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Impact of an Antimicrobial Stewardship Intervention on Usage of Antibiotics in Coronavirus Disease-2019 at a Tertiary Care Teaching Hospital in India

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ABSTRACT

Background: There was evidence that antibiotic usage increased in hospitalized COVID-19 patients during the early days of the pandemic.

Objective: We assessed the impact of stewardship interventions on antibiotic usage in these patients.

Methods: We designed a quasi-experimental study using an interrupted time series. Patients were stratified according to the severity category of the illness – mild and moderate-to-severe (O₂ saturation \geq 94% and $<$ 93% respectively). Baseline antibiotic usage data was collected in the pre-intervention phase. Intervention was given in the form of focus group discussion (FGD) and followed up with feedback-audit during the post-intervention phase. Primary outcome was the change in days of therapy (DOT) per 1000 patient-days.

Results: 361 adult patients were recruited in both phases during July to December, 2020. In the post-intervention phase, DOT per 1000 patient-days reduced from 589 to 523 (P=0.013) and from 843 to 585 (P <0.0001) in mild and moderate-to-severe categories, respectively. De-escalations at 48 hours increased significantly from 21% to 41% (P=0.0079) and from 31% to 62% (P=0.0006), respectively. No difference in mortality was observed.

Conclusion: We found high usage of empirical antibiotics in adult patients hospitalized with COVID-19. FGD and feedback audits can successfully reduce antibiotic overuse in these patients.

Introduction

The first case of Coronavirus Disease- 19 (COVID-19) was reported from China in December 2019 (World Health Organization, 2020a). During the year 2020, India reported more than 10 million cases, the second largest number in the world (next only to the United States) (Ministry of Family and Health Welfare, 2020). This stressed the already languishing healthcare system. Globally as well as in India, there is a definite increase in the irrational prescription of antibiotics. 70-80% of patients diagnosed with COVID-19 were prescribed antibiotics (Rawson et al., 2020). This raised fears of spread of multi-drug resistant bacteria, fueled by the immense antibiotic pressure. In July 2020, the World Health Organization (WHO) released guidance on tackling antibiotic resistance in the COVID-19 pandemic (Getahun et al., 2020). Following this, we

attempted to develop antibiotic stewardship protocols at our teaching hospital and analyzed the impact of focus group discussion (FGD) and feedback audits on antibiotic consumption during COVID-19 care.

Materials and methods

A quasi-experimental model using interrupted time series was used to evaluate the effects of the FGD and feedback audits on antibiotic usage in COVID-19 patients. All adult patients hospitalised during a six-month period with a positive COVID-19 real-time polymerase chain reaction (RT-PCR) test were included. Case definitions of Ministry of Health and Family Welfare (MoHFW), India were adapted for categorizing the patients based on O₂ saturation, measured by a finger pulse oximeter (Ministry of Health and Family Welfare, 2020). We categorized severity of illness into mild (O₂ saturation \geq 94%) and moderate-to-severe (O₂

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Table 1
Comparison of patient populations between the two phases.

	Mild category (O ₂ saturation ≥94%)		P-value	Moderate-to-severe category (O ₂ saturation < 93%)		
	Phase I (n= 183)	Phase II (n=49)		Phase I (n=97)	Phase II (n=32)	P-value
Gender						
Males	129	33	0.6	67	20	0.49
Females	56	16	0.68	30	12	0.49
Age						
Average age	47.2 (SD: 16.6)	52.4 (SD: 14.85)	0.047	53.7 (SD: 15.2)	58.7 (SD: 11.2)	0.089
Severity						
Number of patients	183 (65.4%)	49 (60.5%)	0.41	97 (34.6%)	32 (39.5%)	0.41

Table 2
Change in the days of therapy (DOT)/ 1000 patient-days between the two phases for antibiotic classes used in the mild category.

