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Original Article

Pharmacology Section

Prescription Pattern for Antimicrobials and the Potential Predictors for Antibiotics among Patients with COVID-19: A Retrospective Observational Study

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ABSTRACT

Introduction: Long-term repercussions of Coronavirus Disease-2019 (COVID-19) on antimicrobial resistance have been raised as a grave concern due to the rampant use of antibiotics in the management of COVID-19. As per meta-analysis, the prevalence of antibiotic prescribing was 74.6% which was significantly higher than the estimated prevalence of bacterial co-infection. World Health Organisation (WHO) recommended that antibiotic therapy should not be used in patients with mild/moderate COVID-19 unless there is any bacterial suspicion. Also, the guidelines laid down by the Ministry of Health and Family Welfare, Government of India, does not recommend systematic empiric antibiotic therapy in patients hospitalised with COVID-19. Despite not being recommended, antimicrobials are still given in clinical practice.

Aim: To analyse prescriptions for antimicrobials and to identify potential predictors for antibiotic prescription.

Materials and Methods: A retrospective observational study was conducted at a tertiary care teaching Institute, Nagpur, Maharashtra, India. Data (demographic profile, co-morbidities, disease category, prescribed antimicrobials, laboratory investigations, and duration of hospital stay) were collected from case files of 184 patients with laboratory-confirmed Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infection. These patients were admitted in the institute from January 2021 to May 2021. Logistic regression was used to analyse factors associated with the empirical use of antimicrobial agents.

Results: A total of 184 case files were analysed. The mean age of patients was 55.84±15.72 years, with a male preponderance (70.10%). Among antimicrobials, antivirals were prescribed in 159 (86.41%) patients, and antibiotics in 152 patients (82.6%). Antivirals prescribed include Remdesivir [109 (68.55%)] and Favipiravir [70 (44.02%)]. Ceftriaxone was found to be the highest prescribed antibiotic, with a median duration of administration of six days. An association was found between disease severity and CRP level with antibiotic prescription. On multivariable analysis, the odds of receiving antibiotics were 6.7 times higher in patients with severe disease.

Conclusion: More than 80% of COVID-19 patients received antibiotics. Duration of hospital stay was similar among patients whether they received antibiotics or not. Disease severity and raised CRP level were strong predictors for prescribing antibiotics for COVID-19.

Keywords: Antibiotic prescription, Coronavirus disease-2019, C-reactive protein, Disease severity

INTRODUCTION

COVID-19 pandemic with millions of cases and a high mortality rate has had an instantaneous and devastating impact on the health sector globally. Despite limited evidence regarding efficacy, several drugs were tried and still are in use for treating COVID-19. As a result of drug repositioning, several drugs have been repurposed, including antimicrobials with potential activity against SARS-CoV-2, like lopinavir/ritonavir, remdesivir, favipiravir, ivermectin, doxycycline, azithromycin, etc [1]. In addition to this, high susceptibility to secondary bacterial infection due to invasive procedures and the inability to discern COVID-19 severe inflammatory reaction from bacterial co-infection contributes to higher use of antibiotics [2]. The long-term repercussions of COVID-19 on antimicrobial resistance have been raised as a grave concern due to the rampant use of antibiotics in the management of COVID-19 [3,4].

According to a recent meta-analysis by Langford BJ et al., the prevalence of bacterial co-infection and secondary infection in COVID-19 is relatively low at 3.5% and 14.3%, respectively [5]. A review article which analysed statistics from 19 studies involving 2,834 patients concluded that the mean rate of antibiotic use was 74.0% though only 17.6% of patients had secondary infections in COVID-19 management [6]. Various other studies also reported that the estimated prevalence of bacterial and fungal co-infection is less than 10% in COVID-19 patients [7,8]. A series of reports from China from January to April 2020, revealed that 72% of patients received broad-spectrum antimicrobials [9]. In another meta-analysis, 154 studies were included, antibiotic data were available from 30,623 patients. The prevalence of antibiotic prescribing was 74.6%. Prescribing was significantly higher than the estimated prevalence of bacterial co-infection [10].

Since the beginning of the pandemic, prescribing antibiotics for optimal management of patients with COVID-19 was a matter of dispute. The WHO recommended that antibiotic therapy or prophylaxis should not be used in patients with mild/moderate COVID-19 unless it is justifiable [11]. The guidelines laid down by the Ministry of Health and Family Welfare, Government of India, does not recommend systematic empiric antibiotic therapy in patients hospitalised with COVID-19 [12]. Interestingly, Adebisi YA et al., conducted a rapid review of national treatment guidelines for COVID-19 in ten African countries and found that some countries still recommended the use of antibiotics in the management of mild COVID-19 cases [13].

