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Prevalence of Drug Resistance Pattern in Bacterial isolates of Endotracheal secretion from Ventilator Associated Pneumonia in COVID-19 Suspected Patients

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KEYWORDS

COVID-19, Endotracheal secretion, Multi Drug Resistance, Ventilator Associated Pneumonia, Extensively Drug Resistance.

ABSTRACT:

Bacterial superinfections in ventilated COVID-19 patients has seen increase in mortality rates in COVID-19 pandemic. Hence, this study was designed to assess the presence of Drug resistant bacteria in COVID-19 suspected patients having symptoms of Ventilator associated Pneumonia (VAP) which can help to deescalate empirical antibiotics to evidence based and right antibiotic treatment. Objective: To assess prevalence of Drug resistant pattern of bacteria from endotracheal secretion in COVID-19suspected patients having Ventilator Associated Pneumonia. Methods: The current study was conducted in MGM Medical College & hospital, Maharashtra from January 2021 to March 2022. Endotracheal aspirate samples were obtained from the all COVID-19 suspected patients with VAP. Isolation, identification of all the bacteria were carried out using standard microbiological techniques (Morphological studies, Microscopy (Gram Staining) and Biochemical test like motility, catalase, Triple sugar Iron, Methyl Red, Urease, Citrate, oxidase and Indole were done). Antimicrobial susceptibility testing (AST) was done by Kirby- Bauer Disc Diffusion method using 0.5 McFarland suspension of each isolates and antibiotic disc. The results were interpreted in accordance with Clinical Laboratory Standard Institute recommendations. Results: Out of the 121 endotracheal secretions received from the VAP patients, 100 (82.64%) showed significant bacterial growth. 47 patients were COVID-19 positive and 53 were negative. Out of these 100 isolates 42% isolates were MDR (Multi Drug Resistance) &58% were XDR (Extensively Drug Resistance). More XDR bacteria were found in COVID-19 Positive patients as compared to COVID-19 negative patients. Bacteria isolated were Acinetobacterspecies, Klebsellia species, Pseudomonas species, Citrobacter species and others. Conclusions: The present study shows that more than 80% of the VAP cases in COVID-19 suspect patients are because of high prevalence of MDR and XDR bacteria. Timely testing of antimicrobial susceptibility is must in treatment of VAP patients as there is very limited Choice of antibiotics if the VAP is due to XDR bacteria.

INTRODUCTION

SARCS-CoV 2 a novel virus from Coronaviridae family became a challenge worldwide and was declared as global pandemic. World Health Organization reported 641 million verified COVID-19 cases, including almost 6 million fatalities as on November 2022 globally and India reported 44 million COVID-19 confirmed cases, including 0.5 million fatalities.[1] Due to its severity, there was increased hospitalization, showing upsurge in need of ventilator and risk of development of (Ventilator Associated Pneumonia) VAP. As defined by Centre of diseases control & prevention, Patients who have been under mechanical ventilation for over forty-eight hours are at risk of a getting infection of lung that is known as VAP which is characterised by purulent tracheal discharge, fever, and respiratory discomfort as well as the presence of microorganisms. Patients with COVID-19 are more likely to develop VAP than those without it, according to Ippolito M. et al.'s by thorough Systematic Review and a meta-analysis.[2]

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The majorly encountered microorganisms that affect the respiratory system in Gram negative bacilli are *Acinetobacter* specie, *Klebsiella pneumoniae*, *E. coli*, *Pseudomonas* spp, and in gram positive organisms are Streptococcus pneumonia, Staphylococcus aureus etc. Due to infection by multidrug resistant (MDR) bacteria, VAP is a significant contributor to the high mortality rate. The European Centre for Disease Control (ECDC) and the Centres for Disease Control (CDC)& Prevention have developed standard international terminology, for multidrug-resistance (MDR) and extensively drug-resistance (XDR).[3] Multidrug resistance bacteria are those which are resistant to minimum one agent in more than three antimicrobial class. Extensively drug resistance bacteria are susceptible to only one or two classes of antimicrobial agents and resistant to other groups. McConnell MJ et al., reported that the overall incidence of MDR/XDR infection raised due to more invasive procedure and also the severity of critically ill patients. [4]

Hence, current study was designed to assess the prevalence of MDR and XDR bacteria in the COVID-19-19 suspected patients having symptoms of Ventilator Associated Pneumonia.

