DOI: 10.7860/JCDR/2023/65769.18790

Original Article

Pharmacology Section

Antimicrobial Usage during COVID-19 Pandemic in Intensive Care Unit at a Tertiary Care Hospital in Eastern India: A Retrospective Study

ANIKET KASHYAP[1], SARMILA NATH[2]

ABSTRACT

Introduction: Antimicrobials, one of the greatest contributions of the 20th century to the field of therapeutics, appear to be crucial defense in severely ill Coronavirus Disease-2019 (COVID-19) patients. However, a major concern is the excessive and, in a few cases, irrational use of antimicrobials, leading to the global crisis of the emergence of multidrug- resistant microbial strains. Thus, prompt action is needed to optimise antimicrobial therapy. In this context, a situation analysis, such as the present study, focusing on medication management in COVID-19 patients, can help identify key gaps so that appropriate measures may be undertaken to ensure rational antimicrobial therapy in the future.

Aim: To analyse the antimicrobial use pattern during the COVID-19 pandemic in the Medical Intensive Care Unit (MICU) of a tertiary care hospital and assess the existing hospital antimicrobial policy.

Materials and Methods: A hospital-based, retrospective observational study was conducted in the Department of Pharmacology at a Tertiary Care Hospital (Government Medical College Kolkata), West Bengal, India. The study duration was two months, September and October, 2022. Data were extracted from the standard clinical records of all diagnosed COVID-19 adult patients (≥18 years) admitted for atleast 24 hours in the MICU between April 2021 and June 2021 {positive result on a Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay of a specimen collected with a nasopharyngeal swab indicated a positive diagnosis}. Records containing incomplete data were excluded. A total of 128 records were analysed. Group A included data on patients who expired (n=100), and group B contained data on patients who survived (n=28) during these two months. For the hospital antimicrobial policy, a personal interview was conducted with the Intensive Care Unit (ICU) incharge. Categorical variables were expressed as frequencies (n), percentages (%), and continuous variables were expressed as mean±Standard Deviation (SD). Pearson's Chi-square test and Mann-Whitney U test were used to assess the significance level for categorical and continuous variables, respectively. A p-value of <0.05 was considered significant.

Results: The mean age of the study participants in group A was 58.31±15.22 years and in group B was 51.93±18.33 years. Out of the 128 records collected, 100 patients (78.12%) had succumbed in the ICU during the particular period. Each patient had received an average of 18 drugs and 4.27 Antimicrobial Agents (AMAs) during their stay in the ICU. More than 80% of patients had received concurrent AMAs. Meropenem was the most frequently prescribed AMA (93 patients, 72.65%), followed by piperacillin/tazobactam (88 patients, 68.75%) and doxycycline (79 patients, 61.71%). More than 80% of patients received antimicrobials in the MICU, and an average of 4 AMAs were used per patient. The choice of AMA was empirical. There was no significant relationship between the number and type of AMAs received by the patients and the final clinical outcome. There was no antibiogram or Institutional antimicrobial policy.

Conclusion: The study indicates extensive, empirical use of antimicrobials in the MICU, often in combination, without an available antibiogram and without any impact on the clinical outcome of the admitted patients. The findings thus warrant the urgent establishment of a hospital antimicrobial policy to encourage rational antimicrobial therapy in the future.

Keywords: Antimicrobial policy, Coronavirus disease-2019, Critical patients, Drug resistance, Pandemic

INTRODUCTION

The healthcare system in India has recently recovered from an acute and critical challenge- "The COVID-19 pandemic." The total number of cases stood at 4.49 crore (May 2023), and the total deaths till May 2022 were 5.31 lacs [1]. Sadly, there is no specific effective treatment or cure for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection till now. In the absence of specific drugs against the disease, physicians all over the world utilised all weapons in their armamentarium, including antimicrobials, in their fight to save as many lives as they could. In May 2020, the World Health Organisation (WHO) first provided guidelines to combat COVID-19. Since then, there have been many updates depending on the evolving concepts about the pathogenesis, as well as the life cycle of the disease [2-4]. The heterogeneous nature of the virus, as well as variations in risk factors, socioeconomic conditions, and health policies across different nations led to the development of country-wise guidelines against this novel disease. The Government of India, in the "Guidelines for the management of co-infection of COVID-19 with other seasonal epidemic-prone diseases," advised the use of empiric antibiotic therapy according to the local antibiogram only in cases of secondary bacterial infection [5].

Since the onset of the COVID-19 pandemic, there has been debate about the prevalence of bacterial and viral co-infection in these patients. While some systematic reviews have reported a prevalence of <4% to 8% [6-8], others have reported a prevalence of 28%, 19%, and 16%, respectively [9-11]. However, bacterial co-infection needs clear distinction from nosocomial infection. Analyses from studies across the world have concluded that unlike bacterial superinfection in patients hospitalised with influenza-like illnesses, patients with COVID-19 are more likely to suffer from nosocomial infections [7,11,12].