Antibiotic classes	Days of therapy per 1000 patient-days for patients in the mild category		
	Phase I	Phase II	P-value
BL/ BLI	209	113	<0.0001
Carbapenems	0	15	<0.0001
Cephalosporins	39	18	0.04
Macrolides	214	230	0.49
Tetracycline	127	116	0.56
Others	0	31	< 0.0001

BL/ BLI = beta-lactam/ beta-lactamase inhibitor combination antibiotics - amoxicillin-clavulanic acid/ cefoperazone-sulbactam/ piperacillin-tazobactam, Carbapenems - meropenem, Cephalosporins - include ceftriaxone/ cefuroxime/ cefotaxime, Macrolides - azithromycin, Tetracyclines - doxycycline, Others - nitrofurantoin/ ciprofloxacin.

saturation <93%). Patients in the mild category were admitted to designated COVID-19 wards (30 bedded) and those in the moderate-to-severe in the ICU-HDU complex (15 bedded). The study was initiated by the infection control team (ICT) composed of Infection Control Officers [Microbiologists (2), Infectious Disease physician (1), and Infection Control Nurses (ICN; 2)]. Institutional research and ethics committee approved the study design (AIMSR/IRB/RC/2020/10/B/7).

The study was conducted in two phases: Phase I (pre-intervention) of the initial three months involved evaluation of antibiotic usage for all the patients. ICN collected patient information from case files using a data collection form during daily rounds. It included parameters such as age, gender, category (mild or moderate-to-severe), start and end date of the antibiotic(s), duration of the therapy in days, dosage, route of administration (oral or IV), and laboratory investigations (leucocyte counts, culture reports). ICN also captured de-escalations, defined as stopping an antibiotic at 48 hours, shifting to a narrow-spectrum antibiotic or from IV to oral form and culture-directed therapy.

Phase II (post-intervention) extended for three months including the intervention phase of three days. Infectious Disease physician prepared standard treatment guidelines for patients with COVID-19. Following this, Infection Control Officer conducted three days of FGD for clinicians involved in COVID-19 patient care (n=15; the clinicians remained the same throughout the study). Training was given daily for two hours regarding the appropriate use of antibiotics in COVID-19 and protocols for de-escalations. Clinicians were requested to justify the initiation or continuation of the antibiotic therapy. ICN collected patient information in the same manner as in phase I. Infection Control Officer reviewed antibiotic prescriptions and provided weekly feedback on antibiotic usage to the clinicians by personal messages on mobile phones. Feedback was indexed by the severity category of the patients rather than the individual prescriber to avoid pointing out any one clinician.

We analyzed the primary outcome measure, i.e., the change in days of therapy (DOT) of antibiotics per 1000 patient-days between the two phases. DOTs represent the number of days a patient receives an antibiotic, independent of dose (World Health Organization, 2019). The patient-days included the day on which the patient was hospitalized until the discharge from the designated areas. Secondary outcomes included are – 1) process measures i.e., percentages of de-escalation and

number of patients in whom bacteriological cultures were performed; and 2) patient-specific outcomes i.e., length of stay (LOS) and all-cause, in-hospital mortality. We analyzed data regarding prescribing patterns of different classes of antibiotics after adjusting for the severity of the illness.

Descriptive statistics (percentages and frequencies) were used to characterize the demographic data and for categorical outcomes (DOTs, de-escalations, cultures performed, LOS and mortality). Chi-square test was applied for the comparison of proportions and averages. $P < 0.05$ was considered statistically significant. We used SPSS version 26 software for analysis.

Results

Study population: A total of 361 adult patients with RT-PCR confirmed COVID-19 were hospitalized between July to December 2020 (six months). Of these, 232 (64%) patients belonged to the mild category. Males were predominant (70% in Phase I and 65.4% in Phase II) Table 1. shows the population distribution.

During Phase I (July to September 2020), 137 (74.8%) of 183 patients in the mild category and 78 (80.4%) of 97 patients in the moderate-to-severe category received at least one antibiotic. DOT per 1000 patient-days was 589 for mild and 843 for moderate-to-severe categories. De-escalations at 48 hours were observed in 21% and 31% in mild and moderate-to-severe categories respectively.

During Phase II (October to December, 2020), 37 (75.5%) of 49 patients in the mild category and 20 (62.5%) of 32 in the moderate-to-severe category received at least one antibiotic. DOT per 1000 patient-days reduced to 523 ($P = 0.013$) and 585 ($P < 0.0001$) in mild and moderate-to-severe categories, respectively. De-escalations at 48 hours increased significantly to 41% ($P = 0.0079$) and 62% ($P = 0.0006$) in mild and moderate-to-severe categories, respectively.