METHODOLOGY

Study Design: This study was prospective. It was conducted in MGM Medical College & hospital, Kamothe, Navi Mumbai Maharshtra from January 2021 to March 2022. Participants included were all VAP patients hospitalized in closed (intensive care unit) ICU in 2nd wave of COVID-19pandemic.(CDC VAP 2020 diagnostic guidelines, adapted in the present study, required at least one of the listed parameter[5] Fever ≥38.5 ℃ or Leukopenia/leucocytosis and two of the listed condition mainelypurulent sputum, increased airway secretions, new or worsening cough, tachypnea, or dyspnea, abnormal bronchial noise or poor gas exchange may require the use of a ventilator).The study was approved by the MGMIHS Institutional Ethics Committee (IEC) (Ref: MGMIHS/RES./02/2020-21/71), and sample collection were done after each participant or their family members provided written informed consent.

Sample collection & Culture: All endotracheal secretions samples were collected by using sterile suction tube from the COVID-19 suspected patients hospitalized to the intensive care unit (ICU) during 2nd wave of COVID-19 pandemic and who were on ventilator for over 48 hours.

Inclusion Criteria: Endotracheal secretions received in sterile containers from patients having Ventilator Associated Pneumonia with COVID-19 suspect were included in study.

Exclusion Criteria: Patients on VAP but not COVID-19suspect or specimens of VAP not received in sterile containers were excluded.

Isolation of Bacteria: The specimens of endotracheal secretion were inoculated by using standard nichrome loop of quantity 0.01ml was streaked on Chocolate, Blood, and Mac Conkey agar and incubated for 24 hours at 37°C. All samples which yielded quantitative threshold of $>10^5$cfu/ml on culture were considered significant & pathogenic. Bacteria with threshold $<10^5$were considered colonization or contamination and were not included in study.[6]

Identification of pathogens: Isolates were identified based on Koneman's Color Atlas.[7]It was done based on Morphological studies, Microscopy (Gram Staining) and Biochemical test like motility, catalase, Triple sugar Iron, Methyl Red, Urease, Citrate, oxidase and Indole were done.

Antimicrobial Sensitivity test (AST): Antimicrobial sensitivity test of the isolated bacteria were done using disc diffusion method (Kirby-Bauer). 0.5 McFarland suspension of each isolates were lawn on Mueller–Hinton agar.[8]ATCC strain of *E.Coli 25922* was used as a reference strain while doing susceptibility test. Antimicrobial impregnation of First line disc of Amikacin(AK 30µg), Amoxyclav (AMC 20/10mcg), Gentamicin(GEN 10 µg), Cefoperazone/Sulbactum(CPZ 30/10mcg) and higher antibiotics disc of Cefipime(CPM, 30µg), Levofloxacin (LE, 5µg), Ceftazidime/Tazobactum(CAT 30/10mcg), Ceftriaxone/Sulbactum (CIS 75/30mcg), Meropenem (10mcg) Piperacillin-Tazobactum(PIT, 100/10µg), supplementary antibiotic disc of Tigecycline (TGC 15mcg) and Polymyxin B(PB, 300U) were used and incubated over 24hr at 37°C. Later zone of inhibition were measured. According to criteria described by ECDC and CDC interpretation were done to assess MDR and XDR bacterial isolates.[3]

RESULTS

A total of 121 ET secretions of COVID-19 suspected patients were received in microbiology lab of Tertiary care Hospital during this study period. Out of 121 ET samples 100 (82.64%) showed significant bacterial growth, out of which 47 were found to be COVID-19 positive and 53 were COVID-19negative as per RTPCR testing report. Organisms identified were *Acinetobacter* species,

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Klebsellia species, *Pseudomonas* species, *Citrobacter* species, *Proteus* species & *Enterobacter* species.

Demographic data showed that age group of patients in this study were 20 years to 80 years. Maximum patient accounting to 43% were from age group between 60-80 years followed by 37% from 40-59 years and rest 20% were between 20-39 years.

Gender wise data showed that out of 100 patients 78% were males and 22% were females. Males were more compared to females.

