RESEARCH ARTICLE

Increased antimicrobial resistance against azithromycin during COVID: role of irrational utilization

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Abstract

Objective: To assess the use of azithromycin during coronavirus disease-2019 pandemic and its impact on antimicrobial resistance in an urban setting.

Method: The retrospective, cross-sectional study was conducted on two different data sets. The first data set was of inpatients (N = 300) during the first wave of COVID 19 i.e. January to December, 2020. Data was collected from tertiary care hospitals in Karachi between October 2021 and November 2022 after approval from the ethics review committee of Ziauddin University, Karachi. Drug utilisation evaluation was done using a structured and validated tool. The treatment protocols were evaluated by comparing against the coronavirus disease-2019 treatment protocol 2020 and the guidelines issued by the Medical Microbiology and Infectious Diseases Society of Pakistan. Second data set comprised of the consumption data (obtained from pharmacies for both inpatients and outpatients) as well as the antimicrobial resistance, (obtained from antibiogram collected from the microbiology departments of the participating hospitals). This data was taken for the period of three years i.e. 2019 (Pre-COVID) to 2021 (Post-first wave of COVID) to establish trends of both consumption and antibiotic resistance. Data was analysed using SPSS 20.

Results: Of the 300 patients, 207(69%) were males and 93(31%) were females. There were 162(54%) adults with mean age 40.06±10.48 years, followed by 120(40%) geriatrics with mean age 70.37±6.94 years, 18(6%) paediatrics with mean age 13.5±3.60 years. All patients were given Azithromycin empirically followed by culture sensitivity test in 21% cases only. Comparison with COVID treatment protocols revealed the non-compliance of just 3%. However, in case of Community Acquired Pneumonia (CAP), sinusitis, typhoid and urethritis, comparison with MMIDSP guidelines revealed non-compliance of 95%, 22%, 75% and 100% respectively. Moreover, in 11% of patients, it was administered for conditions not recommended by guidelines. Furthermore, the Antibiogram exhibited percent increase in resistance against azithromycin.

Conclusion: Enhanced consumption and irrational use of azithromycin during the coronavirus disease-2019 pandemic most likely contributed to increase in antimicrobial resistance.

Key Words: Azithromycin, COVID-19, Misuse, Consumption, Resistance.

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Introduction

Azithromycin (AZM), a synthetic macrolide, exhibits excellent therapeutic efficacy against a wide range of bacterial infections. It has an established safety profile and the generic drug is easily available worldwide[1]. It is among the antibiotics that have been classified as critically important antimicrobials for human medicine by the World Health Organisation (WHO)[2]. The Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) has recommended that empirical use of AZM should be avoided owing to the emergence of the extensively drug-resistant (XDR) strain of typhoid in which AZM is among the last resort for treatment[3]. In order to regulate its use, the Access, Watch and Reserve (AWaRe) programme, was launched by the WHO in an effort to reduce (AMR), placing AZM under the Watch category, which comprises antibiotics that are now recommended for use in selective indications only[4].

The emergence of coronavirus disease-2019 (COVID-19) entailing high mortality was a cause of great concern for healthcare workers (HCWs). The lack of established treatment protocols led the physicians to repurpose the available therapeutic agents by adopting options based on pilot studies, leading to hasty theories. In this scenario, AZM was most widely prescribed because of its reported anti-viral and immunomodulatory efficacy against COVID-19, both as a monotherapy and in combination[5]. It also had previously shown in vitro evidence against various respiratory viruses and had recognised improved outcomes when used in viral pneumonias and acute lung injury[6]. Furthermore, AZM had shown both in vitro and in

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vivo activity against a number of viruses, including Ebola, Zika, respiratory syncytial virus, influenza H1N1 virus, enterovirus and rhinovirus[7]. The dosing protocol in COVID-19 patients was, however, a predicament. Due to uncertain and limited data, there was a lack of clarity regarding the optimal AZM dose for COVID-19 patients. Even though the Randomised Evaluation of COVID-19 thERapY (RECOVERY) trial had specified the use of 500mg/day, pharmacokinetic studies suggested that a lower dose could also achieve the required concentration within the respiratory tract and lungs[1]. However, studies conducted in this regard considered 500mg/day as the standard dose, but reported different therapy duration, like 3, 5, 10 or 14 days[8].

