Microbes and Infectious Diseases 2025; 6(2): 475-486

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Original article

Changing the resistance patterns of respiratory targeting pathogens in intensive care unit during COVID-19 pandemic

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ARTICLE INFO

Article history:
Received 6 November 2024
Received in revised form 20 December 2024
Accepted 24 December 2024

Keywords:
COVID-19
Respiratory pathogens
MDR

ABSTRACT

Background: Antimicrobial resistance is a rising threat worldwide; this problem has been exacerbated especially after emergence of COVID-19 pandemic. The purpose of this work was to describe the change in the prevalence rate and resistance pattern of respiratory targeting pathogens during COVID-19 pandemic compared to the era before **Methods**: A cross-sectional study included retrospective part (before COVID-19) and prospective one (during COVID-19) was conducted on ICU patients in Jizan Armed Forces Hospital. Respiratory and blood samples were obtained. VITEK II compact system (bioMerieux, UK) was used to identify bacterial isolates and their antimicrobial sensitivity pattern. **Results**: Gram-negative bacteria were predominant in both periods, although their proportion slightly decreased during COVID. Conversely, Gram-positive bacteria increased. MDR organisms increased significantly by 12.1% while XDR organisms also showed an increase by 2.3%. The prevalence of *E. coli*, *Klebsiella pneumoniae* has been increased (p = 0.044, p < 0.001, respectively), while *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Proteus Mirabilis* decreased (p = 0.003, p<0.001and p=0.021, respectively). The prevalence of *Staphylococcus aureus* and *Staphylococcus epidermidis* showed no statistically significant difference. For *Pseudomonas aeruginosa*, there was a decrease in sensitivity to gentamicin, ceftazidime, imipenem and piperacillin/tazobactam. Also, a decrease in sensitivity to gentamicin, levofloxacin, cefoxitin, ciprofloxacin, and piperacillin/tazobactam has been encountered with *E. coli* and *klebsiella. Staph. aureus* showed a decrease in sensitivity to ciprofloxacin, clindamycin, azythromycin, gentamicin, and moxifloxacin during COVID. **Conclusion:** Changing the prevalence of bacteria and rising level of their resistance to several antibiotics are critical issues that have emerged during COVID pandemic.

Introduction

The coronavirus 2019 (COVID-19) pandemic has had a considerable influence on healthcare facilities worldwide. The World Health Organization (WHO) stated that COVID-19 is a universal health emergency in January 2020 and declared it a pandemic in March 2020. More than 32.7 million people have been affected since the

DOI: 10.21608/MID.2024.334421.2335

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initial case of COVID-19 in China, with over than 1 million fatalities worldwide [1, 2].

COVID-19 cases often present with high temperature, tiredness, and dry cough with a clinical picture ranging from asymptomatic to severe case of atypical pneumonia [3]. Patients with severe COVID-19 might need prolonged hospitalization whether in general wards or ICUs. It was reported that over 50% of ICU patients were more vulnerable to acquire infections by multi drug resistant organisms (MDROs) [4]. Breaks in the infection control protocols due to increased hospital burden and lack of human resources may further facilitate the transmission of MDROs. The administration of drugs targeting cytokines, like IL-1 and IL-6, could increase the risk of super infections in patients with COVID-19 [5]. Studies that focused on COVID-19 respiratory bacterial infections showed that nearly a third of COVID-19-positive individuals were co-infected with one or more respiratory pathogens [6]. The detected respiratory pathogens in many studies were *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus* [7].

Approximately 72% COVID-19 positive patients were administered wide-spectrum antibiotics, with the most common ones being azithromycin, amoxicillin-clavulanate, and levofloxacin [8,9]. There are several possible reasons that contribute to the elevated level of antibiotic use among COVID-19 infected individuals, especially in cases with severe COVID-19. Despite the possibility that the infection is viral, clinicians prescribe empirical antibiotics. Also, fears regarding the occurrence of bacterial co-infection as is the case in Influenza that shown co-infection of about (58%). The lack of effective therapeutic options in managing SARS-CoV-2 infection along with anxiety and uncertainty about the nature of that outbreak are probable reasons for extensive and unnecessary consumption of antimicrobial agents [10]. Likewise, it is not easy to discriminate between infections with SARS-CoV-2 only and combined or even secondary infections [11].