Bacterial infections and their etiologies: Out of total 100 bacteria, *Acinetobacter* species were 37 (37%), *Klebsellia* species 21 (21%), *Citrobacter* species were 17 (17%), *Enterobacter spp* were 5 (5%) and *Proteus* species 5 (5%) others 2 (2%). Out of these, 42 (42%) isolates were MDR & 58 (58%) were XDR. From total 42 MDR isolates 23 isolates were from COVID-19 Positive patients and from 58 XDR isolates 24 isolates were from COVID-19 positive. (Table no.1)

Table No.1 Spectrum of gram negative bacteria isolated from VAP (Closed ICU)

Organisms (N=100)	MDR		XDR	
	COVID-19 Positive	**COVID-19 Negative**	**COVID-19 Positive**	**COVID-19 Negative**
***Acinetobacter* species (n=37)**	12 (34%)	10 (27%)	6 (16%)	9 (24%)
***Klebsiella* species (n=21)**	8 (38%)	2 (9%)	6 (29%)	5 (23%)
***Citrobacter* species (n=17)**	6 (35%)	0 (0%)	6 (35%)	5 (29%)
***Pseudomonas* species (n=13)**	4 (31%)	2 (15%)	3 (23%)	4 (31%)
***Enterobacter* species (n=5)**	1 (2%)	0 (0%)	3 (60%)	1 (2%)
Others (n=7)	1 (14%)	1 (14%)	2 (28%)	3 (60%)

(n: number of organisms; N=100 (Culture positive))

Antimicrobial resistance pattern of isolates: **(**Table no. 3) & (Fig 1 & 2)

Table 3: Antibiotic Resistance pattern of GNB isolated from VAP

Name of organisms	**More than 75% isolates sensitive to antibiotics**	**More than 75% isolates resistant to antibiotics**	**More than 75% isolates resistant to common antibiotics**
Acinetobacter species	Tigecycline, Polymyxin B, Leofloxacin, Tobramycin, Gentamycin, Cefaparazone,	Piperacillin/ Tazobactum, Aztreonam, Ofloxacin	(Klebsiella and Pseudomonas are inherently resistant to Cefuroxime and Amoxyclav) Ceftazidime/ Tazobactum, Ceftriaxone/ Sulbactum, Cefoperazone/ Sulbactum , Cefotaxime/Clavulanic acid, Ticarcillin/Clavulanic acid, Cefixime/Clavulanic acid, Etrapenam, Meropenem, Imipenem, Cefepime, Ciprofloxacin, Cefotaxime, Ceftazidime, Cefaparazone, Amikacin
Pseudomonas species	Gentamycin, Tobramycin, Tigecycline, Polymyxin B, Leofloxacin, Aztreonam, Piperacillin/ Tazobactum, Ofloxacin,	–	
Klebsellia species	Tigecycline, Polymyxin B, Leofloxacin,	Piperacillin/ Tazobactum, Aztreonam, Ofloxacin, Tobramycin, Gentamycin,	
Citrobacter species	Tigecycline, Polymyxin B, Tigecycline, Gentamycin, Ofloxacin,	Piperacillin/ Tazobactum, Aztreonam, Tobramycin,	
Enterobacter species	Gentamycin, Tobramycin, Tigecycline, Polymyxin B, Leofloxacin, Aztreonam, Piperacillin/ Tazobactum, Ofloxacin, Meropenem,	–	