AZM was among the most frequently prescribed antibiotic by pharmacists and physicians during the active phase of COVID-19. The most important factor influencing this prescribing trend was patient compliance, which was mainly owing to its simple single-dose regimen. Hence, the antibiotic selection was not always based on severity of symptoms or culture sensitivity, adding to AZM misuse. Besides, in developing countries, the general behaviour observed is that of self-medication, which further exuberated both misuse and overuse of antibiotics, particularly AZM, during COVID-19 treatment[9]. However, with the influx of more concrete data and trials, a lack of strong affiliation was observed between AZM and positive therapeutic outcomes in COVID-19 treatment. The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial also endorsed the absence of any benefit in AZM use in patients hospitalised for COVID-19[10]. Furthermore, a meta-analysis compared the treatment outcomes of various studies conducted across Asia, Europe and the United States, and came to the same conclusion that AZM showed no clinical benefit in the management of COVID-19 patients[11]. Presumably, this unjustified exposure has contributed to significant increase in AMR against this important antibiotic against microbes. The rising rate of AMR is a global phenomenon which tends to affect healthcare system at all levels. One study predicted that at the current rate, there could be over 10 million deaths per year by 2050 specifically due to AMR, among which the greatest mortality rate will be observed in the developing countries of Asia[12]. This staggering number is a cause of alert for healthcare authorities, and there is an urgent need to minimise the irrational use of antibiotics to deaccelerate the development of AMR, especially in developing countries.

Pakistan, a developing country in Asia, was also affected by COVID-19, leading to a considerable mortality rate. The current study was planned assess AZM use during COVID-19 and its impact on AMR in an urban setting.

Materials and Methods

The retrospective, cross-sectional study was conducted on two different data sets. The first data set was of inpatients (N = 300) during the first wave of COVID 19 i.e. January to December, 2020. Data was collected from tertiary care hospitals in Karachi between October 2021 and November 2022 after approval from the ethics review committee of Ziauddin University, Karachi.

The data included related to COVID-19 in-patients receiving AZM therapy, while all other patients were excluded. The sample size was calculated using Daniel's formula for cross-sectional prevalence studies, with d = 0.025 and pǵ0.05 for infinite population[13]. Data was collected using a structured and validated data extraction form, which was self-generated and validated with the help of two subject experts and a pilot study[14]. It included demographic profile, admission diagnosis, AZM dosage, frequency and administration, duration of therapy, concurrent medications having been used, adverse effects related to AZM and interactions with other medications, culture and susceptibility results during therapy along with any other laboratory tests that may have been performed in relation to the therapy, and the therapy outcome.

AZM treatment was compared with the COVID-19 protocol 20209 and the antimicrobial guidelines recommended by the MMIDSP (Table 1).

Second data set compromised of the consumption data obtained from pharmacies for both inpatients and outpatients as well as the antimicrobial resistance, antibiogram collected from the microbiology departments of the participating hospitals. This data was taken for the period of three years i.e. 2019 (Pre-COVID) to 2021 (Post-first wave of COVID) to establish trends of both consumption and antibiotic resistance.

Data was analysed using SPSS 20.

Results

Of the 300 patients, 207(69%) were males and 93(31%) were females. There were 162(54%) adults with mean age 40.06±10.48 years, followed by 120(40%) geriatrics with mean age 70.37±6.94 years 18(6%) paediatrics with mean age 13.5±3.60 years.

There was remarkable increase in AZM consumption between in-patients and out-patients in the year 2020 compared to the preceding year, followed by a decline in 2021 primarily in in-patients (Figure).

Table-1: Protocols and guidelines regarding treatment with azithromycin (AZM).

