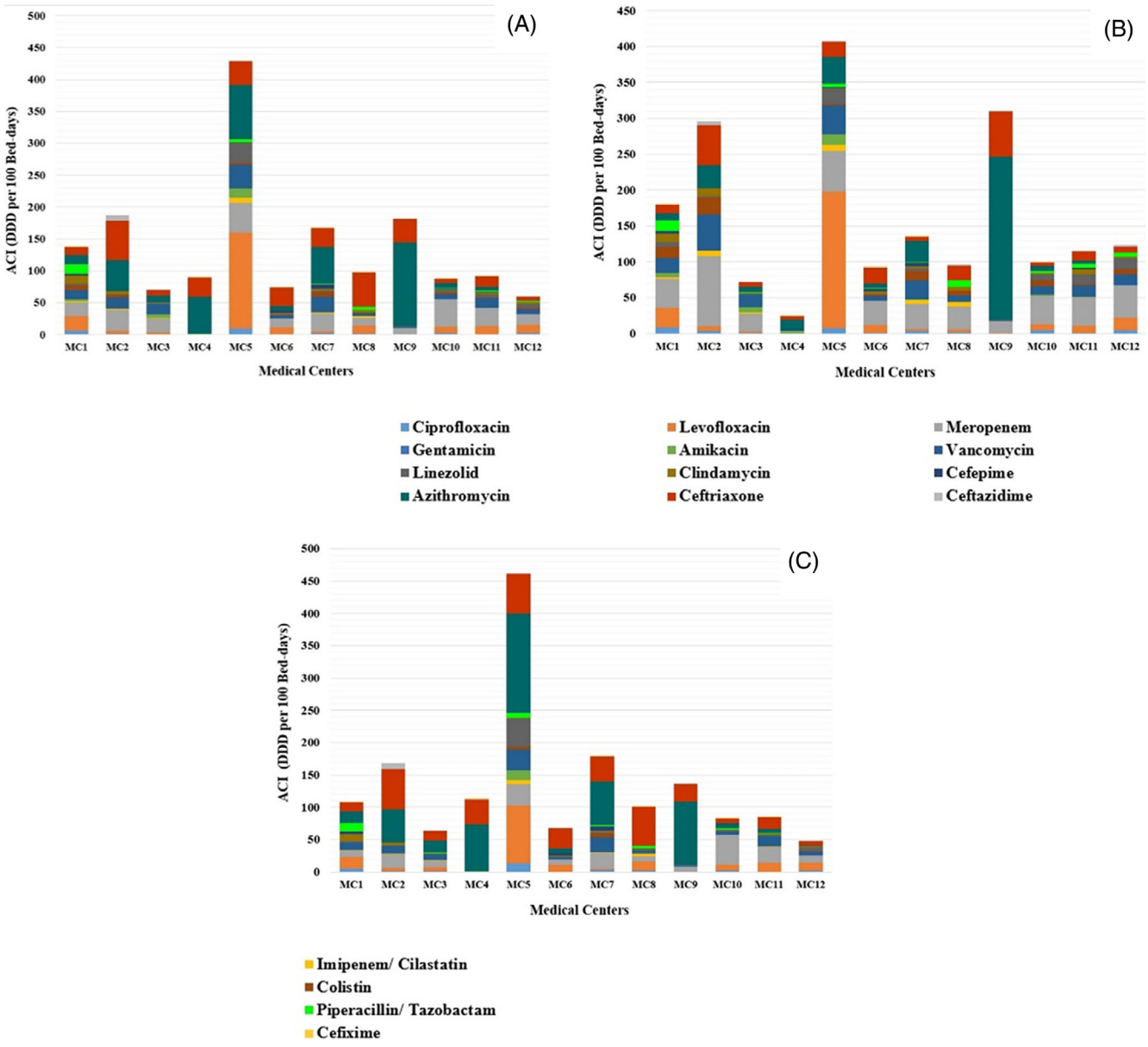

FIGURE 1 Detailed consumption rate (ACI) of each antibiotic in 12 included MCs during the first 6 months of COVID-19 pandemic in Iran; (A) total antibiotic use in ICU and wards; (B) antibiotic use in ICU; (C) antibiotic use in wards

MCs 1, 2, 5, 7, and 9 was more than the reported median of all 12 MCs during the study period (106.8 ACI, IQR: 68.59–177.84).

