Original Research Article

Impact of coronavirus disease pandemic on antimicrobials consumption and antimicrobial resistance during the first and second wave in a tertiary care hospital, in India

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ABSTRACT

Background: This study measured the impact of the first and second wave of COVID-19 pandemic (in the year 2020-21) on the antibiotics uses and their effect on gram nehative bacterial species *Klebsiella, Enterobacter, Pseudomonas* and *Acinetobacter*.
Methods: The number of patient admission month-wise, antibiotic consumption, blood cultures collected, number of positive BCs, and antibiotic resistance were analysed retrospectively for the years 2020, 2021, and 2019 for comparison, in tertiary care hospital (ca. 840 beds).
Results: Half of patients admitted in years 2020 and 2021 in our hospital had COVID-19. A significant increase in total antibiotic consumption during the years 2020 (75.53 DDD per 100 admissions) and 2021 (91.71 DDD per 100 admissions) occurred in comparison to the year 2019 (52.5 DDD per 100 admissions). The rate ratio of BCs per 100 admissions increased by 74% in the year 2020, and 118% in the year 2021 in comparison with the rate ratio to the year 2019. The BSI rate per 100 admissions increased overall by 24% in March 2020 and 115% in April 2020, the rate ratio of BSIs per 100 admissions raised 58.4% for *Klebsiella* and 239.3% for *E. coli*, but remain the same for *Acinetobacter* and *Aeruginosa.* A sharp increase in the rate of BSIs caused by microorganisms resistant to cephalosporins was also observed in the years 2020 and 2021.
Conclusions: present study highlights the impact of the first and second waves of the COVID-19 pandemic on antibiotic consumption and the increasing prevalence hospital-acquired infections and antimicrobial resistance.

Keywords: COVID-19, Define daily dose, AWaRe classification, Hospital-acquired bloodstream infections, Antimicrobial resistance

INTRODUCTION

The COVID-19 outbreak, caused by the SARS-CoV-2 virus declared a pandemic by the World Health Organization (WHO) on 11 March 2020.[1] Its widespread global transmission and unparalleled impact reshaped the world and have strained the medical healthcare services beyond their normal capacity. The increased number of hospitalized patients, prolonged hospitalization with or without mechanical ventilator support and similar clinical characteristics with bacterial respiratory tract infections the coronavirus disease 2019 (COVID-19) has a potential impact on antibiotic overuse.[2] COVID-19 has overlapping clinical and radiological characteristics with bacterial respiratory tract infections. A study conducted by the infectious disease unit in China in January 2020, found that about 71% of patients admitted for COVID-19 had received antibiotics despite 1% confirmed bacterial co-

infection.[3] Other studies by Hughes et al, Zhou et al, and Sharifipour et al reported 3.2%, 15% and 19% bacterial infection rates, depending on the country and the time at which the samples are obtained after the onset of clinical symptoms.[4, 5] It has been widely reported that patients hospitalized with COVID-19 were more susceptible to getting infected by secondary infections caused by bacteria or fungus during their hospital stay (hospital-onset infections) in comparison to the community before hospital admission (community-onset infections).[6] Hence, from the beginning of the COVID-19 pandemic, increased antibiotic prescription and a potential rise in AMR has been a growing concern. A report by CDC shows increased use of some specific groups of antibiotics like macrolides, cephalosporins and tetracyclines, for treatment of COVID-19 and community-acquired pneumonia.[7] The first and second waves of COVID-19 offer opportunities in the institute to implement antimicrobial stewardship programs in line with WHO guidelines, for the education of the critical care team, development of clinical guidelines, surveillance of resistance and antibiotic uses. The present study was undertaken to analyze the impact of COVID-19 pandemic first and the second wave on the use of antibiotics and its correlation with antimicrobial resistance in a tertiary care hospital