Nevertheless, the overuse of antimicrobials in patients with COVID-19 in addition to hospital overloading probably hastened antimicrobial resistance (AMR) emergence and dissemination. The COVID-19 impact on AMR differed greatly based on the country's public health strategy and its healthcare system [12].

The development of antimicrobial resistance is owing to misuse or abuse of antibiotics that develop unnatural selective pressure in clinical settings and natural environments which carries a high risk to both human and animal life [13]. This resistance emerges as a consequence of mutation of a gene or acquiring of new resistance one via different ways of genes exchange [14].

Antibiotic modification or even degradation by enzymes, restriction of antibiotic entry into cells, changes in metabolic pathways, modification of binding sites such as ribosomes, and increased activity of efflux pumps that get antibiotics out of cells before reaching proper levels are considered typical resistance mechanisms [15]. Biofilms, which are extracellular polymeric substances produced by bacteria and alter their metabolic activity besides hindering antibiotics' entry [16].

As a pandemic of a particular pathogen might contribute to remarkable increase in the usage of antibiotics, change in bacterial epidemiology, higher duration of hospital stays and treatment expenses [17]. So, the purpose of this work was to determine the change in the prevalence rate and resistance pattern of respiratory targeted pathogens during COVID-19 pandemic period compared to the era before.

Materials &methods

Study design and participants

This observational cross-sectional comparative study, including a retrospective and a prospective part was conducted in Jizan Armed Forces Hospital.

The retrospective part of the study

It was executed by collection of patients' data from their medical records besides a laboratory information system during the period from July 2018 to December 2019 **(pre COVID- 19 period)**. We enrolled all patients admitted to ICU with different clinical conditions at the time of conducting study.

The prospective part of the study

It was from March 2020 to August 2021 **(during COVID-19 period).** We recruited only ICU patients with positive nasopharyngeal swab and/or BAL for COVID-19 before or until 48 h from admission to ICU wards [18].

During study periods, identification of Gram-negative and Gram-positive bacteria isolated from respiratory specimens and blood collected from ICU patients in addition to determining their susceptibility data were reported emphasizing the most clinically significant respiratory targeted pathogens (*E coli, Klebsiella , Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus*) [7] .

Only the initial isolate of a given species obtained from a patient was considered, regardless of the sensitivity pattern. The categorization of isolates as being sensitive, intermediate, or resistant was determined according to the guidelines set by the Clinical and Laboratory Standards Institute (CLSI) [19].

Specimens with polymicrobial isolates; any inadequate data and positive cultures for fungus were excluded.

For each patient, a thorough history-taking were reported from patients' medical records such as age, sex, associated morbidities, mechanical ventilation, empirical antibiotic therapy and duration of hospital staying and outcome.

The diagnostic criteria, assessments, and treatment for all participants included in the study were conducted according to applicable local guidelines.

The general directorate for Health services in the Ministry Agency for Excellence Services approved the study. It was carried out under the revised Helsinki Declaration. Informed consent was taken from patients or their relatives.

Microbiological assay

Blood and respiratory samples (sputum, bronchial aspirates, and transtracheal aspirates) were obtained from patients, by trained healthcare personnel in ICU. Then, samples were transported directly to the lab; Processing of samples was achieved following laboratory protocols for COVID-19 patients. A Gram stain was done for each specimen. Then, subculture on blood agar and chocolate agar (5% CO2) and on MacConkey agar kept at 37˚ C for 24–48 h.

VITEK II compact system (bioMerieux, UK) was used to identify bacterial isolates and their antimicrobial sensitivity pattern. Isolates that exhibit no susceptibility to one or more agents in three or more antimicrobial categories are classified as MDR organisms, whereas isolates that are non-susceptible to one or more agents in all but two or fewer categories are classified as XDR organisms [20].