It can be seen from the data in Table 2 that azithromycin (73217.4 DDD, 29.55 ACI), ceftriaxone (64801.75 DDD, 26.16 ACI), meropenem (52200.67DDD, 21.07 ACI), and vancomycin (29603.7 DDD, 11.95 ACI) were the most commonly used antibiotics in the 12 included MCs during the study period. This order was different to some extent in ICUs and medical wards. Meropenem (23702.5 DDD, 38.64 ACI), azithromycin (15196.28 DDD, 24.77), vancomycin (11673.45DDD, 19.03 ACI), and levofloxacin (106342.5 DDD, 17.35 ACI) were the most prescribed antibiotics in ICUs, respectively. The order and corresponding values for the highly used antibiotics in medical wards were azithromycin (58021.15 DDD, 31.13 ACI), ceftriaxone (55170.5 DDD, 29.6 ACI), meropenem (28498.17 DDD, 15.29 ACI), and vancomycin (17930.28 DDD, 9.62), respectively. A significant difference was not observed between the median use of azithromycin in ICUs and wards (9.09 (IQR: 4.74–31.2) versus 18 (IQR: 6.59–71.49), $p = 0.08$). This pattern was completely different for meropenem. The median use of meropenem was significantly higher in ICUs (37.4 (IQR: 26.79–43.92) versus 10.58 (IQR: 7.45–24.17), $p = 0.0001$). Cefixime and gentamicin represented the lowest rate of use in wards and ICUs.

3.2 | Identified bacterial infections

During the study period, 6307 positive bacterial cultures were reported for patients admitted with COVID-19 in all 12 MCs. Out of 43,796 patients included in the study, only 14.4% (6307) had a

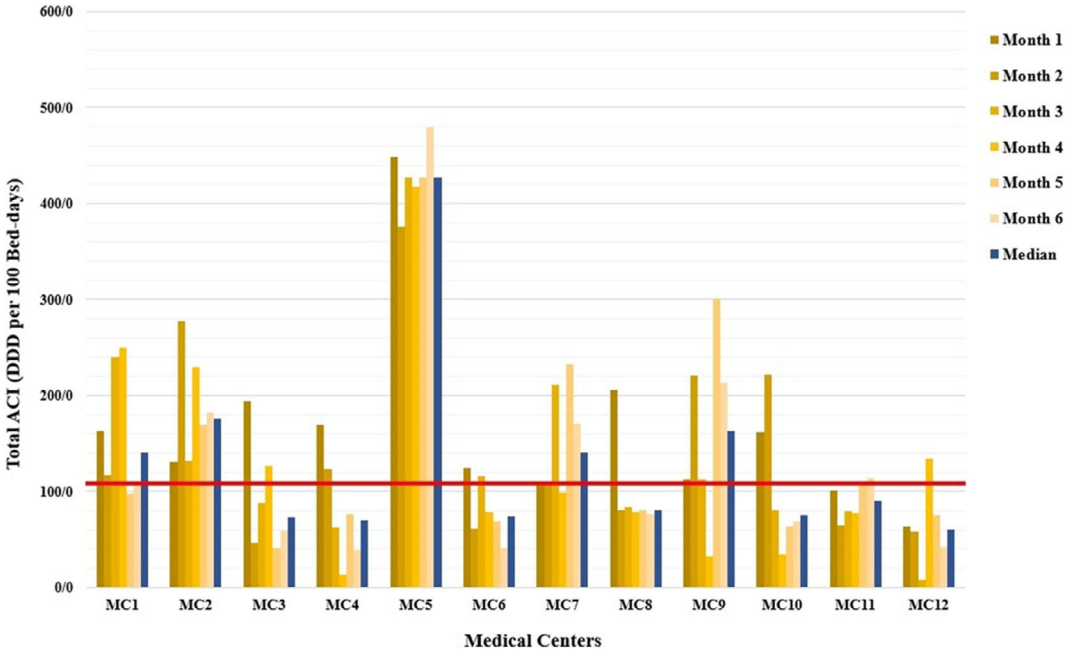

FIGURE 2 The monthly pattern of antibiotic use based on ACI in 12 included MCs during the first 6 months of COVID-19 pandemic in Iran; the vertical dark blue bar represents the median ACI of each centre during the study period. The horizontal red line indicates the median of antibiotic use (106.8) in all included MCs during the study period

confirmed bacterial co-infection. Our results indicated that most antibiotic prescriptions were not culture-based and performed empirically.