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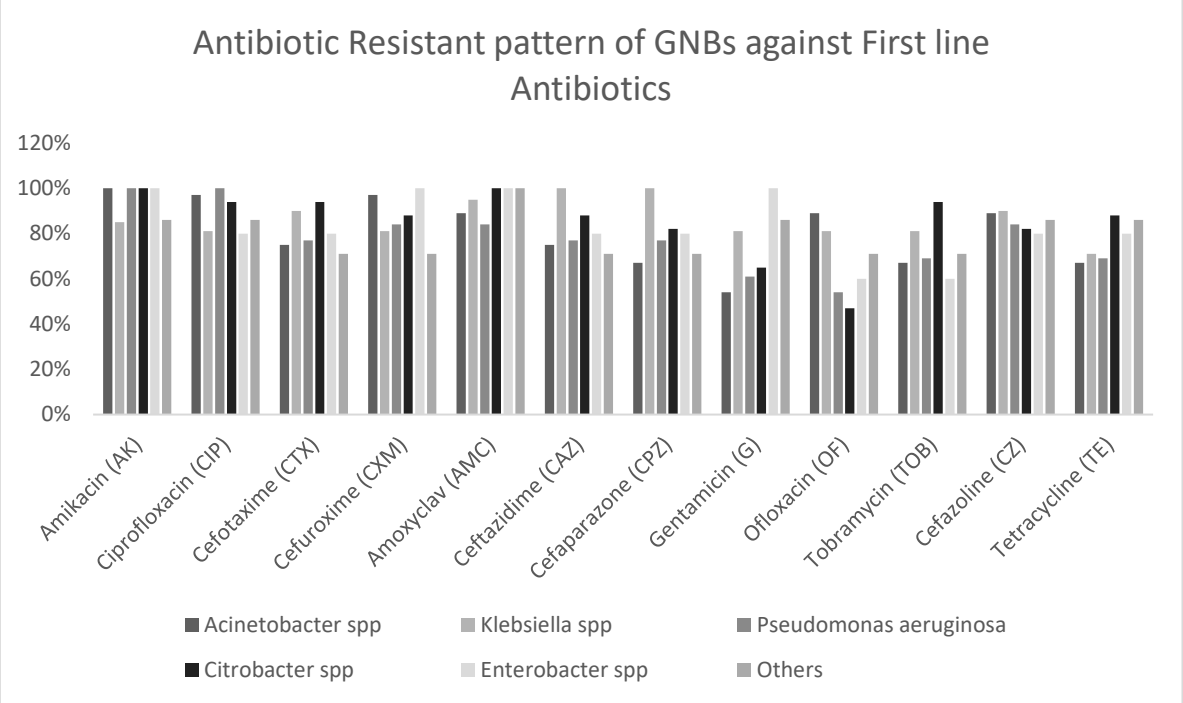
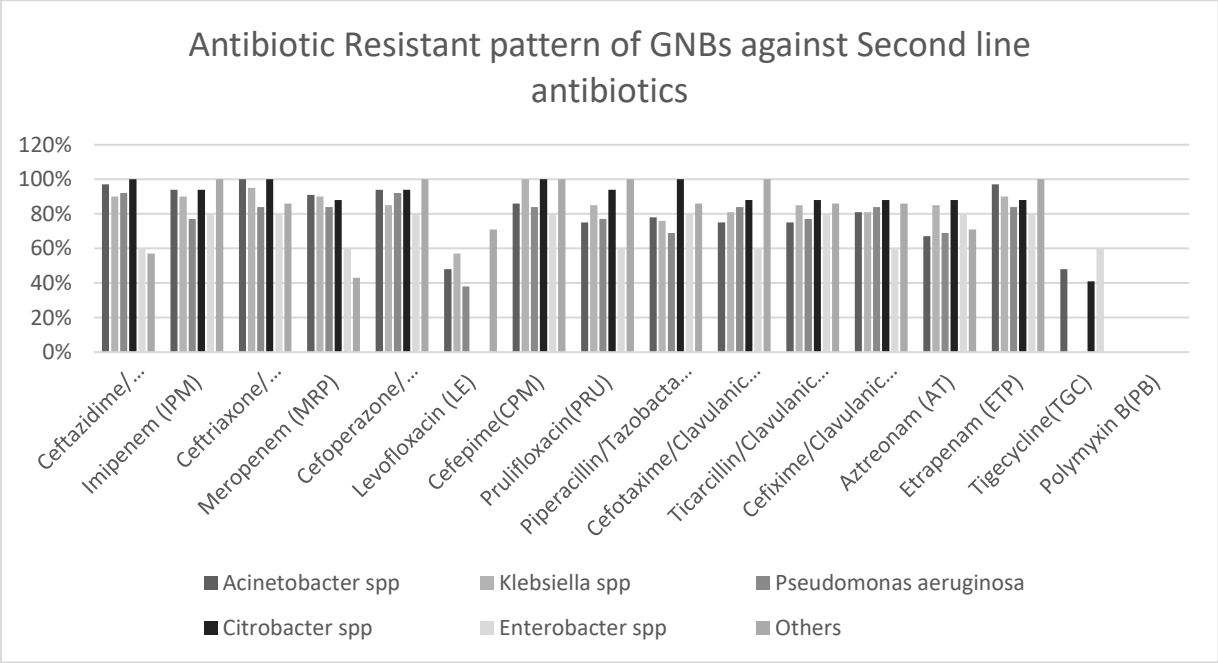
Figure No.1 Graph of Antibiotic Resistant pattern of GNBs against First line antibiotics



(X axis represent different antibiotics & Y axis represent percentage of resistant isolates)

Figure No.2 Graph of Antibiotic Resistant pattern of GNBs against Second line antibiotics



(X axis represent different antibiotics & Y axis represent percentage of resistant isolates)

More than 75% strains of *Acinetobacter* isolates in this study were resistant to Floroqunilones (75%), Carbapenem (90%), Cephalosporin (75%) and Beta lactam inhibitors (78%). Around 48% isolated bacteria were resistant to Tigecycline and Levofloxacin. All the isolated bacteria showed sensitivity towards Polymyxin B.