Gram-positive and Gram-negative antibiotic susceptibility test cards were used according to CLSI guidelines [19].

The antibiotics used for Gram-negative susceptibility testing were amoxicillin /clavulanic acid (AMC), amikacin (AK), gentamicin (GEN), ceftriaxone (CRO), ceftazidime (CAZ), cefepime (FEP), ciprofloxacin (CIP), levofloxacin (LOV), imipenem (IPM), meropenem (MEM), cefoxitin (FOX) , trimethoprim-sulfamethoxazole (SXT), aztreonam(ATM), colistin(CT) and piperacillin/tazobactam (TZP).

For Gram-positive susceptibility testing, the following antibiotics were used: cefoxitin (FOX), oxacillin (OX), vancomycin (VA), trimethoprim-sulfamethoxazole (SXT), ciprofloxacin (CIP), moxifloxacin (MOX), gentamicin (GEN), linezolid (LNZ), tetracycline (TE), clindamycin (DA)and azithromycin (E).

Staphylococcus aureus (S. aureus) ATCC 29213 and *Escherichia coli* ATCC 25922 were used as quality control strains for the VITEK2 Gram-positive and Gram-negative antibiotic susceptibility test cards, respectively.

Statistical analysis

MedCalc software, version 20.218 (MedCalc Software Ltd, Ostend, Belgium), was used to perform the statistical analysis. For continuous variables as (age, length of hospital stay), the data were displayed as mean ± standard deviation (SD); for categorical variables, the data were displayed as frequencies and percentages. Comparative analyses between the prevalence rate and resistant pattern of respiratory pathogens in the pre-COVID and during COVID periods were done using the Fisher's exact test or the chi-squared test, depending on the situation. *p*-values below 0.05 were defined as statistically significant.

Results

This study is divided into two periods; pre-COVID-19 (July 2018 to December 2019) and the COVID-19 period (March 2020 to August 2021). During the pre-COVID period), A total of 361 samples were collected, with 282(78.11%) being Gram-negative and 79 (21.8%) Gram positive. The sample size was 590 during the COVID period, with 437(74.06%) being Gram-negative and 153 (25.9%) Gram positive. The average age was 55 ± 13.17 years pre-COVID and 52 ± 11.23 years during

COVID. The proportion of males was 72.0% pre-COVID and 68.6% during COVID. A statistically significant increase in the average length of hospital stay, empirical antibiotic use and history of mechanical ventilation was detected during COVID besides, increase in mortality from 8.6% to 13.4% **(Table1)**.

In the pre-COVID period, 91 blood samples (25.2%) and 270 sputum samples (74.8%) were collected. During COVID, the number of blood samples was 167 (28.3%), and sputum samples were 423 (71.7%) **(Table 2)**.

Among the pathogens isolated from sputum samples, Gram-negative bacteria were predominant in both periods, although their proportion slightly decreased from 84.1% pre-COVID to 80.4% during COVID. Conversely, Gram-positive bacteria in sputum samples increased from 15.9% to 19.6%. For blood samples, Gram-negative bacteria were also more prevalent, but their proportion decreased from 60.4% pre-COVID to 58.1% during COVID. Similarly, Gram-positive bacteria in blood samples increased from 39.6% to 41.9% **(Table 3)**.

Multidrug-resistant (MDR) organisms highly increased significantly from 29.8% pre-COVID to 41.9% during COVID ($p < 0.001$). Extensively drug-resistant (XDR) organisms also showed an increase, from 1.9% to 4.2%, which was statistically significant ($p = 0.05$) **(Table 4)**.

The prevalence of *E. coli* increased from 26% pre-COVID to 32.2% during COVID ($p = 0.044$). *Klebsiella pneumoniae* showed a significant increase from 14.4% to 22.4% ($p < 0.001$). *Pseudomonas aeruginosa* decreased from 19.9% to 12.7% ($p = 0.003$). *Acinetobacter baumannii* significantly decreased from 13.6% to 5.8% ($p < 0.001$), and *Proteus mirabilis* decreased significantly from 4.15% to 1.7% ($p = 0.021$). The prevalence of *Staphylococcus aureus* and *Staphylococcus epidermidis* showed no statistically significant difference **(Table 5)**.