3.3 | Correlations between antibiotic use, mortality rate, and LOS

The median mortality rate was 10.7 (IQR: 3.1–36.85), which was significantly higher in the ICUs than in the wards (36.7 (IQR: 26.07 54.1) versus 3.2 (IQR: 1.7–6.1), $p = 0.0001$). However, a significant difference was not observed in the median LOS between the ICUs and wards (6.55 (IQR: 5.3–7.9) versus 4.65 (IQR: 3.9–5.6), $p = 0.4$).

The results of the correlational analysis between the quantity of antibiotic consumption based on ACI and the rate of mortality (Table 3) showed a direct correlation between total ACI and the rate of mortality (r [142] = 0.25, $p = 0.006$). This correlation was also seen for meropenem (r [142] = 0.32, $p = 0.003$), imipenem/cilastatin (r [142] = 0.21, $p = 0.03$), colistin (r [142] = 0.29, $p = 0.001$), pipracillin/tazobactam (r [142] = 0.23, $p = 0.02$), and vancomycin (r [142] = 0.31, $p = 0.001$). However, no significant correlation was observed between the median LOS and total antibiotic consumption (total ACI) (r [70] = 0.063, $p = 0.45$).

3.4 | Financial burden

The total antibiotic use during the study period in all MCs was estimated to be 93.2 billion IRR (≈2.2 million USD).

4 | DISCUSSION

Antibiotic overuse and misuse are considered the most important cause of antimicrobial resistance (AMR). Antimicrobial resistance is among the 10 top global health problems according to the World Health Organization (WHO) statement. It already leads to 700,000 deaths annually, and if systematic and sustained interventions are discontinued, this value could increase to 10 million deaths annually by 2050.[11]

The irrational use of antibiotics during the COVID-19 pandemic is a concerning issue. Although antibiotics may be indicated for managing probable or proven bacterial co-infections in patients with COVID-19, it seems to be unnecessary in most conditions.[12] Based on our findings, 121.6 DDDs of antibiotics were used for each 100 hospital bed-days. This estimates that each patient received 1.21 DDDs of antibiotics every day. This finding is merely an overall estimate. Some patients may not have taken antibiotics at all, or conversely, some may have received a combination of several antibiotics. However, our results showed that antibiotics were widely prescribed in Iranian hospitals during the first 6 months of the COVID-19 pandemic. The irrational use of antibiotics has always been a problem in Iran. According to the WHO report on surveillance of antibiotic consumption during 2016–2018, Iran was the second country in terms of antibiotic use based on DDD per 1000 inhabitants per day (DID) among 65 countries.[13] This problem seems to have been worsened during the COVID-19 pandemic. Our findings revealed that some MCs were consistently high or low antibiotic prescribers, but others (notably MC1 and MC9) had spikes in antibiotic prescription in certain months. This increase in antibiotic administration in certain months

TABLE 2 Rate of consumption for each antibiotic during the first 6 months of COVID-19 pandemic for all 12 included MCs in total and by ward and ICU

	Ward				ICU				Total			
Antibiotics	**DDD**	**ACI**	**ACI median**	**IQR**	**DDD**	**ACI**	**ACI median**	**IQR**	**DDD**	**ACI**	**ACI median**	**IQR**
Ciprofloxacin	3925.51	2.11	1.59	0.51–2.75	2358.88	3.84	2.84	0.82–4.71	6284.39	2.54	1.5	0.6–3.01
Levofloxacin	17,491	9.38	10.27	3.4–14.66	106342.5	17.35	7.11	1.98–15.81	28133.5	11.35	10.08	2.68–13.17
Meropenem	28498.17	15.29	10.58	7.45–24.17	23702.5	38.64	37.4	26.79–43.92	52200.67	21.07	21.41	12.01–30.69
Imipenem/Cilastatin	1700	0.91	0.65	0.03–1.39	1699.3	2.77	0.94	0.03–5.55	3399.3	1.37	0.88	0.05–2.16
Gentamicin	600.96	0.32	0.06	0.004–0.27	147	0.24	0.05	0.02–0.17	747.96	0.3	0.04	0.01–0.23
Amikacin	764.1	0.41	0.32	0.11–0.5	1481.7	2.41	0.86	0.25–4.4	2245.8	0.91	0.4	0.23–1.97
Vancomycin	17930.28	9.62	6.85	4.19–14.63	11673.45	19.03	14.78	7.1–25.39	29603.73	11.95	10.98	4.84–16.89
Colistin	3102.8	1.66	0.14	0.02–0.87	5205.81	8.49	4.13	0.5–11.74	8308.61	3.35	1.56	0.19–3.55
Linezolid	4602	2.47	1.07	0.31–2.51	3741.1	6.1	2.51	0.84–12.76	8343.1	3.37	1.66	0.52–4.83
Clindamycin	5735.45	3.08	1.92	0.58–2.7	2704.04	4.41	2.62	0.47–6.65	8439.49	3.41	2.43	0.53–3.05
Cefepime	3704.18	1.99	0.16	0.01–2.52	1310.05	2.13	0.38	0.04–3.17	5014.23	2.02	0.34	0.06–2.82
Piperacillin /tazobactam	3671.07	1.97	0.88	0.02–3.84	2744.82	4.47	1.99	0.16–5.66	6415.88	2.59	1.5	0.09–4.43
Azithromycin	58021.15	31.13	18	6.59–71.49	15196.28	24.77	9.09	4.74–31.2	73217.43	29.55	12.55	6.19–57.38
Ceftriaxone	55170.5	29.6	29.21	14.52–54.68	9631.25	15.7	12.38	5.48–21.56	64801.75	26.16	29.02	9.84–37.15
Ceftazidime	2785.8	1.49	0.16	0.07–0.67	758.25	1.24	0.41	0.25–1.47	3544.05	1.43	0.26	0.16–0.8
Cefixime	609	0.33	0.01	0–0.25	31	0.05	0	0–0.03	640	0.02	0.007	0–0.08