Irrational, over, and misuse of antibiotics arise as a global concern in both hospital and community settings and lead to adverse events including antimicrobial resistance, associated health problems, amplified hospital stay, and cost [4]. The prescription analysis is a

powerful exploratory tool that describes drug use patterns, provides early signals of irrational drug use, and suggests interventions to make medical care more rational and cost-effective [14]. Limited data regarding antimicrobial use in the management of COVID-19 is available from India [15]. A study reported increased sale and consumption of antibiotics particularly azithromycin in India during this pandemic [16]. But data from systematic studies for antimicrobial use in COVID-19 are meagre [17]. Prediction research explores the ability of various markers to predict future outcomes. The potential predictor provides information on an associated dependent variable regarding a particular outcome. It is helpful in assessing the predictive properties of patient characteristics, tests, markers, or combinations of variables [18]. The factors that determine why clinicians prescribe antimicrobials are important to understand. Despite not being recommended, antimicrobials still are given in clinical practice.

Hence, the present study was conducted to assess the overall pattern of antimicrobial drug use in COVID-19 patients with emphasis on antibiotics, to identify predictors for antibiotic prescribing, and to explore whether prescribing antibiotics influences the duration of hospital stay in central India.

MATERIALS AND METHODS

The present retrospective observational study was conducted in AIIMS Nagpur, Maharashtra, India. The approval of the Institutional research cell and Institutional Ethics Committee (IEC) [IEC/Pharmac/2021/267 date 28/07/2021] was obtained. The institute has dedicated facilities for COVID-19 management including Outpatient Department (OPD) services, triage, and an indoor facility. The institution has an inpatient capacity of 350 to treat patients suffering from COVID-19 of any severity. Case files of admitted patients for the duration of January 2021 to May 2021 were collected from the medical record section of the institute, and analysed during the period from August 2021 to October 2021.

Inclusion criteria: For analysis, only those case files were included if the patient's age was more than 18 years, had positive SARS-CoV-2, and had an inpatient stay lasting more than 24 hours.

Exclusion criteria: Case files of patients were excluded from analysis if any data was missing, or patients were discharged against medical advice.

A total of 184 case files were analysed. Data related to demographic profile, co-morbidities, disease category, prescribed antimicrobials, laboratory investigations, and duration of hospital stay were collected from case files of admitted patients with laboratory-confirmed SARS-CoV-2 infection.

Data related to antibiotics prescribed were analysed for number of patients who received particular antibiotic, duration, route of administration and Category as per WHO AWaRe (Access, Watch, and Reserve) classification of antibiotics, 2021 [19].

STATISTICAL ANALYSIS

Results were summarised using frequency and percentage for categorical data and either means and Standard Deviation (SD) or median and Interquartile Range (IQR) for continuous data wherever applicable. Mann-Whitney U test was used to compare the effect of antibiotic prescription on the duration of hospital stay. Logistic regression was used to analyse factors associated with the empirical use of antimicrobial agents. The stepwise selection was used to determine which variables went into the multivariable model, where p=0.20 was the cut-off. Statistical analysis was done using Graph pad prism version 9.0.0 (121) and International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) statistics version 25.0. The $p<0.05$ was considered statistically significant.

RESULTS

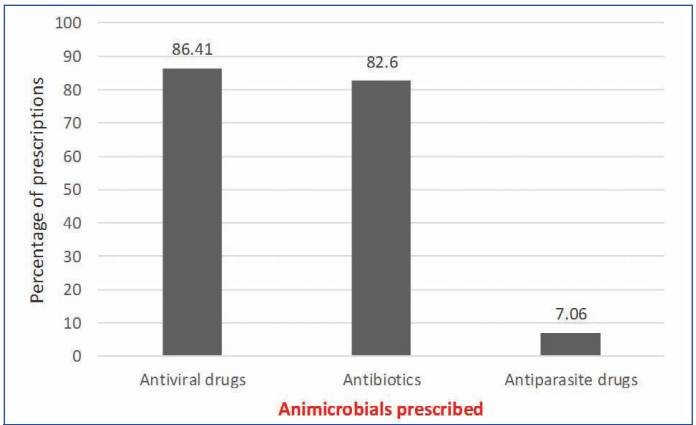
A total of 324 case files were evaluated. Among 324 case files, data entry was missing in 98 case files, 13 patients had hospital stay less than 24 hours, and 29 patients were discharged against medical advice. The remaining 184 case files were analysed.