Respiratory deterioration in COVID-19 could be due to either infection or inflammation [13]. Clinical or radiological distinction between bacterial pneumonitis caused by COVID-19 is difficult. Moreover, inflammatory biomarkers of disease severity in COVID-19, like serum Interleukin 6 (IL-6), ferritin, and C-reactive Protein (CRP), may also be raised in bacterial pneumonia [14]. Taking all these into consideration, routine initiation of antimicrobials is often recommended in the ICU setting, particularly for elderly patients with associated co-morbidities [15]. However, empiric treatment aimed towards broad coverage of diverse microbes may lead to the selective growth of drug-resistant bacteria.

Thus, antimicrobial therapy for COVID-19 ICU patients needs clinical acumen, expertise, knowledge about local antimicrobial susceptibility patterns, and the patient's immune status [16]. An Institutional antibiotic policy is another major guiding factor that helps physicians select appropriate antimicrobial therapy. This is where the rational use of antimicrobials comes into play. A major concern is the excessive and, in a few cases, irrational use of antimicrobials, leading to the global crisis of multidrug-resistant microbial strains emerging.

In 2017, WHO released the Access, Watch, and Reserve (AWaRe) classification of antimicrobials as part of the essential medicines list. It classifies 180 AMAs into "Access, Watch, and Reserve" groups based on their potential to develop resistance [17]. AMAs in the access group have the least potential, watch antibiotics have moderate potential, and reserve antibiotics have the maximum potential to induce resistance among target organisms. Reserve antibiotics are more commonly used in sicker patients in hospital facilities. In the WHO 13th General Programme of Work (GPW 13, Target 4b) released in 2019, WHO stated that to reduce the risk of antimicrobial resistance, atleast 60% of the total antimicrobial use in any country should be from the access group [18].

Several international studies have reflected on the antimicrobial use pattern in critically ill patients admitted to ICUs with COVID-19 [19-21]. Such studies help identify the challenges and gaps in rational antimicrobial therapy in ICUs caring for COVID-19 patients and contribute to planning and implementing appropriate therapeutic guidelines. However, there is a dearth of such studies from India. The present study was undertaken to gain insight into the ground scenario of antimicrobial usage during the second wave of COVID-19 patients in the ICU of a tertiary care hospital in India. It is presumed that the observations from the present study would help formulate the Institution's antimicrobial policy in the future. The aim of the present study was to analyse the antimicrobial use pattern during the COVID-19 pandemic in the MICU of a tertiary care hospital in Eastern India. The objective was to assess the existing hospital antimicrobial policy, if any.

MATERIALS AND METHODS

A hospital-based retrospective, observational study was conducted in the Department of Pharmacology at a Tertiary Care Hospital (Government Medical College Kolkata), West Bengal, India. The study duration was two months, September and October, 2022. The hospital served as one of the state's reference hospitals for caring for critically ill patients affected by COVID-19. After obtaining approval from the Institutional Ethics Committee (IEC) {MC/KOL/IEC/NON-SPON/1472/07/2022 dated 08/07/2022}, data was extracted from the standard clinical records of the MICU over a one-month period (September 2022). The data was then analysed, and the results were compiled over another month (October 2022).

Inclusion and Exclusion criteria: All complete and legible records of MICU patients admitted between April and June 2021 for more than 24 hours were included in the study, irrespective of whether they included an antimicrobial or not. Medical records that were incomplete, illegible, or included data on patients admitted to the MICU for less than 24 hours were excluded from the study.

Sample size calculation: According to WHO guidelines for drug utilisation studies, a minimum of 600 prescriptions needs to be studied over a one-year period [22]. Therefore, in the present study, a minimum of 50 prescriptions/records per month i.e., a total of 150 medical records (50×3 months) should be assessed. However, due to the exclusion of incomplete or inaccessible records, only 128 records could be studied. A pilot study with 10 medical records was conducted over one week to formulate the final standard operating procedure before the main study. The findings of the pilot study have been included in the final result Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. Number of DDD can be calculated as: [No. of packages used×No. of tablets or vials used×No. of g per tablet or vial]/WHO-DDD of antimicrobials used in gm] [23] A bed-day (or inpatient day) is a day during which a person admitted as an inpatient is confined to a bed and in which the patient stays overnight in a hospital [24].

No. of bed-days may be calculated as: No. of beds in ICU×Occupancy index×No. of days

DDD/100 bed days [25] can be calculated as:

[Total dose in mg during the study period×100]/[DDD of the drug×study duration (days)×bed strength×average bed occupancy rate].

Study Procedure

The study population consisted of all diagnosed COVID-19 adult patients (≥18 years) admitted for atleast 24 hours in the MICU. These patients had a positive result on a RT-PCR assay of a specimen collected with a nasopharyngeal swab. The data included patients admitted between April 2021 and June 2021 (three months) since the peak of the second wave occurred around May 14, 2021.

Individual consents from patients were not possible as the present study was a retrospective study, and all patients had already been discharged after recovery or had expired during treatment. A waiver of consent was obtained from the IEC along with ethical clearance. All data were entered using a unique patient identifier, and confidentiality was strictly maintained.

A total of 148 records were collected. Among them, 20 records included incomplete data and had to be excluded. Upon inspection, it was found that 16 of these excluded records contained data on patients who expired during the course of treatment, and four records contained data on patients who had been discharged from the ICU. Data for individual patients were recorded from "day 0" until the day of discharge from the ICU.