Note: Ward bed-days: 186,399. ICU bed-days: 61,344. Total bed-days: 247,743. ACI: Antibiotic consumption index (DDD per 100 bed-days); MC: Medical centres; IQR: Interquartile range (Q1–Q3).

TABLE 3 Correlation between total antibiotic consumption, mortality rate, and length of hospital stay during the first 6 months of COVID-19 pandemic in 12 included MCs

	Correlation between mortality rate and antibiotic use		Correlation between LOS and antibiotic use	
Antibiotics	**Pearson correlation**	***p* Value**	**Pearson correlation**	***p* Value**
Ciprofloxacin	0.16	0.07	0.02	0.85
Levofloxacin	0.05	0.4	−0.06	0.53
Meropenem	0.32	0.003	0.09	0.29
Imipenem/Cilastatin	0.21	0.03	−0.008	0.96
Gentamicin	0.06	0.4	0.04	0.58
Amikacin	0.09	0.4	−0.01	0.82
Vancomycin	0.31	0.001	0.1	0.18
Colistin	0.29	0.001	0.11	0.19
Linezolid	0.08	0.6	−0.05	0.61
Clindamycin	0.07	0.3	−0.06	0.636
Cefepime	0.113	0.18	0.04	0.65
Piperacillin/Tazobactam	0.23	0.02	−0.008	0.93
Azithromycin	0.09	0.26	0.02	0.73
Ceftriaxone	−0.05	0.6	0.04	0.68
Ceftazidime	0.13	0.18	0.16	0.07
Cefixime	−0.12	0.17	−0.05	0.56
Total ACI	0.25	0.006	0.063	0.45

Note: ACI, antibiotic consumption index (DDD per 100 bed-days); MC, medical centres; LOS, length of hospital stay; IQR, interquartile range (Q1–Q3).

may be due to the considerable rise in the number of COVID-19 patients in these centres during those periods, which not only increased the need for antibiotic administration but also may have affected the clinicians' practice.

All four highly consumed antibiotics in this study (azithromycin, ceftriaxone, meropenem, and vancomycin) are among the watch-group antibiotics according to the WHO classification. The watch-group antibiotics have a high potential for AMR and are recommended to prioritize in the antibiotic stewardship programmes.[14] Differently, based on the result of a rapid systematic review of antibiotic use during the COVID-19 pandemic, fluoroquinolones and third-generation cephalosporins comprised 74% of the antibiotic prescriptions.[15] In the early stage of the pandemic, azithromycin was widely used to treat COVID-19 due to its anti-inflammatory, antibacterial, and possible antiviral effects in the absence of relevant clinical data to support its use. Further data rule out the usefulness of azithromycin in treating COVID-19.[16–18] The high rate of azithromycin prescription in the current study could be due to the lack of sufficient data about the ineffectiveness of azithromycin in treating COVID-19 during the study period.