The mean age of patients was 55.84±15.72 years, ranging from 18-96 years, with a male preponderance (70.1%). Out of 184 patients, 125 (67.93%) patients had suffered from one or more co-morbidity, with the highest prevalence of hypertension 84 (45.65%) [Table/Fig-1].

S. No.	Type of co-morbidity present	No of patients (%)
1	Hypertension	84 (45.65)
2	Diabetes mellitus	75 (40.76)
3	Cardiovascular diseases	18 (9.78)
4	Thyroid disorder	13 (7.06)
5	Bronchial asthma	5 (2.71)
6	Psychiatric disorder	2 (1.08)
7	Malignancies	2 (1.08)
8	Others*	16 (8.69)

[Table/Fig-1]: Co-morbidity status of patients (n=184).
*Others include stroke, chronic kideney diseae, rheumatoid arthritis, deep vein thrombosis, glaucoma, G6PD deficiency, benign hypertrophy of prostate, lecocytosis

Among antimicrobials, a total of 179 antivirals were prescribed in 159 (86.41%) patients, whereas a total of 232 antibiotics were prescribed in 152 patients (82.6%). Antivirals prescribed included Remdesivir [109 (68.55%)] by intravenous route and Favipiravir [70 (44.02%)] by oral route. Ivermectin, by oral route, was the only antiparasitic prescribed for treating COVID-19 [Table/Fig-2].



[Table/Fig-2]: Pattern of antimicrobials prescribed among COVID-19 patients (n=184).

Among antibiotics, ceftriaxone, a third-generation cephalosporin was found to be the highest prescribed antibiotic with a median duration of administration of six days. Most commonly prescribed antibiotics include ceftriaxone (66.44%) followed by cefixime (42.76%) and piperacillin/tazobactum (21.05%). All three antibiotics belongs to 'Watch' category as per WHO AWaRe classification of antibiotics, 2021. Doxycycline (9.21%), amoxycillin/clavulanic acid (1.97%) and amikacin (2.63%) belongs to 'Access' category and linezolid (3.28%) included in 'Reserve' category [Table/Fig-3]. [Table/Fig-4] describes antibiotics prescribed for different patient characteristics.

On univariate analysis, factors found to be associated with antibiotic use included age, disease severity, co-morbidity, raised CRP, LDH, Ferritin, and D-Dimer levels. However, on multivariable analysis, disease severity and CRP level were associated with antibiotic prescribing. The odds of receiving antibiotics were 6.7 times higher in patients with severe disease. Similarly, patients with raised CRP levels were 14.66 times more likely to receive antibiotics than those with normal CRP levels [Table/Fig-5].

Name of antimicrobial	Number of patients (%)	Duration of administration in days [Median (IQR)]	Route of administration
Antibiotics (n=152)			
Ceftriaxone	101 (66.44)	6 (5-8)	Intravenous
Cefixime	65 (42.76)	6 (4-7)	Oral
Piperacillin-Tazobactam	32 (21.05)	5 (3-8)	Intravenous
Doxycycline	14 (9.21)	5 (2-5)	Oral
Amoxicillin-Clavulanic acid	3 (1.97)	3 (3-4)	Intravenous
Meropenem	8 (5.26)	4 (3-6)	Intravenous
Linezolid	5 (3.28)	5 (3-6)	Intravenous
Amikacin	4 (2.63)	4 (3.25-4.75)	Intravenous
Antivirals (n=159)			
Remdesivir	109 (68.55)	5 (5-5)	Intravenous
Favipiravir	70 (44.02)	5 (2-7)	Oral
Antiparasitic drugs (n=13)			
Ivermectin	13 (100)	3 (3-5)	Oral

[Table/Fig-3]: Antimicrobial prescription pattern among COVID-19 patients.

Variables		No (%)	Antibiotics prescribed	
			Yes	No
Age (years)	≤60	107 (58.15)	82	25
	>60	77 (41.85)	70	7
Gender	Male	129 (70.10%)	106	23
	Female	55 (29.90%)	46	9
Disease category	Mild	58 (31.52)	31	27
	Moderate	98 (53.26)	93	5
	Severe	28 (15.22)	28	0
Co-morbidity	Patients with co-morbidity	125 (67.93)	113	12
	Patients without co-morbidity	59 (32.07)	39	20
CRP level	Normal	43 (23.37)	18	25
	Raised	141 76.63)	134	7
Serum ferritin	Normal	92 (50)	70	22
	Raised	92 (50)	82	10
LDH	Normal	87 (47.28)	65	22
	Raised	97 (52.72)	87	10
D-dimer	Normal	105 (57.07)	81	24
	Raised	79 (42.93)	71	8