Guidelines / Protocols	Disease	Regimen	Reference
Proposed Protocol	COVID-19	500 mg OD for 3-14 days	(11)
MMDISP Antimicrobial Guidelines	Community Acquired Pneumonia (CAP)	500 mg Loading followed by 250 mg OD for 5 days	(3)
	Sinusitis	500 mg OD for 3 days	
	Typhoid	1 g loading followed by 500 mg OD for 7-10 days	
	Urethritis	1 g per oral for 1 day	

COVID-19: Coronavirus disease-2019, MMIDSP: Medical Microbiology and Infectious Diseases Society of Pakistan

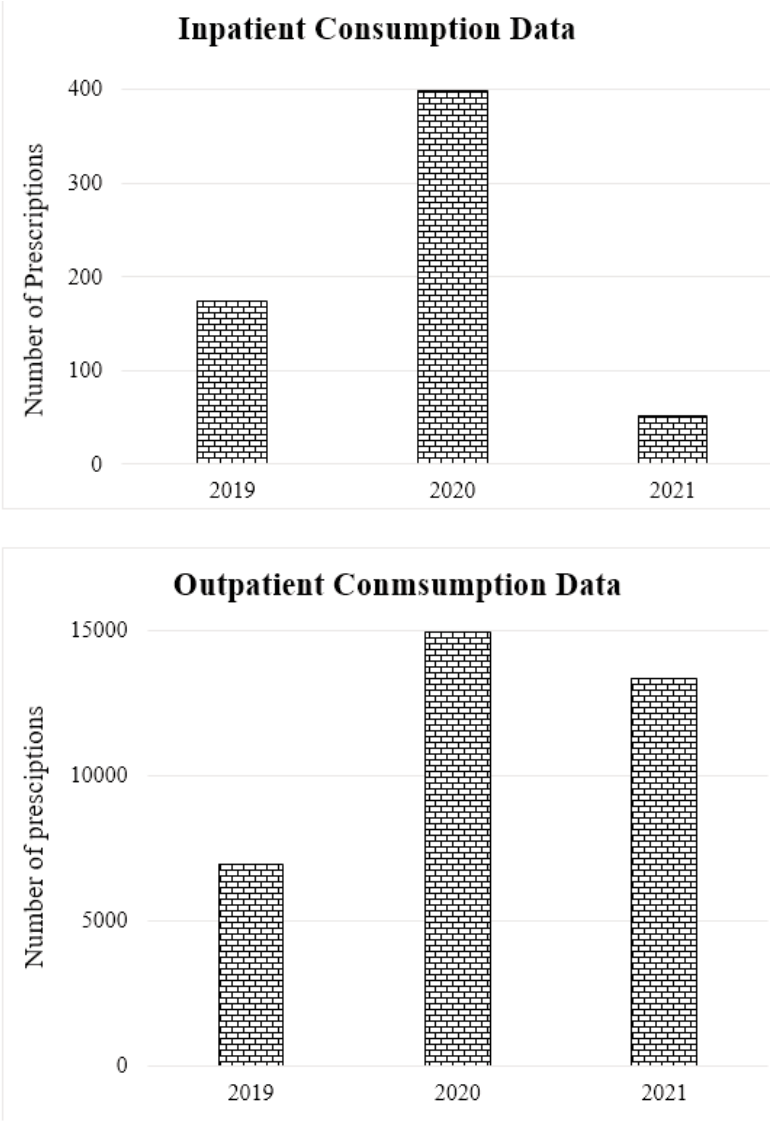

Figure: Consumption of azithromycin (AZM) in outpatients and inpatients.

All patients had been given AZM empirically, and culture sensitivity (C/S) test was conducted in 63(21%) cases. On C/S, 28(44.4 %) samples were susceptible, 4(6.4%) had resistant strains, and 14 (22.3%) did not contain any bacterial infection. The result of 17(26.9%) samples were pending till the end of the therapy, who died before the completion of the treatment. Overall, 248(82.6%) patients were diagnosed with respiratory illnesses, gastrointestinal tract (GIT) ailments 37(12%), genitourinary problems 5(2%) and miscellaneous 10(4%). Overall, 45(15%) patients died; all having respiratory illnesses. AZM in 34(11.3%) of the total cases was prescribed even when not recommended by the relevant guidelines.

The comparison with COVID-19 treatment protocols revealed 3% non-compliance (pŕ0.05), with primary contribution being that of inappropriate duration of therapy (Table 1).