The antibiotic prescription pattern was significantly different between the MCs in our study. Such differences were reported in the outpatient antibiotic prescription during the first year of the COVID-19 pandemic in the United States.[19] The WHO report of antibiotics consumption data from the European countries since 2016 showed a wide intra- and interregional diversity in the total antibiotics use and the choice of antibiotics.[20] Thus, these data indicate a lack of global agreement on a uniform pattern of antibiotic administration in outpatients and inpatients settings before and during the COVID-19 pandemic.

Only 14.4% of patients in our study had least one positive bacterial culture. In a recent meta-analysis of 30 studies and pooled data of 3834 patients, the frequency of confirmed co-bacterial infections in hospitalized patients with COVID-19 was about 7%, with a higher value of 14% among the ICU patients.[6] In another study, the incidence of bacterial and fungal co-infections during hospitalization in individuals with COVID-19 was 8%, while 72% of patients had taken antibiotics.[13] Another similar study evaluated empirical antibacterial administration in hospitalized patients with COVID-19 in 38 Michigan hospitals and found that 56.6% of patients received empiric antibiotics, while the rate of co-infection was only 3.5%.[21] Similarly, the high rate of antibiotic use in our study was not in agreement with the frequency of the isolated microorganisms, and most of the prescriptions were empirical and not culture-based.

Although the median antibiotic use in the ICUs was higher than in the wards, this difference was not statistically significant in our study ($p = 0.15$). In contrast, in a study on 1705 hospitalized COVID-19 patients, the rate of empirical antibiotic administration was significantly higher in patients who needed intensive care at the time of hospital admission.[21] A higher rate of antibiotic use in ICU patients was also reported in a study in Malaysia during the early phase of the COVID-19 pandemic.[22] The antibiotic administration is expected to rise in ICU patients in whom a large proportion of concomitant bacterial infections are associated with intensive care devices such as

central vascular catheters and ventilators.[21] Our results, however, showed that even most patients with no severe clinical manifestations in non-ICU settings received empirical antibiotics.

Our findings showed different patterns of antibiotic use between the ICU and non-ICU settings. Meropenem was mainly prescribed in ICUs, while azithromycin was the most used antibiotic in non-ICU settings.

No significant correlation was observed between the mean LOS and the rate of antibiotic consumption. Although the use of rapid and accurate bacterial identification methods helps reduce the length of hospital stay,[23] there is not enough data to show a definite impact of antibiotic therapy on the LOS.[24,25]

Previous experiences revealed that bacterial co-infection increases the rate of mortality and morbidity in hospitalized patients with viral pneumonia.[26] Similar results have been reported in hospitalized patients with COVID-19.[27,28] The result of a study showed that the mortality rate in patients with COVID-19 increased to 83.14% in bacterial or fungal co-infections.[28]

The direct correlation between mortality rate and total antibiotic use seen in our study, was further observed between mortality rate and consumption of specific antibiotics, including meropenem, imipenem, colistin, piperacillin/tazobactam, and vancomycin. Such correlation was also reported in another study on 242 patients with confirmed COVID-19, in which nearly 70% of patients received antibiotics while bacterial coinfection was identified only in 28% of cases. A significantly higher level of inflammatory markers was observed in patients who received antibiotics.[27] Immune-dysregulation and cytokine storm syndrome contribute to increasing the risk of mortality in severe COVID-19 cases.[29] Hantoushzadeh et al. highlighted the possible impact of antibiotics on the aggravation of cytokines storm in patients with COVID-19.[30] Although our findings could suggest a similar association, the mortality in COVID-19 patients is multifactorial, and other contributing factors were not covered in our study.

The findings in this report are subject to at least two limitations. First, this study could not control the impact of confounding variables such as age, gender, smoking status, comorbidity, clinical severity stage, and corticosteroid use on the mortality rate. Secondly, there is a possibility of missing data and entering inaccurate information.

This study was conducted during the first 6 months of the COVID-19 pandemic when the nature of the disease and its management were not well recognized. Further studies are needed to assess changes in antibiotic prescription patterns following the identification of different aspects of the disease and development of new therapeutic guidelines.