Change in the pattern of sensitivity of the studied isolates to different antibiotics (Tables 6, 7)

For *Pseudomonas aeruginosa*, the sensitivity to gentamicin significantly decreased from 95.8% to 80% ($p = 0.005$). Sensitivity to ceftazidime showed significant decreases, from 94.4% to 73.3% ($p < 0.001$). Sensitivity to Imipenem showed statistically significant decrease from 86.1% to 66.6%, (p=0.006), and sensitivity to piperacillin/tazobactam also decreased from 94.4% to 80% ($p = 0.013$), respectively.

Klebsiella pneumoniae showed significant decreases in sensitivity to several antibiotics during COVID. Sensitivity to amikacin dropped from 100.0% pre-COVID to 57.8% during COVID ($p < 0.001$). Significant reductions were also observed in sensitivity to gentamicin, levofloxacin, cefoxitin, ciprofloxacin, imipenem, meropenem, and piperacillin/tazobactam (all $p < 0.001$).

For *E. coli*, significant decreases were observed in sensitivity to gentamicin, levofloxacin, cefoxitin, ciprofloxacin, and piperacillin/tazobactam. Sensitivity to amoxicillin/clavulanic acid, and trimethoprim-sulfamethoxazole, showed statistically significant increase in sensitivity

All isolates were sensitive to colistin; No reported cases of colistin resistance during the study.

Regarding sensitivity of *Staphylococcus aureus*, it showed a decrease in sensitivity to ciprofloxacin, clindamycin, azithromycin, gentamicin, and moxifloxacin during COVID. While sensitivity to cefoxitin showed statistically significant increase from 48.9% to 72.3 % **(Table 7)**.

Table1. Demographic data and risk factors

Item	**Pre- COVID-19 N= 361**	**During- COVID-19 N= 590**	*p*-value
Age	55 ± 13.17 (range 21-98)	52 ± 11.23 (range 18-87)	**<0.001**
Sex			
Males	260 (72.0%)	405 (68.6%)	0.271
Females	101 (28.0%)	185 (31.4%)	
Underlying co-morbidity			
DM	116 (32.1%)	167 (28.3%)	0.211
Obesity (BMI >32)	87 (24.1%)	195 (33.1%)	0.330
Hypertension	78 (21.6%)	136 (23.1%)	0.605
Trauma	32 (8.9%)	56 (9.5%)	0.746
Malignancy	9 (2.5%)	16 (2.7%)	0.520
Mechanical ventilation	91 (25.2%)	246 (41.7%)	**<0.001**
Length of hospital stay	5.7 ± 4.8 (range 2-24)	8.2 ± 7.3 (range 2-56)	**<0.001**
Empirical antibiotic	147 (40.1%)	403 (68.3%)	**<0.001**
Mortality	31 (8.6%)	79 (13.4%)	0.130

Table 2. Distribution of various clinical samples.

Samples	**Pre- COVID-19 (n=361)**	**During COVID-19 (n=590)**
Blood	91 (25.2%)	167 (28.3%)
Sputum	270 (74.8%)	423 (71.7%)

Table 3. Distribution of commonly isolated pathogens.

Bacteria	**Sputum**		**Blood**	
	Pre- COVID-19	**During COVID-19**	**Pre- COVID-19**	**During COVID-19**
Gram negative	227/270 (84.1%)	340/423 (80.4%)	55/91 (60.4%)	97/167 (58.1%)
Gram positive	43 /270 (15.9%)	83/423 (19.6%)	36/91 (39.6%)	70/167 (41.9%)

Table 4. Type of antibiotic resistance.