Among the antibiotic classes, there was a significant reduction in usage of beta-lactams in both mild ($p < 0.0001$) and moderate-to-severe ($p = 0.017$) categories. The change in DOT/ 1000 patient-days for different classes of antibiotics between both the phases is shown in Tables 2 and 3.

Table 3

Change in the days of therapy (DOT)/ 1000 patient-days between the two phases for antibiotic classes used in the moderate-to-severe category.

Antibiotic classes	DOT/ 1000 patient-days for the moderate-to-severe category		
	Phase I	Phase II	P-value
BL/BLI	342	186	0.0001
Carbapenems	71	98	0.21
Cephalosporins	102	126	0.34
Macrolides	91	38	0.018
Tetracyclines	177	0	<0.0001
Others	60	137	0.0004

BL/ BLI = beta-lactam/ beta-lactamase inhibitor combination antibiotics - amoxicillin-clavulanic acid/ ceftazidime-sulbactam/ piperacillin-tazobactam, Carbapenems - meropenem, Cephalosporins - ceftriaxone, Macrolides - azithromycin/ clarithromycin, Tetracyclines - doxycycline, Others - ciprofloxacin/ clindamycin/ colistin/ fosfomycin/ levofloxacin/ linezolid/ nitrofurantoin/ ofloxacin/ trimethoprim-sulfamethoxazole

The proportion of patients for whom samples were sent for bacterial cultures did not change significantly in the mild category (5% to 6%; $P=0.7$) but increased significantly (21.6% to 50%, $P=0.0021$) in the moderate-to-severe category.

Out of the total cultures that were sent ($n=49$), 13 (26%) had positive growth and 4 (8%) were carbapenem-resistant bacteria. During phase II, antibiotics were continued or escalated in 24 (59%) patients in the mild category and 14 (38%) in the moderate-to-severe category. Suspicion of bacterial infections was the most common reason for the continuation of antibiotics in the mild category, whereas rising or high leukocyte count was the most common reason in the moderate-to-severe category. Other reasons were persistent fever, rising procalcitonin, worsening pneumonia or positive microbiological cultures. The length of hospital stay did not change significantly in the moderate-to-severe category, but reduced significantly in the mild category ($P=0.007$). All-cause mortality did not change significantly in both the categories (Table 4).

Discussion

Cases with COVID-19 peaked in the month of September 2020 in India, marking the first wave of the pandemic in the country (Dong et al., 2020). Different states experienced the first wave at different time periods and magnitudes. National guidelines on management of COVID-19 were adapted by various states to suit the local scenario (Ministry of Health and Family Welfare, 2020). For the state of Telangana, cases peaked in the month of September 2020 and then gradually declined toward the end of the year (Dong et al., 2020). More than 260,000 cases were detected in this state during the year 2020. According to the state policy, at the beginning of the epidemic, patients in the mild category were admitted in the isolation wards, while those in the moderate and severe categories needed ICU-HDU care (Ministry of Health and Family Welfare, 2020).

More than a year into the pandemic, the evidence is emerging on the incidence of coinfections in COVID-19. It has become apparent that bacterial coinfections are infrequent (Karaba et al., 2021). Rawson et al. reviewed 18 studies and more than 1400 cases to conclude that only 8% of patients had bacterial coinfections. However, 72% of these hospitalized patients received antibiotics. Townsend et al. also observed a similar trend, where 6% of the cases had evidence of bacterial coinfections but 72% received an antibiotic (Townsend et al., 2020). Coinfections with bacterial or fungal pathogens have been commonly reported with Influenza virus infections (Morens et al., 2008, Schuauwvlieghe et al., 2018). However, such evidence has not emerged from infections with SARS-CoV-2. Additionally, based on previous coronavirus outbreaks, it can be said that the incidence of bacterial or fungal co-infections remains low in these viral infections (Rawson et al., 2020). Calcagno et al. observed 52 COVID-19 cases and analyzed the results from commercially available multiplex-PCR (BioFire Diagnostics, bioMerieux, Marcy