Data collected for the study included the following:

- **Patient demographics:** This included the identification number, age, sex, co-morbidities, and duration of stay for each patient.
- **Antibiotic data:** This included the number of AMAs prescribed, the Anatomical Therapeutic Chemical (ATC) code of the AMA, the class of AMA according to the WHO AWaRe classification, dose, frequency, route of administration, time of initiation of antibiotic (before/after admission to the ICU), the number of antibiotics given to each patient, and whether they were given concurrently or sequentially. Any changes in antibiotic treatment during the ICU stay and the reason for the change were also noted.
- **WHO core prescribing indicators [22]:** This included the average number of medicines prescribed per consultation, the percentage of drugs prescribed by their generic name, the percentage of encounters where an antibiotic was prescribed, and the percentage of medicines prescribed from the essential drugs list.
- Reports of culture and sensitivity tests, if conducted.
- **Laboratory investigations:** This included complete haemogram, serum biomarkers such as CRP, Procalcitonin (PCT), IL-6, and ferritin.

- Final clinical outcome of the patient.
- **Duration of stay:** This was measured as the total number of days in the MICU minus the day of discharge.
- **Volume of antimicrobial use:** This was assessed as Defined Daily Dose (DDD)/100 bed-days. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, as defined by the WHO.
- Information about the hospital's antimicrobial policy was gathered from the ICU incharge of the Institution through a one-to-one interview conducted over the telephone.

STATISTICAL ANALYSIS

For statistical analysis, categorical variables were expressed as frequency and percentage and continuous variables were described as mean±SD. The level of significance for categorical variables was assessed using the Chi-square test, while the Mann-Whitney U test was used for continuous variables. A p-value of less than 0.05 was considered significant at an alpha error of 5% and a confidence interval of 95%.

RESULTS

A total of 128 records met the inclusion criteria and were analysed. These records were divided into two groups based on the clinical outcome of the patients. Group A (n=100) included patients who expired during their stay in the MICU, while group B (n=28) included patients who were discharged from the MICU and shifted to the recovery ward. [Table/Fig-1] represents the characteristics of the study population. From the table, it is evident that the two groups were comparable in terms of demographic characteristics, the presence of co-morbidities, Length of Stay (LoS) in the ICU, and antimicrobial usage. The Mann-Whitney U test was used for numerical variables (age, days between hospitalisation and ICU admission, and number of AMAs used), and the Chi-square test was used for categorical variables (sex, co-morbidities, and the percentage of patients where more than one AMA was used concurrently). A p-value of less than 0.05 was considered significant.

Variables	Group A (n=100)	Group B (n=28)	Statistical test used	p-value	Level of significance
Age (in years) (Mean±SD)	58.31± 15.22471	51.92857± 18.33218	Mann-Whitney U	0.1443	Not significant
Sex	M-59	M-17			
	F-41	F-11	Chi-square	0.870	Not significant
Co-morbidities n (%)	61 (61%)	17 (60.71%)	Chi-square	0.978	Not significant
Days between hospitalisation and ICU admission (Mean±SD)	4.72± 4.7462	3.43± 2.51	Mann-Whitney U	0.5485	Not significant
Number of AMAs used (Mean±SD)	4.28± 1.8039	4.28± 1.5600	Mann-Whitney U	1	Not significant
Concurrent AMAs n (%)	82 (82%)	24 (85.71%)	Chi-square	0.645184	Not significant

[Table/Fig-1]: Characteristics of the study population.
SD: Standard deviation; M: Male; F: Female; ICU: Intensive care unit; AMA: Antimicrobial agent

Based on this table, it is evident that the two groups were comparable. [Table/Fig-2] represents the co-morbidities in the patients admitted to the MICU. It is observed that the most common co-morbidity was hypertension, with 47 out of 128 patients (37%) having this condition. Diabetes mellitus was the second most common co-morbidity, present in 22 (17%). Additionally, 28 patients (20%) had both diabetes mellitus and hypertension. There was significant overlap of co-morbidities, as many patients had multiple co-morbidities.

[Table/Fig-3] presents the drug use data. It can be observed that there was no significant difference between the average number of drugs the average number of antimicrobials used per prescription in the two groups. The average number of antibiotics prescribed per record was 4.28 and 4.03, respectively, which was comparable across the two groups. In group A, 78% of the antimicrobials used were prescribed by generic name, while in group B, the percentage was 81%. For both groups, 87% and 91% of the drugs respectively were from the essential drug list. These percentages were also comparable between the two groups. The percentage of antimicrobials among total drugs was also similar in both groups. It is worth noting that all patients had received atleast one AMA prior to their admission to the ICU. Among the total 128 patients, 78.125% succumbed before discharge from the ICU. In group A, 82% of the patients and in group B, 86% of the patients had received more than

Co-morbidity	Group A (n=100)	Group B (n=28)	n (%)
HTN	42	5	47 (36.71)
DM	18	4	22 (17.18)
DM+HTN	25	3	28 (21.8)
CKD	2	0	2 (1.5)
Resp disease	8	2	10 (7.81)
IHD	6	0	6 (4.68)
Hypothyroidism	3	2	5 (3.90)
Pregnancy	4	1	5 (3.90)
Others			3 (3.84)