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More than 80% *Klebsiella pneumonia* strains were resistant to Aminoglycosides (80%), Carbapenem (90%), Cephalosporin (90%) and Beta lactam inhibitors (80%). All the isolates were sensitive to Polymyxin B and Tigecycline. More than 75% *Pseudomonas* strains were resistant to Amikacin (100%), Floroqunilones (94%), Carbapenem (77%), Cephalosporin and Beta lactam inhibitors (69%). All the isolates showed sensitivity towards Polymyxin B and Tigecycline.

Amongst *Citrobacter* strains more than 88% were resistant to Aminoglycosides (90% except Gentamicin 65%), Floroqunilones (100% except Levofloxacin 47%), Carbapenem (88%) and Beta lactam inhibitors (88%). All the isolates showed sensitivity towards Polymyxin B and 41% resistant to Tigecycline.

DISCUSSION

Due to COVID-19pandemic there was increase in rate of ventilated patient which led to high risk of Ventilator associated Pneumonia by MDR & XDR. In current study 47 patients were found COVID-19positive and 53 were COVID-19 negative. Most COVID-19positive patients were found to be infected with XDR bacteria.

In the present study it was found that VAP was more common in age group above 60 years with the median age of 65 years. Similar results were found in studies of Baskaran et al., (59 years), Gauthier et al., (63.9 years) &Moretti et al., (62 years).[9- 11] Also it was observed that VAP was more common in males (78%) than females (22%). Male preponderance was also reported by Baskaran et al., (64.6%), Gauthier et al., (72%) &Moretti et al., (78.2%).[9-11]

Out of 121 ET samples 100 (82.64%) showed significant bacterial growth predominately by GNBs. Same was found by Ferlicolak L et al., Baskaran et al., and Moreno, J et al., where Gram-negatives bacteria being the most predominant in COVID-19-19 patients having VAP.[12, 9&13]

Bacterial infections and their etiologies: In this study the most predominant bacteria was found to be *Acinetobacter* species (37%), followed by *Klebsellia* species (21%), *Citrobacter* species (17%), *Pseudomonas* species (13%) and *Enterobacter* species (5%).

Similar findings have been reported by Ferliçolak L et al., where mostly XDR (60%) bacteria were isolated. They have reported that from 22 endotracheal aspirates most predominant pathogens were *Acinetobacter* species (52%) followed by *Klebsiella* species(49%).[12]Mutua et al., also reported that that *Acinetobacter baumannii* (30.8%) and *Pseudomonas aeruginosa* (30.8%) were the most encountered bacteria for lower respiratory tract infection, whereas for upper respiratory tract infection *Klebsiella pneumoniae* (23.8%) was the most prevalent.[14]In study done by Miguel et al., results showed similar findings whereorganisms found were *A. baumannii* (26.4%), *P. aeruginosa* (9.4%) and *K. pneumoniae* (9.4%). [15]

Different findings was observed in Moretti et al., where *Klebsiella* species (44%) was most predominant followed *by Pseudomonas aeruginosa* (18%), and *Enterobacter* species. (11%).[11]

Moreno, J et al., also reported that *Pseudomonas* species, *Klebsiella* species, and *Staphylococcus aureus* were responsible for 60% of infections.[13] Also Baskaran et al., reported *Klebsiella* species to be most predominant followed by *Escherichia coli*.[9]Gauthier et al., reported *Enterobacteria* (49.8%) as the predominant organisms followed by *Pseudomonas* species, *Staphylococcus aureus* and few other gram negative bacteria like *Haemophilus*, *Acinetobacter baumannii*, other *Pseudomonas*, etc.[10]

This shows that the causative organisms of VAP varies with time & different hospital environment and different geographical location.

Antimicrobial resistance profiles of bacteria isolated in our study shows that out of 100 bacterial isolates 42 (42%) isolates were MDR & 58 (58%) were XDR. MDR bacteria isolated were, *Acinetobacter* species (42%) followed by *Pseudomonas* species (23.8%) *Klebsellia* species (19%) *E.coli* (10%), *Citrobacter* species (4%), & *Enterobacter* species (2%).XDR bacteria isolated were *Acinetobacter* species (34.4 %) followed by *Citrobacter* species (24%), *Klebsellia* species(20.6%), *Pseudomonas* species(10.3%), & *Enterobacter* species(5%).