l'Etoile, France). Their results were consistent with the low bacterial coinfection rates, mostly reflecting carriage states (Calcagno et al., 2021). Similarly, using the same platform, Lehman et al. concluded that only 3% of patients with COVID-19 had community-acquired coinfections (Lehmann et al., 2021). A worrying observation is the incidence of superinfections, or hospital-acquired infections, which seems to be high in COVID-19 patients requiring prolonged hospitalization (Westblade et al., 2021). In one such study from India, Khurana S et al. encountered secondary infections in 13% of hospitalized patients within the first 14 days of admission (Khurana et al., 2021). They also noted a high rate of multidrug resistant organisms, pointing toward the need for strengthening infection control and antibiotic stewardship protocols in COVID-19. Many studies have shown that the empiric usage of broad-spectrum antibiotics increases the antibiotic pressure and predisposes to acquiring multidrug resistant nosocomial bacterial infections (Ang and Sun, 2018). Fearing concomitant spread of antibiotic resistance during COVID-19, WHO released a guidance for clinicians in July 2020, urging them to use antibiotics rationally (Getahun et al., 2020).

In our present study, with all the background information available at the time, it was decided to categorize the cases as mild and moderate-to-severe. Since patients in the mild category were managed in wards and those in the moderate-to-severe category were managed in ICU-HDU, this also provided for separation of patients, location-wise. Patients in the mild category were managed by the general physicians and those in the moderate-to-severe category were managed by the intensivists. This prevented any overlap in the prescribers during the study period. MoHFW definitions provided for the clarity and simplicity in categorizing the cases as per the Indian guidelines (Ministry of Health and Family Welfare, 2020). Antibiotic data was captured as days of therapy (DOT). DOT is easy to capture in resource-limited settings, where information on the total grams of antibiotics dispensed by the pharmacy is not available (British Society for Antimicrobial Chemotherapy, 2018, World Health Organization, 2019). DOT per 1000 patient-days was the standard formula used to compare antibiotic usage between the two time periods in both the categories.

The ratio of males to females as well as the mix of cases by severity remained similar during the two phases. Although the time period was three months each for both the phases, the number of cases decreased due to a waning first wave of the epidemic in the state during October-December, 2020. Significant improvement was observed in both DOT/1000 patient-days and number of de-escalations. Although the percentage of patients who received antibiotics was not significantly different between the two phases in the mild category, the decrease in DOTs points towards increased de-escalations and reduction in overall antibiotic usage. This is in contrast with the study undertaken by Mathew P et al, who implemented similar stewardship interventions in seven participating rural hospitals in India which did not result in any significant change in antibiotic usage or de-escalations (Mathew et al., 2020).

In-hospital, all-cause mortality did not change significantly during the two phases. A similar observation was made in a large systematic review which found that the reduced antibiotic usage did not result in adverse mortality (Davey et al., 2017). LOS in the hospital did not change significantly for patients in the moderate-to-severe category. For patients in the mild category, there was a significant reduction in the LOS during phase II. This is in line with the observations of Swamy A et al, who observed significant reduction in the LOS in medicine units after stewardship interventions (Swamy et al., 2019). Number of cultures sent for microbiological investigations increased significantly for the moderate-to-severe category, indicating an attempt at de-escalations. A relatively low (8%) prevalence of carbapenem-resistant bacteria in our set-up probably reflects the low usage of higher antibiotics, resulting in lower antibiotic pressure. This is in contrast with the observations of up to 69% carbapenem resistance made by Khurana S et al, mentioned earlier in the discussion. A higher rate of culture positivity during the hospital stay (26%) highlights the need to perform microbiological test-

Table 4

Changes in the secondary outcomes among the 361 patients (Phase I - 280; Phase II - 81), indexed by the two categories (mild and moderate-to-severe).