[Table/Fig-2]: Prevalence of co-morbidities.
HTN: Hypertension; DM: Diabetes mellitus; CKD: Chronic kidney disease; IHD: Ischemic heart disease

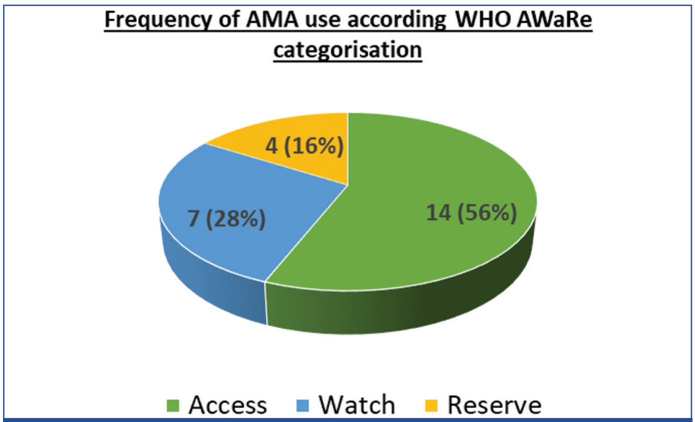
ICU patients with COVID-19	Group A (n=100)	Group B (n=28)	Statistical test used	p-value	Level of significance
Average no. of drugs used per prescription {Median (Q1-Q3)}	17(13-21)	17(15-19)	Mann-Whitney U test	0.61	Not significant
Average no. of antibiotics prescribed per record {Median (Q1-Q3)}	4.28 (3-5)	4.03 (3-5.25)	Mann-Whitney U test	1	Not significant
AMAs prescribed by generic name n (%)	78 (78.0%)	23 (81.0%)	Chi-square test	0.59	Not significant
AMAs from EDL n (%)	87 (87%)	25.4 (91.0%)	Chi-square test	0.37	Not significant
Percentage of AMAs in total drugs (Mean±SD)	24.25±8.01	26.20±10.69	Mann-Whitney U test	0.58	Not significant
Frequency of concurrent use of AMAs n (%)	82 (82%)	24 (85.71%)	Chi-square test	0.44	Not significant
Laboratory Investigations (complete haemogram, serum biomarkers including CRP, PCT, IL-6, ferritin)	Total 128 (100%), i.e., while admitted in ICU, all patients in both groups had undergone investigations)				
Percentage of patients who succumbed to COVID-19 while in ICU	A total of 100 (78.12%) {Out of 128 total records collected, 100 patients had succumbed in ICU}				
Time of initiation of AMAs	All 128 (100%) patients had received atleast one AMA before their admission in ICU				

[Table/Fig-3]: Drug use data N=128).
Q1: First quartile; Q3: Third quartile; EDL: Essential drug list; ICU: Intensive care unit; AMA: Antimicrobial agent; CRP: C-reactive protein; PCT: Procalcitonin; COVID-19: Coronavirus disease-2019

one AMA simultaneously. [Table/Fig-4] represents the names of the AMAs used according to WHO AWaRe classification. From [Table/Fig-5], it is evident that when considering the total number of AMAs used, the maximum number of AMAs were from the access group. However, AMAs from the reserve group were also frequently used, accounting for 16% of the total AMAs.

Access group	Doxycycline, clindamycin, amikacin, amoxycillin+clavulanic acid
Watch group	Piperacillin/tazobactam, levofloxacin, meropenem, teicoplanin, clarithromycin, cefoperazone, ofloxacin, metronidazole
Reserve group	Colistin, imipenem-cilastatin, linezolid, polymyxin B, tigecycline

[Table/Fig-4]: Antimicrobial Agents (AMA) used according to WHO AWaRe classification.



[Table/Fig-5]: Frequency of AMAs used as per WHO classification.
AMA: Antimicrobial agent

[Table/Fig-6] represents the total number of AMAs received by the patients from their admission until their discharge or demise. From the table, it can be observed that 33 patients from group A and nine patients from group B had received 1 to 3 AMAs. Additionally, 55 patients from group A and 16 patients from group B had received 4 to 6 AMAs. Furthermore, 12 patients from group A and 3 patients from group B had received more than 6 AMAs during their stay in the hospital.

Groups	Total number of AMAs used		
	1-3 n (%)	4-6 n (%)	>6 n (%)
Group A (n=100)	33 (33)	55 (55)	12 (12)
Group B (n=28)	9 (32.14)	16 (57.14)	3 (10.71)

[Table/Fig-6]: Average number of AMAs used per patient.

[Table/Fig-7] represents the frequency of use of individual AMAs. From this table, it is evident that 73% of patients from group A and 71% of patients from group B received Inj. meropenem. Inj. piperacillin-tazobactam was the second most commonly used AMA in both groups. Other antimicrobials prescribed to the patients included remdesivir, ivermectin, clotrimazole, fluconazole, caspofungin, and voriconazole.