METHODS

This is a retrospective record-based analysis of systemic antimicrobial (J01) consumption. Trend analysis of antimicrobial consumption and its correlation with antibiotic resistance pattern (using antibiogram) in blood samples was done for 3-years (2019-2021). The study was conducted in the Pharmacology and Microbiology department of 840 bedded Saraswathi institute of medical sciences, Pilakhuwa, Hapur, Uttar Pradesh from the year 2019-2021. The procurement data for antibiotics were obtained from the hospital Central drug store (CDS) for the years 2019-2021. As we have no antibiotic use data at the patient level, the antibiotic procured by different medical units is used as a proxy for antibiotic consumption assuming that the same has been dispensed to patients. Antibiotics which were classified as J01 category for systemic use under the ATC classification system and antibiotics dispensed between 2019 to 2021 from the hospital were included in the study. Any antibiotic or fixed-dose combination not recommended by the WHO AWaRe classification were excluded from the study.

Classification of antimicrobials

Antimicrobial drugs were coded based on the Anatomical Therapeutic Chemical (ATC) classification and antibiotics for systemic use ATC code J01 were considered.[8] Antibiotics were classified as access, watch and reserve (AWaRe classification) (WHO EMLc 2019).[9] The number of antimicrobial drugs in grams was converted into the number of defined daily (DDDs)/100 bed-days using AMC Tool 2019.

Drug Utilization 90%

Consumption of antibiotics was ranked based on their percentage volume of DDD accounted for drug utilization 90% (DU90%) of total antibiotics consumed.

AWaRe classification

The World Health Organization (WHO) in the year 2017 updated the Essential Medicine List (EML) and categorized the antibiotic into three groups AWaRe Sharlend et al.[10] In the Access-group Antibiotics agents with a narrow spectrum and lower resistance potential such as amoxicillin/ampicillin, benzathine penicillin, trimethoprim-sulfamethoxazole, amoxicillin-Clavulanic acid, Cloxacillin were kept as a first-choice. In the Watch group antibiotics with high resistance potential in comparison to the Access, group were kept which includes third-generation cephalosporins, fluoroquinolones, and carbapenems. The Reserve group includes antibiotics used as last-resort like polymyxins, fourth and fifth-generation cephalosporins.

Blood samples

Antibiotics susceptibility testing of pathogens was done by Pathogen-specific surveillance AST panels outlined in the Standard Operating Procedures (SOP) of Surveillance of priority bacterial pathogens under National Program for Containment of Antimicrobial Resistance by National Center for Diseases Control (NCDC), Government of India.[11] A positive blood culture (BC) set was defined as positive microbial growth after 24-48 hrs of culture. A clinically significant episode of bloodstream infection (BSI) was defined as positive BC set to grow a recognized pathogen. Commensal skin microbiota (*Staphylococci, Corynebacteria*, and *Propionibacteria*) growing in culture was considered as contaminants and did not count in the study.

Statistical analysis

Aggregated data will be entered in Microsoft excel sheet and each antibiotic consumption will be explored for trend over time using linear regression and p value ($r^2 > 0.3$, $p \leq 0.05$) was considered statistically significant. Rate ratio and their confidence were computed using Poisson models, with a linear time trend to account for possible changes in rate over time. To account for multiple analyses, 99% confidence intervals (99%CI).

RESULTS

Patients

The COVID-19 pandemic first wave rise was observed at the beginning of March 2020 in India, peaked at the beginning of April and declined at the end of May. Similarly, the second wave of the COVID-19 pandemic was at its peak in May 2021.

Table 1: DDD Trend in Systematic antibiotic consumption over the years 2019-21.