Secondary outcomes	Mild category (O ₂ saturation ≥94%)		P-value	Moderate-to-severe category (O ₂ saturation < 93%)		P-value
	Phase I (n= 183)	Phase II (n=49)		Phase I (n=97)	Phase II (n=32)	
Number of patients in whom cultures were performed	9 (5%)	3 (6%)	0.7	21 (21.6%)	16 (50%)	0.0021
De-escalations	36 (21%)	17 (41%)	0.0079	30 (31%)	20 (62%)	0.0006
Average Length of stay (days)	10.6 (95% CI 10.0 - 11.3)	8.8 (95%CI 7.7 - 9.9)	0.007	12.8 (95%CI 11.3 - 14.3)	10.2 (95%CI 8.4 - 12.0)	0.067
Mortality	0	0	-	16 (16%)	5 (15%)	0.89

ing in hospitalized patients, who might develop superinfections during their stay. This also guides the clinician in taking de-escalation decisions.

A significant reduction in beta-lactam/ beta-lactamase inhibitor DOTs in both the patient groups points towards effective implementation of antibiotic stewardship guidelines in COVID-19 at our center. It might be noted that azithromycin remained the most commonly prescribed antibiotic in the mild category. Similarly, cefoperazone-sulbactam remained the highest consumed antibiotic in the moderate-to-severe category. This points towards individual physician bias and prescription trends in the region. The argument for azithromycin prescription is that the baseline prevalence of atypical bacterial agents (*Mycoplasma* and *Chlamydia*) causing community-acquired pneumonia is not clearly known in this population. Diagnosis of these atypical agents of pneumonia requires molecular tests in acute infections or paired sera for demonstrating a rise in antibody titers (Hardy, 2017). However, these tests are seldom available in resource-limited settings. Many epidemiological studies in India lack such testing for confirming the diagnosis of atypical bacterial pneumonia (Kumar et al., 2018, PB Pooja, 2019). Hence, empiric coverage for atypical bacteria is a routine practice. Moreover, discussions about the anti-inflammatory role of azithromycin in COVID-19 have added fuel to the fire, setting off a flurry of irrational prescriptions of this antibiotic (Echeverría-Esnal et al., 2021). The evidence is emerging on the redundancy of using this antibiotic in COVID-19 (PRINCIPLE Trial Collaborative Group, 2021, RECOVERY Collaborative Group, 2021). Despite this, it remains the drug of choice for many physicians in India, owing to its easy availability and safety profile. Azithromycin is classified under WHO's 'Watch' group under the AWaRe classification due to its increased potential to promote antibiotic resistance (World Health Organization, 2020b). This issue needs to be urgently addressed in this region.

Our study showed an increase in the use of carbapenems (in mild category), cephalosprins and "others" which includes fosfomicin, fluoroquinolones, colistin and linezolid in the post-intervention phase. These antibiotics were used for culture positive secondary bacterial pneumonias and/or for concomitant infections other than respiratory etiology, such as urinary tract infection; and skin and soft tissue infections.

Antibiotic stewardship as a program is still in its infancy in India. A status survey by Walia et al. documented that only 25% of hospitals regularly analyzed antimicrobial usage data (Walia et al., 2015). Indian Council of Medical Research (ICMR) and MoHFW are spearheading the fight against AMR in the country, and included it in the national action plan in 2017 (Ministry of Family and Health Welfare, 2017). Since then, there have been concerted efforts to regularize the sale of antimicrobial agents by legislative means, with only marginal success in achieving stewardship awareness at grassroots levels (Farooqui et al., 2020, Travasso, 2016). However, since healthcare is primarily a state subject in India, implementation and awareness about stewardship is unequal in different states. Some states like Kerala have established a model of public-private partnership for implementing stewardship in the state (Singh et al., 2021). Although very encouraging, such efforts are rare.

Additionally, all these efforts, public or private, have been thwarted by the raging pandemic of COVID-19. It is also worthwhile to note that in some parts of the world, the antibiotic usage balanced out by the time pandemic advanced into successive waves as more information became available (Gillies et al., 2021). However, there is no such data available from India.

The second wave of COVID-19 hit the country in April 2021, leaving the entire medical community struggling to cope up with the increasing workload. The spread in 2021 was more rapid as compared to 2020 (Ranjan et al., 2021). It was expected that the stewardship efforts would be sidelined with changing priorities and increasingly scarce manpower. By this time, patients in the mild category were mostly being managed at home, in line with the revised guidelines by the MoHFW. We did not conduct any FGD during the second wave. We captured antibiotic prescription data for the month of April 2021. This sample audit was conducted to assess if the interventions conducted in the first wave had sustainable effects in the massive second wave of COVID-19.