80% isolates of XDR were resistant to Cephalosporins, Carbapenems, Beta lactam with Beta lactam inhibitors and few Aminoglycosides. All XDR were sensitive to Polymyxin B. More than 75% MDR isolates were resistant to Cephalosporins, Carbapenems, Beta lactam with Beta lactam inhibitors, few Aminoglycosides and Fluroquinolones. Most of the MDR GNBs were senstitive to Tigecycline, Gentamicin, Levofoxacin, Ofloxacin and Tobramycin

Similar findings were observed by Ferlicolak L et al., where majority of the isolated microorganisms were XDR (60%). They reported *Klebsiella* species and *Acinetobacter* species were more dominant organisms.[12]Miguel et al., study found *Acinetobacter baumanniias* XDR by phenotype and also most prevalent carbapenemase-producer followed by *P.*

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aeruginosa, *Escherichia coli* and *E. cloacae*. Remaining isolates of *P. aeruginosa, A. baumannii and K. pneumoniae* strains were found to be MDR.[15]

Different findings were observed in Moretti et al., study where majority of the super infections in VAP were MDR bacteria (67%) out of that 29% were *Klebsiella* species. Only *Pseudomonas aeruginosa* was identified as XDR which showed resistant to all antibiotics except Aztreonam.[11]In study of Mutua et al., it was found that majority of isolates (64.3%) were MDR. Most of the MDR organisms were *Klebsiella pneumonia* (25%), *Enterococcus cloacae* (42.9%), *Escherichia coli* (40%) and *Acinetobacter calcoaceticus* which involved Beta-lactamase inhibitors, Gentamicin, Cefotaxime, Ciprofoxacin, Aztreonam and Trimethoprim/sulfamethoxazole resistant. All gram negative MDR bacteria except Escherichia coli and *Klebsiella pneumoniae* showed susceptibility to Colistin.[14]

In study conducted by Moreno et al., reported that 31% VAPs were caused by multidrug resistant bacteria (MDR). 41% of isolates were resistant to cephalosporin, 24% *Pseudomonas aeruginosa* isolates were resistant Ceftazidime.[13]

The high level antibiotic resistance could be attributed to empiric use of higher antibiotics in critical patients with VAP.

CONCLUSION

The current study highlights, an increased prevalence due to MDR and XDR bacterial infections in VAP patient during COVID-19 pandemic.

During COVID-19 outbreak, there was rampant use of antibiotics in critically ill patients. Since the fatality rate was very high, all higher antibiotics were poured in for saving the patients. This perhaps could be the reason for development of MDR & XDR strains.

We strongly recommend culture-based diagnosis which should be done even though the empiric antibiotics treatment is started in critical patients and also deescalate empirical antibiotics to evidence based antibiotic treatment. In our hospital set up we have Hospital Infection Control Committee (HICC) members who decides antimicrobial stewardship to be followed according to antimicrobial resistance pattern of the isolates which is periodically assessed and followed. This helps in adhering with the recommendations of Antibiotic Policy of our hospital.

Our study's limitations: It cannot be possible to generalise the study's findings to the entire community because it was only conducted at single tertiary healthcare facility.

AUTHOR CONTRIBUTION

SS (PhD Medical Microbiology) designed and supervised study, CA (PhD Scholar Medical Microbiology) conducted study and wrote original manuscript, KH (MD Medical Microbiology) edited and reviewed original manuscript and Statistical study done by SK (M.Sc Student Medical Biotechnology). All author contributed to the article and approved the submitted version.

DECLARATION

Human participation: Each participant in this study provided their consent.

Forum for Institutional Research: MGM Medical College & Hospital.

This Institutional Research forum certifies that:

1. The work presented above falls under acceptable ethical guidelines.
2. The aforementioned study has not been duplicated in this institution.
3. The forum recognises the significance of the research.

Animal subjects: This study did not use any animal subjects or tissue, according to all authors.

CONFLICT OF INTEREST

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

DATA AVAILABILITY

The data presented in this article are not readily available because informed consent signed by participants stated that data were only accessible to the authors of this study. Request to access the data should be directed to anamikamchalwadi@yahoo.co.in.

ETHICAL APPROVAL

The study was approved by the institution's ethics committee. The Institutional Human Ethics Committee (IHEC) at MGMIHS approved the study (Ref: MGMIHS/RES./02/2020-21/71)

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