Product name	FY1 Sorted	DDD	DDD 2019	DDD 2020	DDD 2021	DU 90%
Tab Azithromycin 500mg	J01FA10	0.3	23.93	31.68	35.92	39.1
Ceftriaxone 1 gm/vial	J01DD04	2	12.16	22.93	29.23	71.0
Cap. Augmentin 625 mg	J01XD01	1.5	4.65	6.32	6.53	78.1
Inj Metronidazole 500mg	J01XD01	1.5	4.24	4.48	5.71	84.4
Cap Doxycycline 100mg	J01AA02	0.1	1.27	2.38	5.45	90.3
Tab Ciprofloxacin 500mg	J01MA02	1	1.40	1.24	1.57	92.0
Cefotaxime 1 gm/vial	J01DD01	4	0.62	1.22	1.14	93.3
Amikacin 500mg/vial	J01GB06	1	1.12	1.03	1.10	94.5
Augmentin 1.2g/vial	J01CR02	3	0.62	0.77	0.92	95.5
Cefoperazone+ sulbactam 1 gm/vial	J01DD62	1	1.34	1.87	2.49	98.2
Meropenem 1 gm/vial	J01DH02	2	0.27	0.48	0.47	98.7
Ceftazidime 1 gm/vial	J01DD02	4	0.13	0.33	0.43	99.2
Piperacillin + Tazobactam 4.5 gm/vial	J01CR05	14	0.35	0.18	0.24	99.4
Vancomycin 500mg/vial	J01XA01	2	0.15	0.17	0.18	99.6
Gentamicin 80 mg/2ml	J01GB03	0.24	0.25	0.32	0.21	99.8
Inj Ampicillin 500mg/vial	J01CR01	6	0.05	0.14	0.10	100
Total	-		43.64	52.55	75.53	91.71	-

Table 2: Blood cultures and bloodstream infections during the 3-year period (2019-2021).

Parameters	2019	2020	2021
Number of admitted patients	6364	11855	12590
Number of BC sets collected per 100 admitted patients	15.8	19.8	25.5
Number of positive BC sets per 100 admitted patients	1.12	2.01	2.45
BSIs per 100 admitted patients	1.1	1.5	2.0
Klebsiella	0.6	0.7	0.9
E. coli	0.2	0.5	0.7
Acinetobacter	0.2	0.2	0.2
P. Aeruginosa	0.1	0.1	0.1

BSIs-Bloodstream infections

Correspondingly the number of COVID-19 inpatients present in our hospital increased progressively during both the waves (Figure 1). During the plateau period, COVID-19 patients represented half of all patients. Most of the major medical units were dedicated entirely to the admission of COVID-19 patients who did not require intensive care. The number of Intensive Care Unit (ICU) beds was increased by 3 times. Other beds were closed for admission, particularly in surgery, since the non-emergency surgical procedure was postponed.

Drug utilization 90% (DU 90%) using DDD methodology

The (Table 1) depicts the antibiotics (J01) consumption pattern using AWaRe, DDD and DU90% methodology to interpret the change in utilization pattern over the year 2019-2021. A significant increase of about 1.5 folds in total antibiotic consumption during the first COVID-19 wave (75.53 DDD per 100 admissions) in the year 2020 and 2 folds during the second wave (91.71 DDD per 100 admissions) in the year 2021 occurred in comparison to the year 2019 (52.5 DDD per 100 admissions). A total of 16 antibiotics 5 from Access and 11 from watch were consumed. No Reserve category antibiotic was used from the year 2019-21 (Figure 2). Out of 16 antibiotics

consumed 5 antibiotics (3 Access, and 2 from the Watch group) accounted for DU90%. Average DDD rates were highest for azithromycin (30.5 ± 6.08) followed by ceftriaxone (21.4 ± 8.63), augmentin (5.83 ± 1.03), metronidazole (4.83 ± 0.79), and doxycycline (3.03 ± 2.17) (Figure 3). Though the consumption of the Watch group was significantly higher in the year 2019 which further increased by 2% in the year 2020 as there were not any defined guidelines for antibiotic use in COVID-19 management. There was an overall increase in antibiotics DDD rates from the year 2019 to 2021 for all antibiotics with maximizing DDD in 2021.