Antibiogram data showed continuous increase in the resistance against AZM after COVID-19 (Table 2).

Discussion

AZM is a first-line treatment option in several diseases. However, an increased AMR against this antibiotic has emerged globally due to irrational use owing to premature theories about its efficacy in COVID-19[9]. Keeping this in view, the present study was designed to assess the practice trends involved in AZM utilisation during COVID-19 and its impact on AMR in Karachi.

The consumption data (2019-21) of AZM clearly indicated steep inclination in prescribing of AZM for both in-patients and out-patients in the year 2020 compared to that of 2019 (Figure). A similar trend reported earlier in Pakistan[15] as well as globally[16-18]. It is of note that the subsequent year (2021) observed a decline in the consumption primarily in in-patients, most probably due to decline in COVID-19 cases, which is in

Table-2: Comparison of patient prescription data with COVID-19 protocols and MMIDSP guidelines.

System	Disease	Similarity	Regimen			Total(%)	p -value
			Dose	Frequency	Duration		
Respiratory(N= 248, 82%)	COVID-19*N = 152, (61.3%)	Compliant	150	151	142	443 (97)	<0.05
		Non-compliant	2	1	10	13(3)	
	Community Acquired Pneumonia N = 29, (11.7%)	Compliant	0	0	4	4(5)	<0.05
		Non-compliant	29	29	25	83(95)	
	Sinusitis N = 3, (1.3%)	Compliant	3	3	1	7(78)	>0.05
		Non-compliant	0	0	2	2(22)	
	Irrelevant N = 19, (7.6%)	Non-compliant	19	19	19	57(100)	N.A
	Mortality N = 45, (18.1%)	-	-	-	-		N.A
Gastrointestinal Tract(N = 37, 12%)	Typhoid N = 33, (89.1%)	Compliant	2	2	21	25(25)	>0.05
		Non-compliant	31	31	12	74(75)	
	Irrelevant N = 4, (10.9%)	Non-Compliant	4	4	4	12(100)	N.A
Genitourinary(N = 5, 2%)	Urethritis N =4, (80%)	Compliant	0	0	0	0(0)	N.A
		Non-compliant	4	4	4	12(100)	
	Irrelevant N =1, (20%)	Non-compliant	1	1	1	3(100)	N.A
Miscellaneous(N = 10, 4%)	Irrelevant N =10, (100%)	Non-compliant	10	10	10	30(100)	N.A

* Comparison with the COVID_19 treatment protocols

COVID-19: Coronavirus disease-2019, MMDISP: Medical Microbiology and Infectious Diseases Society of Pakistan, NA: Not available due to value of zero in one of the rows for comparison.

Table-3: Antimicrobial resistance against azithromycin (AZM).

Year	Percent Resistance Against Azithromycin (Total number of isolates)			
	S. aureus	Strep. Pneumoniae	BHS Group A	Coag. Neg. Staph.
2019	44 (1055)	41 (116)	41 (94)	71 (2489)
2020	62 (687)	45 (96)	56 (99)	57 (1941)
2021	62 (8)	57 (7)	85 (21)	93 (31)

S: Staphylococcus, Strep: Streptococcus, BHS: Beta-haemolytic streptococci, Coag. Neg Staph: Coagulase-negative staphylococcus.

conformity with an earlier report[19]. However, the unremarkable change in out-patient noted in the present study can be due to self-medication is a prevalent practice. Apparently, in a state of panic, the general population resorted to its use based on the information available on media. Such practice is evident from a report showing that over 53% patients were using medications, including AZM, without prescriptions during COVID-19, which was attributed to lack of stringent legislation for drug dispensing, and limited access to healthcare providers[20].