Type of resistance	total	Pre- COVID-19	During COVID-19	*p* value
MDR	352	105 (29.8%)	247 (41.9%)	**<0.001**
XDR	32	7 (1.9%)	25 (4.2%)	**0.05**

Table 5. Prevalence of the isolated organisms.

	Pre-COVID (N=361)		**During COVID (N=590)**		***p*-value**
Organism	N	%	N	%	
E coli	94	26%	190	32.2%	**0.044**
Klebsiella pneumoniae	52	14.4%	132	22.4%	**<0.001**
Pseudomonas aeruginosa	72	19.9%	75	12.7%	**0.003**
Acinetobacter baumannii	49	13.6%	30	5.08%	**<0.001**
Proteus mirabilis	15	4.15%	10	1.7%	**0.021**
Staphylococcus aureus	49	13.6%	105	17.8%	0.086
Staphylococcus epidermidis	30	8.3%	48	8.1%	0.924

Table 6. Comparison of the sensitivity of Gram –negative isolates to different antibiotics

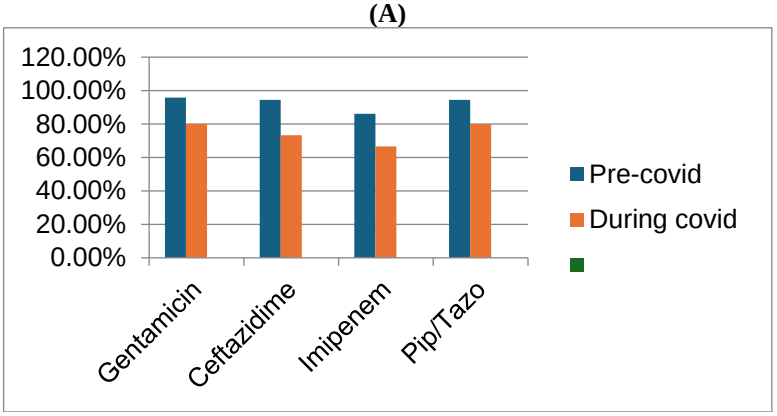
Isolates	***Pseudomonas aeruginosa***			***Klebsiella pneumoniae***			***E.coli***		
Antibiotics	**Pre-covid (N=72)**	**During covid (N=75)**	***p* value**	**Pre-covid (N=52)**	**During covid (N=132)**	***p* value**	**Pre-covid (N=94)**	**During covid (N=190)**	***p* value**
Amikacin	100.00 %	93.30%	0.059	100.00 %	57.80%	**<0.001**	97.80%	94.70%	0.348
Amox/Clav	-	-	-	46.10%	43.90%	0.786	30.80%	43.60%	**0.038**
Gentamicin	95.80%	80%	**0.005**	96.10%	56.00%	**<0.001**	82.90%	69.40%	**0.015**
Levofloxacin	63.80%	66.60%	0.725	84.60%	34.80%	**<0.001**	42.50%	17.80%	**<0.001**
Aztreonam	51.30%	44%	0.372	50.00%	41.60%	0.307	47.80%	45.70%	0.741
Cefepime	69.40%	73.30%	0.603	53.80%	34.80%	**0.018**	30.80%	33.60%	0.633
Cefoxitin	-	-	-	75.00%	25.00%	**<0.001**	87.20%	44.70%	**<0.001**
Ceftazidime	94.40%	73.30%	**<0.001**	44.20%	34.80%	0.238	28.70%	31.50%	0.623
SXT	-	-	-	53.80%	50.00%	0.639	28.70%	43.60%	**0.015**
Ceftriaxone	-	-	-	44.20%	34.80%	0.238	28.70%	31.50%	0.624
Ciprofloxacin	76.30%	66.60%	0.194	84.60%	34.80%	**<0.001**	42.50%	17.80%	**<0.001**
Imipenem	86.10%	66.60%	**0.006**	78.80%	49.20%	**<0.001**	93.60%	89.40%	0.255
Meropenem	90.20%	84%	0.258	90.30%	49.20%	**<0.001**	95.70%	92.60%	0.11
Piperacillin/Tazobactam	94.40%	80%	**0.013**	80.70%	34.80%	**<0.001**	93.60%	31.50%	**<0.001**

Table 7. Comparison of the sensitivity of *Staphylococcus aureus* to different antibiotics.