Isolates

The number of isolates was assessed by computing the rate ratios of blood culture per 100 admissions (Table 2). During the periods of the first and second wave of COVID-19 in the year 2020 and 2021, there was a dramatic increase in the numbers of BCs in comparison to the year 2019 (15.89 BCs per 100 beds) i.e., 19.8 BCs per 100 beds in 2020 and 25.8 BCs per 100 beds in the year 2021. This represents an increase of 25% in the year 2020 and 113% in the year 2021 (Figure 4).
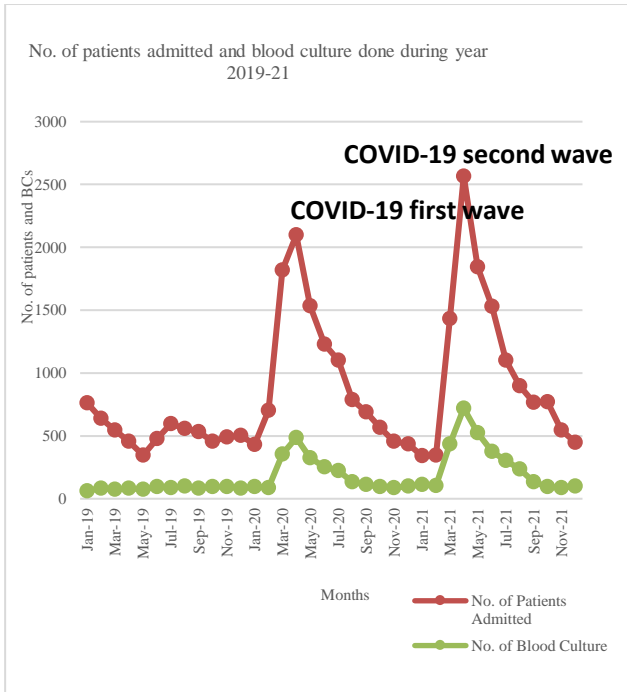
Figure 1: Monthly changes in the number of patients and blood culture during the year 2019-21.
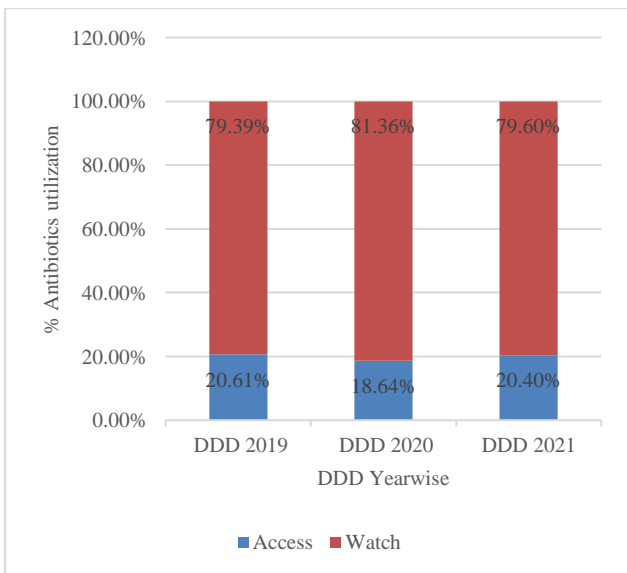

Figure 2: Trend analysis of percentage antibiotic consumption AWaRe group over the year 2019-21.