During the second wave in April 2021, we audited antibiotic use for 45 and 55 patients in the mild the moderate-to-severe categories, respectively. They accounted for a total of 250 and 478 patient-days in the mild and moderate-to-severe categories, respectively, during a three-week sample audit. DOT/ 1000 patient-days was found to be 456 in the mild category, down from 523 in phase II in 2020 (P=0.005). Similarly, DOT/ 1000 patient-days fell to 255 in the moderate-to-severe category, down from 585 in the phase II (P < 0.0001) (Figure 1). This suggests a behaviour change among the prescribers. Although these findings need to be confirmed with continuous audits throughout the pandemic, it is an encouraging observation. This is in contrast with the findings of Wattal et. al, who observed poor sustainability of interventions at six months (Wattal et al., 2017).

This is the first study from India which attempted to implement stewardship interventions in the COVID-19 patient population. Limitations of the study include decrease in the number of cases in phase II, owing to the waning first wave in the state of Telangana. Additionally, we did not analyze the timing of initiation of the antibiotic therapy. Furthermore, bacterial growth patterns were not analyzed to differentiate between colonizer or pathogen.

Conclusion

In conclusion, we found a high use of empirical antibiotics in adult patients hospitalized with COVID-19 in both mild and moderate-to-severe categories. We demonstrated that focus group discussion and regular feedback audit can successfully reduce antibiotic overuse in these patients without adversely affecting clinical outcomes like length of stay and mortality. In addition, we achieved sensitization of clinicians involved in COVID-19 patient care to the emerging threat of antimicrobial resistance. However, there is an urgent need to investigate the extent of coinfections in COVID-19 in India. This will help further reduce the empiric usage of macrolides and beta-lactam/ beta-lactamase inhibitor combinations in this region. We further conclude that existing infection

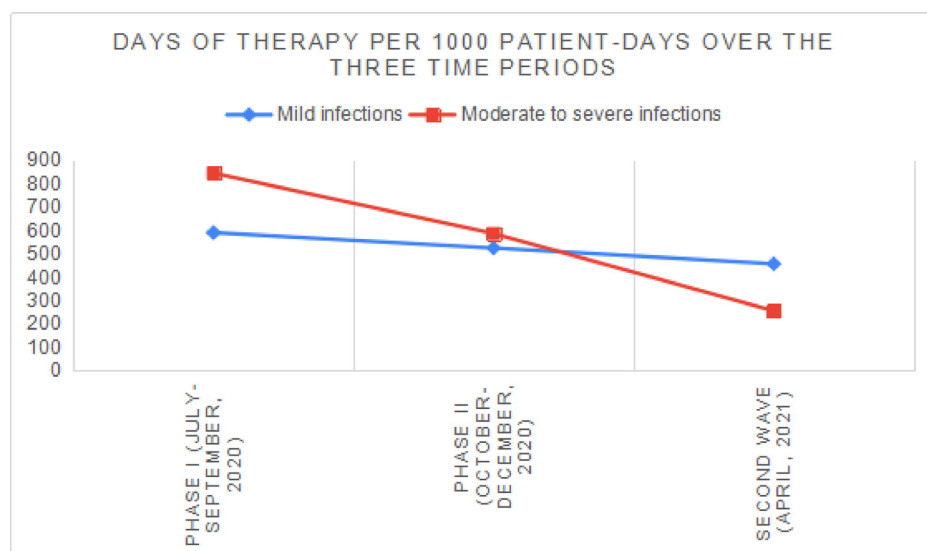


Figure 1. DOT/ 1000 patient-days for all the antibiotics during the three time periods of phase I, phase II and the second wave.

control nurses can be trained to collect antibiotic usage data in targeted patient populations, in resource-limited settings.

Author's Contributions

Study design – MKM and KB
 Study Implementation – BSM and SN
 Data collection – ABR, AP and PB
 Data Analysis – KB and MKM
 Writing – KB, MKM, MSD, DM
 All authors reviewed the final manuscript.

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Conflict of interests

We authors declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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