For the other objective of the study, which was assessing the hospital's antimicrobial policy, a one-to-one interview was conducted with the then ICU incharge. As the ICU incharge had been transferred to another Institution, the interview was conducted over the telephone. The following points were noted:

- There was no antibiogram available for the period under consideration, which was April, May, and June 2021.
- The hospital did not have an antimicrobial protocol committee or an antimicrobial protocol policy during the concerned period.
- In the ICU, patients were treated empirically based on their disease severity and the level of inflammatory biomarkers such as CRP, PCT, IL-6, ferritin, etc.
- There was no operational antimicrobial stewardship programme during the concerned period.

Individual AMA used (percentage of total number of AMAs used)	Group A (n=100)	Group B (n=28)
Inj. Meropenem	73	71
Inj. Piperacillin+tazobactam	69	67.85
Inj. Doxycycline	61	64.28
Inj. Clindamycin	55	53.57
Inj. Teicoplanin	26	28.57
Inj. Tigecycline	23	35.71
Inj. Colistin and polymyxin B	18	10.71
Inj. Levofloxacin	7	3.57
Inj. Linezolid	4	3.57
Inj. Amikacin	3	3.57
Inj. Metronidazole	3	0
Inj. Co-trimoxazole	3	0
Inj Amoxycillin/clavulanic acid	2	0
Inj. Clarithromycin	1	0
Inj. Cefoperazone	1	0
Inj. Imipenem+cilastatin	1	0
Inj. Ofloxacin+ornidazole	1	0

[Table/Fig-7]: Frequency of use of individual AMAs (N=128).

- Due to the ongoing lockdown and restrictions on available staff, only skeletal service could be maintained, and proper maintenance of records was hampered.

DISCUSSION

Intensive Care Units (ICUs) harbour critically ill patients who are often affected by multidrug resistant bacteria, including resistance to third-generation cephalosporins, aminoglycosides, beta-lactam/beta-lactam inhibitors, fluoroquinolones, and carbapenems [26]. In 2017, the Indian Council of Medical Research (ICMR) laid down guidelines for the empirical use of AMAs in the ICU [27]. However, the AMA protocols still differ from institution to Institution. The present study aimed to analyse antibiotic use in the MICU of the Institution and explore the rationale behind it. Additionally, an attempt was made to correlate AMA use with the final clinical outcomes of the patients. The findings from the present study could be utilised to identify crucial gaps in the hospital's antimicrobial policy, contributing to the necessity of implementing an antimicrobial stewardship program that promotes judicious use of AMAs in the future.

The demographic characteristics of the patients who recovered after being admitted to the ICU did not significantly differ from those who did not survive. Hypertension was the most common co-morbidity, followed by diabetes. This finding was similar to a study from Spain by Llorach A et al., in 2022, which reported hypertension, diabetes, and cardiovascular disease as the leading co-morbidities in the overall study sample [28]. The mean LoS in the ICU in the present study was around seven days (7.43). The values in both groups were comparable. A study conducted by Rees EM et al., in 2020 compared LoS in the ICU within and outside of China [29]. They found a median value of eight days (IQR 5-13) for China and seven days (IQR 4-11) for outside of China. In another retrospective study conducted in the United Kingdom [30], the mortality rate was found to be 1.9% in patients who stayed <7 days compared to 11.2% for patients who stayed for 7-14 days.

A total of 100% of patients admitted or referred to the ICU received atleast one antibiotic prior to their admission. The majority of patients received two antibiotics concurrently. A meta-analysis by Langford BJ et al., and a study by Chen N et al., on antibiotic use in COVID-19 report a similar prevalence of AMA use around 75% [7,31]. Therapy was empiric and based on the clinical acumen of the physician and laboratory markers of inflammation, including CRP and PCT, as well as High-resolution Computed Tomography (HRCT) of the chest. According to Schouten J et al., [16] PCT has been found to be valuable in guiding antimicrobial therapy in COVID-19 patients. If the value is low, AMAs may be withheld. If the value is high, serial measurements could reflect the increased inflammatory status of the patient and guide AMA therapy.

Among the antimicrobials used, meropenem followed by piperacillin/tazobactam, doxycycline, and clindamycin were the most common drugs. Both meropenem and piperacillin belong to the watch group in the WHO AWaRe classification, indicating an increased potential to develop resistance. Gram-negative organisms, including Enterobacteriaceae, play a major role in ICU-associated infections such as Bloodstream Infections (BSI), Hospital-acquired Pneumonia (HAP), Ventilator-associated Pneumonia (VAP), complicated Urinary Tract Infections (cUTIs), and complicated Intra-abdominal Infections (cIAIs). Carbapenems, which until recently had good activity against these organisms, were commonly used in ICUs worldwide, including India. The present study study also found an increased use of carbapenems in the ICU during the COVID-19 pandemic [32].

Clindamycin belongs to the access group in the WHO AWaRe classification and is recommended for empiric therapy against infectious diseases. A 61% of patients received parenteral doxycycline during their stay in the ICU. Colistin and polymyxin B were used in 18 patients. These drugs belong to the reserve group and were possibly used as a last resort in carbapenem-resistant infections.