Microbial pathogens isolated from blood cultures

We only considered clinically significant microorganisms isolates recovered from positive BCs, and the rate ratio of BCs per 100 admissions increased by 74% in the year 2020, and 118% in the year 2021 in comparison with the rate ratio to the year 2019. When the rate ratio was computed according to the bacterial species, the rate ratio of BSIs per 100 admissions raised 58.4% for *Klebsiella* and 239.3% for *E. coli*, but remain the same for *Acinetobacter* and *Aeruginosa*.
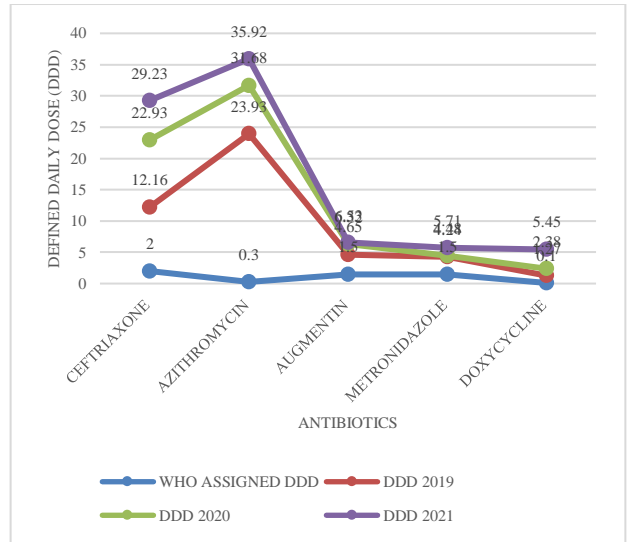

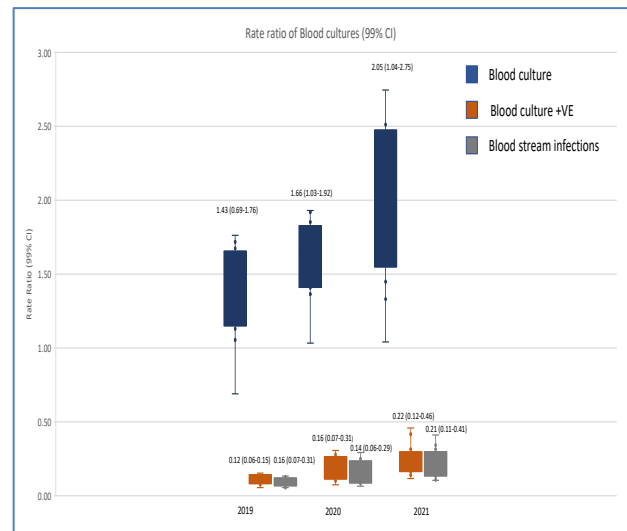**Figure 3: Trend analysis of drug utilization (DU 90%) over the year 2019-21.**

Figure 4: Rate ratios of blood cultures collected, positive blood cultures (BC+), and bloodstream infections per 100 admissions in the year 2019-21 compared to expected values; 99% confidence intervals.

The (Figure 5) shows a high increase in the rate of resistance in Klebsiella to third-generation cephalosporins (60%; 88%), aminoglycosides (77%; 97%), fluoroquinolones (60%; 75%) and carbapenems (10%; 55%) from year 2019 to 2021. Likewise, the resistant profile of *E. coli* to third-generation cephalosporins (20%; 49%), aminoglycosides (65%; 82%), fluoroquinolones (10%; 30%) and carbapenems (14%; 45%) were lower compared to *Klebsiella*. *Acinetobacter* also shows trends of increasing resistance towards cephalosporins (50%), aminoglycosides (40%), fluoroquinolones (79%). *Klebsiella* and *E. coli* develop no resistance against Beta-lactam/inhibitor combinations. Pseudomonas showed a