[Table/Fig-4]: Assessment of antibiotics prescribed as per patient's characteristics (n=184).
CRP: C-reactive protein; LDH: Lactate dehydrogenase

Variables	Univariate		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age >60 years (Y/N)	3.51 (1.16-10.58)	0.019	4.55 (0.97-21.28)	0.054
Gender (M/F)	1.03 (0.44-2.44)	1.00	-	-
Co-morbidity (Y/N)	4.13 (1.83-9.32)	0.001	2.34 (0.65-8.42)	0.19
Disease severity (Y/N)	0.05 (0.01-0.15)	<0.001	6.78 (2-22.94)	0.002
CRP (R/N)	28.80 (10.66-77.77)	<0.001	14.66 (4.09-52.55)	<0.001
D-dimer (R/N)	2.88 (1.16-7.12)	0.025	1.26 (0.34-4.61)	0.72
Sr ferritin (R/N)	2.72 (1.17-6.33)	0.027	1.26 (0.32-4.92)	0.73
LDH (R/N)	3.88 (1.62-9.28)	0.002	4.11 (0.97-17.50)	0.05

[Table/Fig-5]: Univariate and multivariable analysis of factors potentially associated with empirical antimicrobial prescribing (n=184).
OR: Odds ratio; R/N: Raised/Normal; Y/N: Yes/No

[Table/Fig-6] shows that the duration of hospitalisation did not significantly differ among those who received antibiotics as compared to those who did not. Prescribing antibiotics did not affect the duration of the hospital stay.

Variables	No (%)	Duration of hospital stay in days median (95% CI)	p-value
Antibiotics prescribed	152 (82.6)	8 (8.68-10.12)	0.08
Antibiotics not prescribed	32 (17.4)	7 (7.05-10.88)	

[Table/Fig-6]: Impact of antibiotic prescription on the duration of hospital stay (n=184).
Mann Whitney U test

DISCUSSION

Antimicrobial resistance is a hidden threat prowling behind the COVID-19 pandemic attributed to the irrational use of antibiotics which has facilitated the emergence and spread of resistant pathogens. The present study assessed the utilisation pattern of antimicrobials in general and antibiotics in particular among COVID-19 patients admitted to the tertiary care teaching institute in central India. The present study also analysed predictors for prescribing antibiotics and the effect of antibiotic administration on the length of hospital stay.

The present study observed that 41.85% patients were elderly. A retrospective analysis by Buetti N et al., reported that median age of patient was 66.5 year (IQR 61-70) [20]. In a study by Stevens RW et al., 62.8% patients had age more than 60 years [21]. The majority of patients were suffering from co-morbidity. The most common co-morbidity was hypertension which was in accordance with a previous study which described that 55.4% patients were hypertensive [21].

The present study found that the majority (82.6%) of the study population received antibiotics, which was in agreement with the study conducted in France where 174 (78%) out of 222 patients received antibiotic therapy [22]. One of the reasons for overprescribing antibiotics may be the difficulty in distinguishing viral from bacterial aetiology based on only clinical criteria. For patients who are critically ill and hospitalised, the diagnosis of a potential bacterial co-infection is uncertain. So physicians tend to use broad-spectrum antibiotics to manage such patients [23].

Though, WHO does not recommend antibiotic use in mild/moderate COVID-19, national guidelines in some countries recommend antibiotic use in mild to moderate cases also [13]. In India, Ministry of health and family welfare released guidelines that stated antibiotics should not be prescribed routinely unless there is clinical suspicion of a bacterial infection [12]. However, the Maharashtra COVID-19 task force recommends the use of antibiotics in COVID-19 from stage IC onwards [24]. Discrepancies in guidelines by various regulatory authorities also might be responsible for the overuse of antibiotics.

However, in a retrospective study by Stevens RW et al., antibiotics were prescribed to only 37.9% of the study cohort. The author explained that the lower rate of antibiotic prescribing was due to the implementation of passive and active antimicrobial stewardship techniques like prospective audits with intervention and feedback using real-time alerts during the study period [21].

The current study observed that the most commonly prescribed antibiotic was ceftriaxone followed by cefixime. A study by Stevens RW et al., showed that ceftriaxone followed by cefepime was most commonly prescribed with a median length of antibiotic therapy was five days [21]. In a meta-analysis of 28 studies by Langford BJ, the most common antibiotic classes prescribed were fluoroquinolones (20.0%) [10]. Whereas, in a study by Buetti N et al., and Morettoa F et al., the most frequently used antibiotic was amoxicillin-clavulanic acid (68%) [20,22].