A study conducted in Brazil in 2020 to assess the use of antibiotics in the ICU during COVID-19 reported an increased use of meropenem followed by piperacillin/tazobactam, similar to the present study. However, another study from Croatia by Mustafa et al., reported Imipenem as the most frequently used antibiotic in COVID-19 patients admitted to the ICU, followed by ceftriaxone and fluoroquinolones [33]. Meropenem was used very sparingly in the above study. Cravedi P et al., conducted a multihospital cohort study in the USA in 2020 and reported the prophylactic use of a wide range of broad-spectrum antibiotics such as piperacillin-tazobactam, meropenem, amoxicillin, beta-lactam-beta-lactamase inhibitor, imipenem, etc., similar to the present study [34]. Concurrent use of antimicrobials was practiced in 82% of records from expired patients and 85.71% of records from patients who survived. This percentage was much higher than the study by Chen N et al., who reported a 45% use of combination antibiotics [31].

The present study found that 78.125% of patients admitted to the ICU with COVID-19 infection did not survive. This rate is quite high compared to a study conducted in Maharashtra, which reported a mortality rate of 26.1% among patients suffering from COVID-19 and admitted to the ICU [35]. Agarwal R et al., conducted a mortality assessment of 328 deceased patients with COVID-19 in the ICU of a tertiary care hospital and reported a mortality rate of 37.7% [36]. Thus, present study revealed a much higher mortality rate than other facilities. This high rate may be due to the increased severity of infection among the admitted patients, decreased immunity, or drug resistance.

As shown in the “results” section, the final outcome did not depend on the number of antibiotics used. In the present study, the DDD per 100 bed days was considered a predictor of antibiotic consumption. The assumed average maintenance dose per day for a drug used for its main indication in adults [37]. It is calculated as the number of grams of antibiotic dispensed, divided by the WHO DDD. Meropenem had the maximum Antimicrobial Consumption Index (ACI) as calculated by DDD/bed-days×100, followed by oral doxycycline. Piperacillin/tazobactam was the third most commonly used antimicrobial. Saxena S et al., in their study conducted in the ICU of a tertiary care hospital found that beta-lactams and metronidazole were the most commonly used antimicrobials [38]. The selection of antibiotics depends on the local antibiogram, type and severity of infection, and the implementation of an antibiotic stewardship programme. In the present study, bacteriological study of the ICU has not been done. AMAs were prescribed purely based on the clinical condition of the patient and their immune status, as reflected by levels of serum biomarkers of inflammation.

To meet the secondary objective of assessing the hospital’s antimicrobial policy, a one-to-one interview was conducted with the then ICU incharge over the telephone. However, there was no antibiogram, hospital antimicrobial policy, or protocol during the study period. The antimicrobial use was guided by the clinical condition and levels of inflammatory biomarkers including PCT, CRP, IL-6, and ferritin. Ideally, antimicrobial therapy should be based on bacteriological identification, but this often proves to be a practical challenge and is not always possible in an overpopulated, low-income, developing, and resource-poor country like India, particularly during a pandemic. The second wave of COVID-19, with over 400,000 deaths, has been considered the worst tragedy since partition, as reported by the Washington-based think tank Centre for Global Development (CGD) and co-authored by India’s former chief economic adviser, Arvind Subramanian [39]. Only skeleton staff could be maintained during that time to cater to the huge number of affected patients, leading to gaps in ideal practices.

Kakkar A et al., stated some factors limiting the successful implementation of an antimicrobial stewardship programme in a resource-poor country like India [40], including lack of clear political commitment, inadequate funding, overcrowded healthcare systems, and lax legal and regulatory frameworks.

One of the most challenging aspects of conducting the present study was the absence of electronic records, which could have solved the problem of illegible and incomplete data entries in treatment sheets. Although mentioned in bed head tickets, not all investigation reports were physically available. This problem could have been solved with electronic data entry. The transfer of some nursing staff and physicians directly involved in ICU patient care during the study period also hindered data collection. For example, the reason for a change in antibiotic regimen was not mentioned in any record and could not be included in the results.

The COVID-19, in a way, exposed the unpreparedness of the tertiary care hospital in meeting the challenges of the previously unknown SARS-CoV-2 infection and its consequences. Antimicrobials were prescribed solely based on the clinical suspicion of the treating physicians and lacked microbiological investigations to support the ongoing therapy. There was no Institutional antibiotic policy or available antibiogram. The empirical use of a large number of high-end antimicrobials could not save the patients, as seen by the clinical outcome.

Preparation of antibiograms and the implementation of an antimicrobial stewardship programme are urgently needed to avoid such a catastrophe in the future. Awareness about antibiotic stewardship programmes should be generated at all levels in order to promote rational antimicrobial practice.

Limitation(s)

The present study was conducted in only one tertiary care hospital, involving a small sample size. More studies across hospitals from different corners of India are needed for a proper assessment of antimicrobial use in COVID-19 ICUs.