Staphylococcus aureus	**Pre-COVID (N=49)**		**During COVID (N=105)**		***p*-value**
	N	%	N	%	
Ciprofloxacin	45	91.8%	80	76%	**0.026**
Clindamycin	46	93.8%	83	79%	**0.020**
Azithromycin	39	79.5%	47	44.7%	**<0.001**
Gentamicin	48	97.6%	92	87.6%	**0.039**
Linezolid	49	100.0%	105	100.0%	-
Nitrofurantoin	49	100.0%	105	100.0%	-
Oxacillin	24	48.9%	42	40%	0.296
TMP-SMX	46	93.8%	89	84.7%	0.124
Tetracycline	42	85.7%	92	87.6%	0.744
Moxifloxacin	49	100.0%	89	84.7%	**0.003**
Cefoxitin	24	48.9%	76	72.3%	**0.004**
Vancomycin	49	100.0%	105	100.0%	-

Figure1. Frequency distribution of antibiotics with a statistically significant change in the sensitivity during pre –COVID period compared to during –COVID period. (**A)**: *pseudomonas*,(B)*: Klebsiella*,(**C)***:** E coli, and* (**D)***: S. aureus)*

(A)



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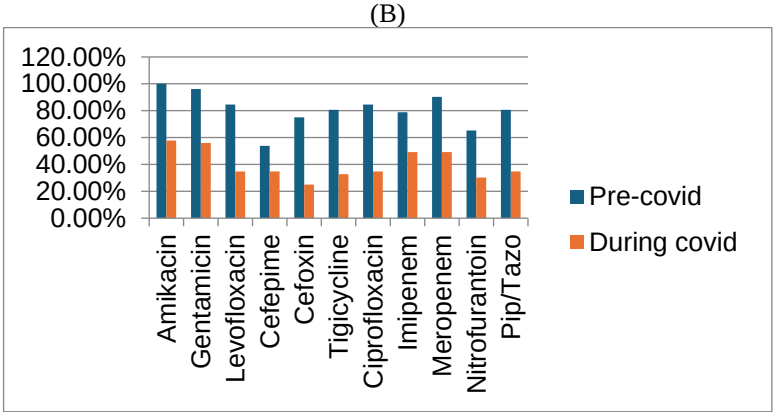

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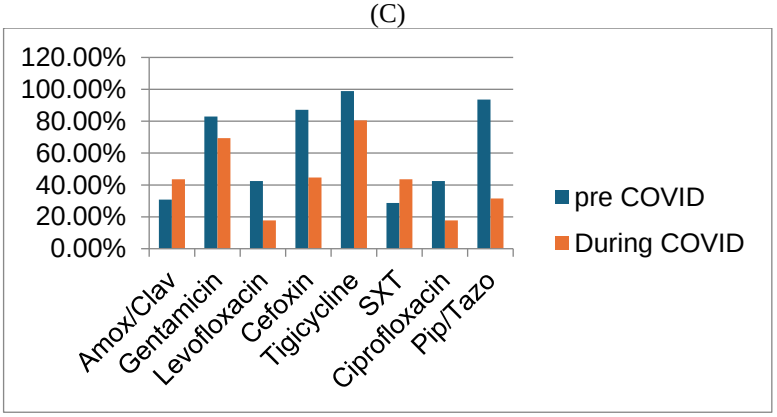