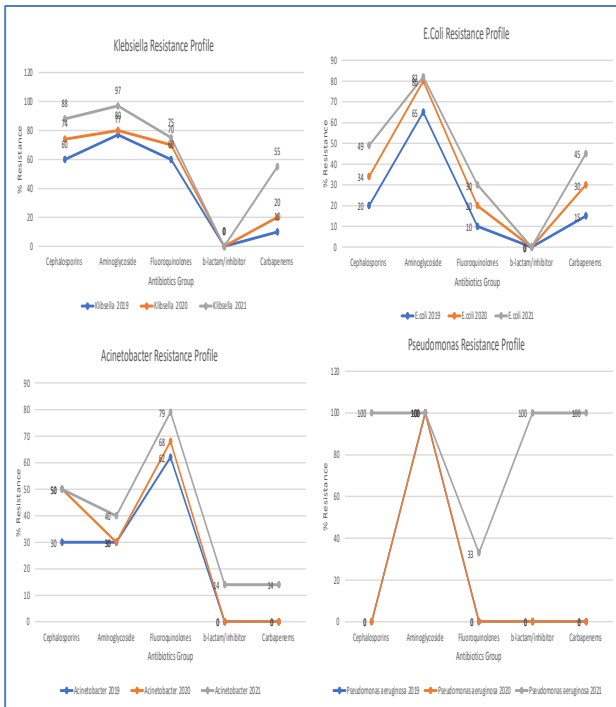100% resistance rate against all the major antibiotics panels, which is an emerging alert.

Figure 5: Resistance profile of gram-negative species.

DISCUSSION

The COVID-19 pandemic has led to growing concern over a potentially propagating antimicrobial resistance with increased consumption of antibiotics in COVID-19 patients. The development of AMR can have a catastrophic impact on health systems in countries in the short and long term.[12,13] The present study showed an impact on antibiotic use, a surge of blood culture, BSIs and antibiotic resistance during the first and second wave of the COVID-19 pandemic (2020-21) in a tertiary care hospital in India. In the present study, we find a significant increase in the use of antibiotics classes like macrolides, cephalosporins and tetracyclines during COVID-19 wave first and second in comparison to the pre-COVID-19 period. Similar findings were observed in other studies.[12,14-16] This increase in consumption is of importance as their increased use has been linked to the development of antimicrobial resistance in various studies.[17-21] In the present study, the total antibiotic consumption in the pre-COVID-19 and during-COVID-19 periods were 52.5 DDD per 100 beds. Data suggest an increase in 1.5-fold of antibiotic use during 2020, and 2-fold increase during 2021 in compared to its consumption in 2019. However, there was no associated marked changes in the use of antibiotics categorized within the WHO Access, Watch, Reserve 'AWaRe' classification. The findings of our study showed that the use of antibiotics in our institute, in the pre and post-COVID-19 period, was not in line with the recommended WHO targets, i.e., the percentage use of the Access group of antibiotics was

around 20.6% in pre-COVID, which further decreased to 18.64% as lack of treatment guidelines during the first wave in the year 2020. An increase of 2% in the use of the Access group of antibiotics was seen during the year 2021 following guidelines WHO guidelines for the management of COVID-19. The excessive use of antibiotics during the COVID-19 pandemic has further undermined the efforts of the WHO target of consuming 60 % of all antibiotics from the Access group by 2023.[22-24]

The current study shows increased consumption of azithromycin. This increased consumption is consistent with other studies reporting it as a potential treatment for hospitalized patients with COVID-19.[25,26] Azithromycin is a widely available antibiotic with an overall safety profile and was suggested to have activity against some viruses in vitro, including SARS-CoV-2.[27-29] It also can reduce the levels of proinflammatory cytokines, thus could reduce the triggering of cytokine storm, along with associated tissue damage by SARS-CoV-2 infection.[30,31] Azithromycin can be effective against secondary bacterial co-infection either alone or in combination with other antibiotic groups.[32-34] However many other studies reported that azithromycin is not sufficiently effective in treating patients with COVID-19. Of note, azithromycin when given with hydroxychloroquine for the treatment of COVID-19 associated respiratory symptoms is associated with an increased risk of cardiac arrhythmias.[35] Thus the routine use of azithromycin without secondary bacterial infection in COVID-19 is not justified. This increased use of azithromycin is concerning and can contribute to antimicrobial resistance and thus diminished effectiveness for recommended indications.[36]