The AWaRe classification of antibiotics was developed in 2017 by the WHO Expert Committee and classified antibiotics into three groups, Access, Watch, and Reserve, taking into account the potential for antimicrobial resistance [19]. The present study observed that majority of the antibiotics prescribed were from the "watch" (antibiotics that have higher resistance potential) and "reserve" categories. This is worrisome since it contributes further to antimicrobial resistance.

On univariate analysis, factors associated with antibiotic prescribing include elderly patients, co-morbidity, disease severity, and raised blood levels of CRP, LDH, Ferritin, and D-Dimer. However, the multivariable analysis of the current study revealed that disease severity and raised CRP level were significantly associated with empirical antibiotic use. Patients with higher disease severity are more prone to complications and fatal outcomes. They are more prone to mechanical ventilation and fatal infection. So antibiotic prescribing is highly common in patients suffering from severe diseases. Similar findings have been reported in another study where antibiotic prescribing was highest in the ICU setting (86.4%) and patients in maximum three quartiles requiring mechanical ventilation (80.6%) [10].

Studies had observed that CRP is usually increased on presentation in patients with COVID-19. Serial CRP measurement over time may help to diagnose or rule out nosocomial bacterial infections and will be helpful for appropriate use of antibiotic therapy [25]. A study by Guan W et al., from China mentioned that 81.5% patients with severe diseases had CRP level >10 mg/L as compared to 56.4% patients suffering from mild disease. However author had not mentioned exact CRP level of patients [26]. In a study by Pink I et al., CRP level on admission in patient with secondary bacterial infection, was 130.6 mg/L (68.8-186.65) which was increased further upto 292.5 mg/L (183-341.8) in contrast to patients without secondary bacterial infection in whom CRP level increased from 73.4 mg/L (31.2-119.5) to 93.9 mg/L (50-171). Receiver Operating Characteristic (ROC) analysis of CRP yielded Area Under Curve (AUC) of 0.86 ($p<0.001$) for all patients. At a cut-off of 172 mg/L, CRP had a sensitivity of 81% and a specificity of 76% for the detection of secondary bacterial infection. Thus, CRP measurement on admission and during disease progression in patients with COVID-19 may help identify secondary bacterial infections and guide the use of antibiotic therapy [27].

The odds of receiving antibiotics were four-times higher in elderly patients and patients with raised LDH level. These findings have clinical significance though not significant statistically. Though serum LDH level is not a biomarker for infection, elevated LDH levels signify tissue hypoperfusion indicating the severity of the disease. Studies reported that raised LDH was associated with a six-fold increase in odds of developing severe disease and a 16-fold increase in odds of mortality in patients with COVID-19 [28,29].

Though present study findings stated that older age, co-morbidity, raised level of ferritin and D-dimer were not associated with increased frequency of antibiotic prescribing, some previous studies documented that disease severity, presence of co-morbidity, and older age group were associated with empirical antibiotic use [10,21]. The present study observed no significant difference in the duration of hospital stay among patients receiving antibiotics as compared to those who did not receive antibiotics. Also, a study by Beutti N et al., concluded that early administered antibiotics do not impact mortality in critically ill patients with COVID-19 [20].

Thus, the present study findings reiterate the need to apply antimicrobial stewardship strategies, such as prospective audits with intervention and feedback, multidisciplinary approaches, and training, to curb antimicrobial overuse in COVID-19. As there is significant diagnostic uncertainty in identifying bacterial infection in patients with COVID-19, uniform regulatory guidelines can advocate appropriate empiric antibiotics for patients who derive the greatest benefit, and in which patients the risks of antibacterial therapy exceed the benefits. At the same time, lack of access to antibiotics could also be dangerous if there is diagnostic uncertainty. Therefore, it is advised to use a correct and speedy diagnostic test like culture-independent rapid technologies which can be used for point of care use in settings such as emergency, Intensive Care Unit (ICU), or even OPD.

Limitation(s)

The present study analysed data from a single institution with a limited sample size which limits the external validity of the findings.

CONCLUSION(S)

Finally, to conclude, more than 80% of COVID-19 patients received antibiotics during their hospital stay. Duration of hospital stay was similar among patients whether they received antibiotics or not. Disease severity and raised CRP level were strong predictors for prescribing antibiotics for COVID-19.

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