5 | WHAT IS NEW AND CONCLUSIONS

The results of the present study indicated an irrational use of broad-spectrum antibiotics during the first 6 months of the COVID-19 pandemic. Most prescriptions did not match the bacterial identification. In addition, antibiotic use patterns in the MCs showed different treatment approaches in patients with a similar infectious syndrome. This irrational use of broad-spectrum antibiotics was associated with increased mortality, which can be an alarming finding.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX

STUDY PROTOCOL

Included medical centres: Imam Khomeini hospital complex (Tehran), Masih Daneshvari Hospital (Tehran), Loghman Hakim hospital (Tehran), Ziaeian Hospital (Tehran), Rasool akram hospital (Tehran), Shahid Sadoughi Hospital (Yazd), Alzahra hospital (Isfahan), Imam Ali hospital (Alborz), Imam Rez a hospital (Mashhad), Razi hospital (Mazandaran), Kamkar hospital (Qom), Shahid Chamran hospital (Shiraz).

Study population: All COVID-19 hospitalized patients (The diagnosis of COVID-19 was based on a positive SARS-COV2 PCR of the nasopharyngeal swab or the presence of clinical and radiological symptoms that are consistent with the disease and have caused the patients admitted in COVID-19 wards). Cases under 18 years of age and patients discharged from the emergency room or discharged or died within 48 hours of hospitalization were excluded.

Study antibiotics: Colistin, imipenem/cilastatin, meropenem, vancomycin, amikacin, gentamicin, linezolid, clindamycin, cefepim, ceftazidime, cefixime, ceftriaxone, piperacillin/tazobactam, azithromycin, ciprofloxacin, and levofloxacin.

The rate of broad-spectrum antibiotic use in hospitalized COVID-19 patients in these MCs was calculated and reported based on DDD for each antibiotic according to ATC/DDD list, which is published by the WHO Collaborating Centre for Drug Statistics Methodology. In the next step, the calculated doses of antibiotics based on DDD was adjusted per 100 bed-days that is called antibiotic consumption index (ACI) in this study. ACI is a standard method to compare antimicrobial consumption among different wards and centres. Hospitalized patients in the current study were defined as those who were hospitalized for more than 24 h. Where the number of bed-days was calculated by multiplying specific rate of bed occupation (O), number of available beds (N), and time period in days (T). In addition, pure rate of mortality was considered as a valuable index in our study. In calculating this index, deaths in the first 24 h of admission are not attributed to hospital deaths in the hospital.

The following formulas represent calculations mentioned above:

$$\mathrm{ACI} = [\mathrm{DDD\ number}/\mathrm{number\ of\ bed-day}] \times 100.$$

Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults. Defined daily dose for each included antibiotic summarized in Table A1.

$$\mathrm{Number\ of\ bed-days} = O \times N \times T.$$

O, rate of bed occupation; *N*, number of available beds; *T*, time period in days.

$$\mathrm{Rate\ of\ mortality} = [(A-B)/(C-B)] \times 100.$$

A, the total number of deaths in a given period; *B*, number of deaths reported within the first 24 h of hospitalization in the same period. *C*, number of all hospital discharges (patients admitted with Covid-19 diagnosis) in the same period.

Length of stay (LOS) in hospital is calculated by summing the number of days for all stays (where partial days, including non-overnight stays, are omitted) and dividing by the number of patients.

TABLE A1 Corresponding defined daily doses (DDD) for each included antibiotic in the study

	Antibiotic	Route of administration	DDD (g)
1	Ciprofloxacin	IV	0.8 g
2	Ciprofloxacin	Oral	1 g
3	Levofloxacin	IV/Oral	0.5 g
4	Meropenem	IV	3 g
5	Imipenem-cilastatin	IV	2 g
6	Gentamicin	IV	0.24 g
7	Amikacin	IV	1 g
8	Vancomycin	IV	2 g
9	Colistin	IV	9 MU
10	Linezolid	IV/Oral	1.2 g
11	Azithromycin	IV	0.5 g
12	Azithromycin	Oral	0.3 g
13	Clindamycin	IV	1.8 g
14	Clindamycin	Oral	1.2 g
15	Cefepim	IV	4 g
16	Piperacillin/tazobactam	IV	12 g
17	Ceftriaxone	IV	2 g
18	Ceftazidime	IV	4 g
19	Cefixime	Oral	0.4 g

IMPORTANT POINTS TO REMEMBER

1. How to convert mg to g: The weight in grams is equal to the milligrams divided by 1000.
2. Rout of administration: In case of ciprofloxacin, azithromycin and clindamycin DDD is different for oral and injectable dosage forms.
3. DDD for Piperacillin/tazobactam: The DDDs assigned for combination products are based on the main principle of counting the combination as one daily dose, regardless of the number of active ingredients included in the combination. In the case of Piperacillin/tazobactam, main ingredient is Piperacillin and calculation should be performed based on piperacillin quantity.