CONCLUSION(S)

The COVID-19 pandemic in 2019 posed a major challenge to the protagonists of rational antimicrobial use. The deficiency of prior knowledge about the pathophysiology, transmission, and prognosis of the disease on one hand, and the deaths of millions of people on the other, forced physicians to resort to widespread empirical use of broad-spectrum antibiotics, along with other drugs, in their bid to save the patient. Now that the situation is slightly under control, it is time to take necessary steps to prevent such mishaps in the future.

REFERENCES

[1] Worldometer. India Coronavirus cases [internet]. [Updated 2023 August 11; cited 2023 May. Available from: https://www.worldo meters.info/coronavirus/country/india/.

[2] Clinical management of Covid-19. Interim guidance. World Health Organization [internet]. 2020 May 27; cited 2023 May. Available from: https://apps.who.int/iris/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5-eng.pdf.

[3] Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS. et al. Coronavirus Disease 2019–COVID-19. Clin Microbiol Rev. 2020; 33(4):e00028-20.

[4] Living guidance for clinical management of COVID-19. World Health Organization [internet]. 2021 Nov 23; cited 2023 April 24. Available at: https://www.who.int/publicatio ns/i/item/W HO-2019-nCoV-clin ical-2021-2.

[5] Guidelines for management of co-infection of COVID-19 with other seasonal epidemic prone diseases. Government of India Ministry of Health & Family Welfare Directorate General of Health Services (EMR Division) [intern et]. Cited 2023 May. Available from: https://www.mohfw.gov.in/pdf/GuidelinesformanagementofcoinfectionofCOVID19withotherseasonalepidemicpronediseases.pdf.

[6] Westblade LF, Simon MS, Satlin MJ. Bacterial co-infections in coronavirus disease 2019. Trends in microbiology. 2021;29(10):930-41.

[7] Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. Clin Micro biol Infect. 2020;26(12):1622-29.

[8] Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and su perinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. PLoS ONE. 2021;16(5):e0251170.

[9] Puzniak L, Finelli L, Kalvin CY, Bauer KA, Moise P, De Anda C, et al. A multicenter analysis of the clinical micro biology and antimicrobial usage in hospitalised patients in the US with or without COVID-19. BMC Infect Dis. 2021;21(1):01-09.

[10] Contou D, Claudinon A, Pajot O, Micaëlo M, Flandre PL, Dubert M, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care. 2020;10(1):119.

[11] Weiner-Lastinger LM, Pattabiraman V, Konnor RY, Patel PR, Wong E, Xu SY, et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemio l. 2022;43(1):12-25.

[12] Karami Z, Knoop BT, Dofferhoff ASM, Blaauw MJT, Janssen NA, van Apeldoorn M, et al. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalised patients with COVID-19: Results from a multicentre retrospective cohort study in The Netherlands. Infect Dis (Lond). 2021;53(2):102-10.

[13] Brosnahan SB, Jonkman AH, Kugler MC, Munger JS, Kaufman DA. COVID-19 and respiratory system disorders: Current knowledge, future clinical and translational research questions. Arterioscler Thromb Vasc Biol. 2020;40(11):2586-97.

[14] Lampart M, Zellweger N, Bassetti S, Tschudin-Sutter S, Rentsch KM, Siegemund M, et al. Clinical utility of inflammatory bio markers in COVID-19 in direct comparison to other respiratory infections-A prospective cohort study. PLoS One. 2022;17(5):e0269005.

[15] Klein Kluwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: A cohort study. Crit Care. 2015;19(1):319.

[16] Schouten J, De Waele J, Lanckohr C, Koulenti D, Haddad N, Rizk N, et al; Alliance for the Prudent Use of Antibiotics (APUA). Antimicrobial stewardship in the ICU in COVID-19 times: The known unknowns. Int J Antimicrob Agents. 2021;58(4):106409.

[17] WHO releases the 2019 AWaRe Classification Antibiotics. World Health Organization. [Internet] 2019 October. Cited September 2023. Available at: https://www.who.int/news/item/01-10-2019-who-releases-the-2019-aware-classification-antibiotics.

[18] Target ≥60% of total antibiotic consumption being Access Group-Antibiotics (GPW13target 4b). THE GLOBAL HEALTH OBSERVATORY. World Health Organization [Internet] cited Sepetmeber 2023. Available at: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/5767.

[19] Vâţă A, Roşu FM, Do rneanu OS, Lehaci AE, Luca Ş, Loghin II, et al. Antibiotic usage in the COVID-19 intensive care unit of an infectious diseases hospital from Nord-Eastern Romania. Medicina (Kaunas). 2023;59(4):645.

[20] Silva ARO, Salgado DR, Lopes LPN, Castanheira D, Emmerick ICM, Lima EC. Increased use of antibiotics in the intensive care unit during coronavirus disease (COVID-19) Pandemic in a Brazilian Hospital. Front Pharmacol. 2021;12:778386.

[21] Shaz K, Elsa H, Abdullah M, Benjamin P, Olivia M, Zohra R, et al. Antimicrobial use in the second and third wave of COVID-19 Infections in a UK intensive care unit. Critical Care Medicine. 2023;51(1):207.

[22] Introduction to Drug Utilisation Research 2003. World Health Organization [Internet]. Oslo Norway 2003 [cited May 2023]. Available at: https://apps.who.int/iris/bitstream/h andle/10665/42627/924156234X.pdf?sequence=1 &isAllo wed=y.