The drug utilisation evaluation (DUE) was performed on 300 patients, which comprised primarily of male subjects (69%) belonging to the adult age group (54%). The higher number of male patients was consistent with the data observed the world over[21]. The current data regarding the therapy initiation protocol suggested 100% empirical therapy. Empirical initiation of antibiotics is justified in certain situations to avoid complications and mortality in patients. This practice can be justified during the early stages of the COVID-19 pandemic as the mortality rate was rising significantly due to supra-infections. However, in the retrospective review of the situation it may have contributed significantly in the increment of AMR against AZM. It is of note that sensitivity/S test was also not performed subsequently in 79% of patients, which was in

line with an study reporting 88%[22]. Out of the 63(21%) samples which were submitted for C/S test after the initiation of therapy, 28 were found to be susceptible and 4 samples had resistant strains, while 14 samples did not contain any bacterial infection. The result for 17 samples were pending till the end of the therapy. Taken together, lack of adherence to standard therapy initial protocol may have contributed to enhanced AMR.

The current data further showed that majority of in-patients (83%) were diagnosed with respiratory diseases (Table 1). Presumably, 79% of total respiratory illness were that of COVID-19 due to the general trend reported and observed worldwide during that time period where hospital admissions for other diseases had significantly decreased[23, 24]. The nature of prescribing practices is the fundamental cause of AMR. Therefore, in the present study, local practices were compared with globally suggested regimens. In this regard, 97% compliance was noted, which is suggestive of strong adherence by the local healthcare providers. However, by the end of 2020, the RECOVERY Trial published its results1 and reported the absence of any clinical benefit of AZM in the treatment of COVID-19 patients. This was further authenticated by various meta-analysis and studies conducted on larger populations over a longer period of time[11]. Hence, the aforementioned adherence may still have contributed to the AMR due to extensive and unjustified exposure of AZM during COVID-19.

The second highest percentage (12.3%) of diseases for which AZM was used in the current study was related to GIT. Among them, most of the cases (89%) were that of typhoid. This is indicative of another significant concern faced by the healthcare authorities of Pakistan. Since the emergence of the highly resistant XDR strain of typhoid, the Pakistani population was reported to be the most vulnerable for contracting typhoid globally, with high prevalence of typhoid[25]. AZM is the drug of choice for its treatment. Any increase in resistance will deprive the people of the oral antibiotic option for the treatment of XDR typhoid. The comparison with the MMIDSP for treatment of typhoid exhibited a weaker compliance of 25%. This is a major cause of concern as variation in the dose and frequency are the leading causes of the rise of resistance against any antibiotic. The outbreak of typhoid during COVID-19 further exacerbated the situation due to diagnostic limitations related to unavailability of resources[26]. Hence, the probable misuse has increased the risk of development of resistance against AZM.

The current data further showed the diagnosis of genitourinary illnesses, primarily urethritis, in 5% patients. The comparison with MMDISP guidelines revealed 100% non-compliance in the current study. It is noteworthy that 11% of patients in the study were suffering from diseases for which AZM treatment was not recommended by standardised treatment guidelines. The aforementioned scenario is extremely alarming and have most likely contributed to the resistance against AZM.

In order to verify the observations of the current study, the resistance pattern of AZM was compared for three consecutive years, from 2019 to 2021 since the onset of COVID-19 with the help of antibiograms. This is a compiled official document suggesting resistance pattern (as percent change) in thousands of microbial isolates over the years against different antibiotics. The patients were all treated with AZM for infections caused by gram-positive organisms, and the resistance pattern for these organisms was available only for erythromycin. This is based on the fact that the cross-resistance between erythromycin and AZM is well established and well documented[27], thus the data for erythromycin was considered. However, data was compared for only 4 microbes; coagulase-negative staphylococcus, staphylococcus aureus, streptococcus pneumoniae and beta-hemolytic streptococci (BHS group A). This was done because these 4 were the most dominant bacteria affecting the patients in the current study. In all four strains, it was observed that the resistance increased periodically over 2 years since 2019 (Table 2). This, in turn, supported the finding about the usage of AZM following the emergence of COVID-19.

The current study has limitations as it covered population only in Karachi. Larger multi-centre studies are required to determine the factors responsible for rising rate of resistance across the country.

Conclusion

Lack of implementation of therapeutic guidelines within the healthcare system was noted, which led to enhanced consumption and irrational use of AZM during the active phase of COVID-19 pandemic. This has most likely contributed to increase in AMR.

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Author's Contributions
ST: Performed all the work.
AS and AK: Conceptualize the work.
FA: Provided the antibiograms.