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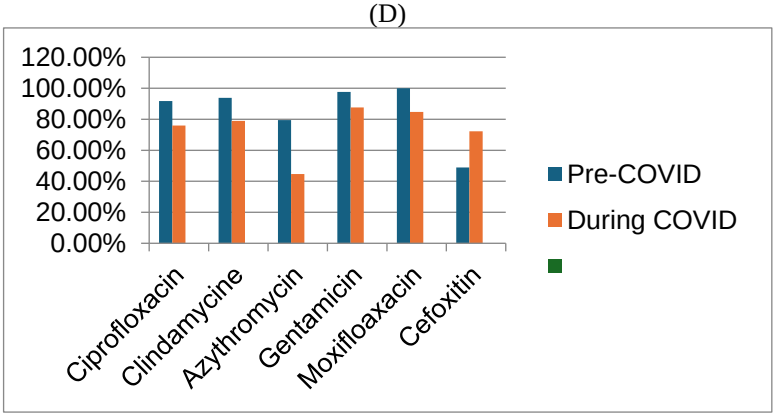

Discussion

The COVID-19 pandemic significantly strained national healthcare structures, particularly during its first wave. This impact hits primarily ICUs since the excessive number of patients in need of critical care led to a profound disruption in these departments. The increase in ICU beds, the reduced nurse-to-patient ratio, the continual wearing of personal protective equipment (PPE), and the implementation of novel antimicrobial surveillance strategies may have significantly affected the normal flora in these wards. Additionally, the overuse of antimicrobial therapies in patients with COVID-19, as reported in many studies, could have further influenced this aspect [21].

Regarding our study, there was statistically significant difference between patients in pre-COVID and during COVID periods regarding length of hospital stay, usage of empirical antibiotcs and history of mechanical ventilation (p<0.001). This is in a line with **Bengoechea and Bamford** who reported that prolonged hospitalization might be required for sever COVID patients whether in general wards or ICUs and a notable number of them have been treated with broad spectrum antibiotic empirically which increases the risk of MDRO selection [22, 23].

Meanwhile, **DeVoe et al.** [24] have reported higher rates of ventilator associated pneumonia (VAP) among COVID-19 patients than those without COVID-19 or influenza and this may be caused by MDR pathogens. Several researches have documented over use of antibiotics empirically among COVID positive patients [25, 8].

All the above mentioned factors can contribute collectively to the emergence of developing antimicrobial resistance.

In this study, there was a variation of microbiological respiratory isolates before and during COVID-19 pandemic. The prevalence of *E. coli* increased from 26% pre-COVID to 32.2% during COVID (p = 0.044). Also, *Klebsiella pneumoniae* showed a significant increase from 14.4% to 22.4% (p < 0.001).

Similarly, **Zuglian et al.** [21] found an increase in *Enterobacterals* during COVID period compared to pre- COVID one. Also, **Taleb et al.** [26] reported an increase in *Klebsiella spp.* in Gaza during COVID.

As regards *Acinetobacter baumannii, Proteus mirabilis, Pseudomonas aeruginosa* there was a significant decrease in their prevalence during COVID period.

The prevalence of *Staphylococcus aureus* and *Staphylococcus epidermidis* showed no statistically significant difference.

This was in alignment with a study conducted in Egypt that reported a decrease in *Acinetobacter* isolates during COVID [27]. Conversely**, Polemis et al.** [28] **and Taleb et al.** [26] found that the prevalence of *Acinetobacter baumanii* has increased during COVID-19.

The decrease in prevalence of *Acinetobacter* may be related to the expanded use of chlorine for environmental disinfection and strict infection control measures like hand hygiene and PPE use at the emergence of the COVID-19 pandemic. Another significant cause for decreased *Acinetobacter* prevalence is the strict transmission of long-term cases from other hospitals as many of the reported cases in our hospital in the pre-COVID-19 Period were received from other hospitals inoculated by the infection.

Also, **Taleb et al.** [26] in Gaza reported a decrease in *Pseudomonas* prevalence. On the other hand, **Zuglian et al.** [21] found that *Pseudomonas spp*., has increased during COVID from (13.2%) to (25.9%).

However, *S. aureus* was found to be the most frequent causative Gram-positive pathogen for VAP among COVID patients [29].

When used as a salvage therapy in COVID patients in ICU, the significant level of immunosuppression induced by steroid therapy might have an effect on the pattern and frequency of respiratory microbial flora when compared with non- COVID patients [30].