[23] Monnet DL. How to Measure Antimicrobial Consumption. National Center for Antimicrobials and Infection Control, Statens Serum Institut, Copenhagen, Denmark. [Internet] Cited May 2023. Available from: https://www.researchg ate.net/profile/Ali_Aldallal2/post/Antibiotics_consumption_calculation_tools/attachment/59d6291479197b80779878d c/AS%3A333596058505217%401456546906572/download/How+to+Measure+Antimicrobial+Consumption.pdf.

[24] OECD Health Statistics. Definitions, Sources an d Methods Hospital (inpatient) bed-days by diagnostic categories. 2022 July [cited May 2023]. Available from: https://stats.oecd.org/fileview2.aspx?IDFile=ca8d 522d-31ed-40b5-a1474bc5eda1c97d.

[25] Patel MK, Barvaliya MJ, Patel TK, Tripathi C. Drug utilisation pattern in critical care unit in a tertiary care teaching ho spital in India. Int J Crit Illn Inj Sci. 2013;3(4):250-55.

[26] Haque OI, Shameem M, Hashim W. Secondary infections in critically ill patients with COVID-19: A retrospective single-center study. Lung India. 2023;40(3):210-14.

[27] Treatment Guidelines for Antimicrobial Use in Common Syndromes [internet]. Indian Council of Medical Research. Department of Health Research. New Delhi, India 2017 [cited May 2023]. Available at: https://main.icmr.nic.in/sites/default/files/guidelines/Treatment_Guidelines_2019_Final.pdf.

[28] Roso-Llorach A, Serra-Picamal X, Cos FX, Pallejà-Millán M, Mateu L, Rosell A, et al. Evolving mortality and clinical outcomes of hospitalised subjects during successive COVID-19 waves in Catalonia, Spain. Glob Epidemiol. 2022;4:100071.

[29] Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, Pearson CA, et al. COVID-19 length of hospital stay: A systematic review and data synthesis. BMC Med. 2020;18(1):270.

[30] Fluck D, Fry CH, Rankin S, Lewis A, Robin J, Rees J, et al. Does the length of stay in hospital affect healthcare outcomes of patients without COVID-19 who were admitted during the pandemic? A retrospective monocentric study. Intern Emerg Med. 2022;17(5):1385-93.

[31] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-13.

[32] Das S. The crisis of carbapenemase-mediated carbapenem resistance across the human-animal-environmental interface in India. Infect Dis Now. 2023;53(1):104628.

[33] Mustafa L, Tolaj I, Baftiu N, Fejza H. Use of antibiotics in COVID-19 ICU patients. J Infect Dev Ctries. 2021;15(4):501-05.

[34] Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, et al. COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium. Am J Transplant. 2020;20(11):3140-48.

[35] Zirpe KG, Dixit S, Kulkarni AP, Pandit RA, Ranganathan P, Prasad S, et al. The second- vs first-wave COVID-19: More of the same or a lot worse? A comparison of mortality between the two waves in patients admitted to intensive care units in nine hospitals in western Maharashtra. Indian J Crit Care Med . 2021;25(12):1343-48.

[36] Aggarwal R, Bhatia R, Kulshrestha K, Soni KD, Viswanath R, Singh AK, et al. Clinico epidemiological features and mortality analysis of deceased patients with COVID-19 in a tertiary care center. Indian J Crit Care Med. 2021;25(6):622-28.

[37] Definitions and general considerations. World Health Organization. ATC DDD Toolkit [internet]. Cited 2023 May. Available at: https://www.who.int/tools/atc-ddd-toolkit.

[38] Saxena S, Priyadarshi M, Saxena A, Singh R. Antimicrobial consumption and bacterial resistance pattern in patients admitted in ICU at a tertiary care center. J Infect Public Health. 2019;12(5):695-99.

[39] 2nd Covid wave was India's worst tragedy since Partition, saw up to 49 lac excess deaths: Report. India Today [internet]. 2021 July; cited 2023 April. Available at: https://www.indiatoday.in/coronavirus-outbreak/story/2nd-covid-wave-was-india-worst-tragedy-since-partition-saw-up-to-49-lac -excess-death s-1830894-2021-07-21.

[40] Kakkar AK, Shafiq N, Singh G, Ray P, Gautam V, Agarwal R, et al. Antimicrobial steward ship programs in resource constrained environments: Understanding and addressing the need of the systems. Front Public Health. 2020;8:140.

PARTICULARS OF CONTRIBUTORS:

1. MBBS Student, Government Medical College, Kolkata, West Bengal, India.
2. Associate Professor, Department of Pharmacology, Government Medical College, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Sarmila Nath,
BB-11/C, Salt Lake, Kolkata-700064, West Bengal, India.
E-mail: sarmilanath13@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jun 06, 2023
- Manual Googling: Oct 24, 2023
- iThenticate Software: Oct 27, 2023 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 01, 2023**
Date of Peer Review: **Aug 04, 2023**
Date of Acceptance: **Oct 30, 2023**
Date of Publishing: **Dec 01, 2023**