Cephalosporins are the second class after macrolides used widely for the treatment of moderate to severely ill patients in an indoor and outdoor patient hospital setting.[37] The rate of dispense of cephalosporins is among the main indicators used worldwide to assess antibiotic consumption and resistance.[38,39] They observe increased consumption of antibiotics, mainly concerned gram-negative bacterial species (*Klebsiella, Enterobacter, Pseudomonas and Acinetobacter*) resistance known to cause hospital-acquired infections via ESBL and cephalosporinase production. Arcari et al and Belvisi et al also reported similar findings of an increase in multiresistant gram-negative species during the COVID-19 epidemic.[40,41] In addition, we also observe an increase in the rate of aminoglycosides, fluoroquinolones, b-lactam/ inhibitor and carbapenems.

During the first and second wave of the COVID-19 pandemic, the rate ratios of blood culture collection per 100 admissions in our hospital increased by an increase of 25% in the year 2020, and 113% in the year 2021. Similar trends were reported in Amarsy et al in 25 hospitals, and Sepulveda et al by using rates of 1000 patients per day as an indicator (data not shown) in five hospitals in New York City.[42,43] While, in contrast, Denny et al., 2021 reported no variation in BCs during the first wave of COVID-19 in five

London hospitals.[44] Concomitantly with an increase in infections during the first and second COVID-19 pandemic, there was an increase in clinical blood culture samples. The rate ratio of BSIs per 100 admissions increased by 74% in the year 2020, and 118% in the year 2021 in comparison with the rate ratio to the year 2019. This increase was also observed during a separate analysis of the major pathogens E. coli, and Klebsiella, but no changes were seen in Acinetobacter and Aeruginosa. Similar findings were reported by Cataldo et al, Søgaard et al, Zhang et al in single-centre studies in China, Italy, and Switzerland, stating that patients with COVID-19 admitted in ICU are at a high risk of developing BSIs.[45-47] A sudden increase in BSIs with the COVID-19 pandemic is not surprising, since serious bacterial and fungal infections, frequently occur during the hospital stays of severely ill patients.[48]

The present study clearly shows the impact of overuse of antibiotics during COVID-19 first and second wave and prove a positive relationship between COVID-19 and antibiotics resistance, as excessive use of antibiotics during the pandemic will likely increase AMR, particularly in hard-hit areas that already have a high prevalence of drug-resistant pathogens. Looking at the current status, in future, there would be a significant selection pressure on antibiotics for resistant pathogens in hospital units. Unfortunately, the use of broad-spectrum antibiotics in comorbid COVID-19 patients who were at risk of secondary bacterial co-infections could exacerbate the problem. Virtual healthcare visits and the inability of clinicians to do a complete medical examination of patients, lack of blood culture sensitivity reports and more use of irrational antibiotics in patients will affect overall antimicrobial resistance.

Limitations

Ours is a single smaller centre setting study and our results did not assess prescribing practice. Another limitation in the measurements of antibiotic consumption in DDDs/100 bed-days is its inability to adjust antibiotic use, according to variations in the case-mix over time. The high antibiotic consumption rate in the hospital is possible due to a higher case mix index (CMI). Kuster et al.[49] Despite this limitation our study can provide insights about the correlation between the consumption of antibiotics and antimicrobial resistance which can help in the development and implementation of antimicrobial stewardship program needed for patient safety and to address potential AMR issues, during and beyond the COVID-19 pandemic.

CONCLUSION

The collateral effects of the COVID-19 pandemic crisis on antibiotic consumption, antimicrobial resistance rate and BSIs have not been reported simultaneously. We need more comprehensive studies in larger population groups to assess the impact of antibiotic use during COVID-19 on antimicrobial resistance patterns. Implementation of institutional antibiotics stewardship program and promotion of rational use of antibiotics in combination with good prescribing practice, need to be maintained during a pandemic and post-pandemic period to prevent future issues associated with AMR.

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