The current study showed that the frequency of MDRO during the COVID-19 pandemic were highly increased (from 29.1% to 41.9%, p <0.001). Similarly, a retrospective analysis in ICU in India showed that up to a 40% increase in antimicrobial resistance was observed among these isolated bacteria obtained during the COVID-19 period compared to pre-COVID-19 times [31]. Another observational study in Brazil showed that the prevalence of MDR infections significantly increased by 23% (p < 0.005) during COVID-19 [32] and significant increases were observed for carbapenem-resistant *Acinetobacter baumannii* and

MRSA in both ICU and non-ICU settings. **Meawed et al.** [33] also reported an increase in the prevalence of MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* during COVID period than pre COVID in a study conducted in Egypt.

In this study, *Klebsiella pneumoniae* showed highly significant decreases in sensitivity to several antibiotics during COVID: to amikacin, gentamicin, levofloxacin, cefoxitin, ciprofloxacin, imipenem, meropenem, and piperacillin/tazobactam (all $p < 0.001$).

These findings were comparable to *Klebsiella* spp. resistance rates documented in the Arab region (63% – 86%) [34].

A possible explanation for this may be the irrational use of antibiotics during the pandemic, such as community pharmacies' prescriptions or self-medication for respiratory and urinary tract infections due to outpatient clinic closures and patients' anxiety about visiting hospitals during the pandemic.

Regarding *E. coli*, highly significant decreases were observed in sensitivity to levofloxacin, cefoxitin, ciprofloxacin, and piperacillin/tazobactam. (All $p< 0.001$). And still significant decreases were observed in sensitivity to gentamicin and Amox/Clav (p=0.015, p= 0.038, respectively).

Similar findings of an increase resistance rate of *E. coli* against piperacillin-tazobactam during COVID-19 pandemic was documented in Saudi Arabia [35] and Gaza [26].

A possible explanation of this increase in *E. coli* resistance against piperacillin-tazobactam might be attributed to non-compliance with hospital restriction policies regarding piperacillin-tazobactam prescription during the COVID-19 pandemic period.

For *Pseudomonas aeruginosa*, the sensitivity significantly decreased to gentamicin p= 0.005, ceftazidime $p < 0.001$, imipenem p=0.006 and piperacillin/tazobactam. p=0.01. This may be attributed to common use of these antimicrobials in ICU Settings. Although the prevalence decreased.

On the other hand, *Staphylococcus aureus* showed a decrease in sensitivity to ciprofloxacin, clindamycin, gentamicin, and moxifloxacin during COVID. While there was highly significant decrease in sensitivity to azithromycin ($p < 0.001$); this may owe to very high empirical prescription of this antibiotic during COVID-19.

It was noticed also that cefoxitin sensitivity controversially showed statistically significant increase from 48.9% to 72.3 % (p=0.004); this is because of very low rates of prescriptions of this antibiotic.

Increasing resistance of isolates to some antibiotics may be multifactorial. Due to the overwhelming strain on hospitals during the pandemic, clinicians were compelled to use empirical treatments to treat bacterial infections caused by common pathogens like *E. coli, K. pneumoniae, A. baumannii, P. aeruginosa*, without evaluating the cost on anti-microbial resistance. Also, the susceptibility of healthcare workers (HCWs) with prolonged contact with the patient, and the presence of new HCWs lacking work experience in ICU settings might play a role [36].

Limitations

- Single center study with its own local epidemiology that makes the results not generalized on AMR.
- Retrospective design reduces control over multiple cofounders and data collection.
- Antibiogram doesn't distinguish isolated organism from patient as a pathogen or a colonizer despite the accurate identification method used.

Conclusion

There is an association between the development of AMR and COVID 19 pandemic, this is an emerging health care issue. An unbalanced approach concerning antimicrobial consumption may play a role. Effective antimicrobial stewardship program beside quality diagnosis and comprehensive infection control measures are mandatory to combat AMR.

Conflict of interest

` All authors affirm no conflict of interest in the work.

Financial disclosures

This research did not take any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

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