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Short Communication

Impact of COVID-19 Pandemic on Antimicrobial Resistance Pattern; Transition from Resistivity to Susceptibility

Sarmad Iqbal[1,2], PharmD, CRCP, Syed Saad Hussain[2,3], PharmD, CRCP, PhD

[1]Department of Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, [2]Bosch Pharmaceuticals (Pvt.) Ltd., [3]Department of Pharmacy, Iqra University North Campus, Iqra University, Karachi, Sindh, Pakistan.

***Corresponding author:**
Syed Saad Hussain,
Department of Pharmacy, Iqra University North Campus, Iqra University, Sindh, Karachi, Pakistan.

saad.hussain@bosch-pharma.com

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ABSTRACT

Objective: The study aimed to assess the antibiotic resistance pattern before and after the pandemic to provide the physicians with general guidance for antibiotic prescribing.

Material and Methods: The yearly antibiograms of different tertiary care hospitals were extracted from Pakistan Antimicrobial Resistance (AMR) Network. The data timeline observed was from January 2016 to December 2020. The data were scrutinized to the most common organism studied with the most recurring antimicrobial used.

Results: Among the Gram-positive organisms, increased resistivity against penicillin was observed against both the organism, while a good susceptibility was observed against vancomycin. Among the Gram-negative organisms, the highest resistance was observed in Ceftriaxone, Ciprofloxacin, and Cotrimoxazole. *Staphylococcus aureus* and *Escherichia coli* are the most prevalent organisms in tertiary care hospitals.

Conclusion: While satisfactory susceptibility was observed in Amikacin and Piperacillin/Tazobactam. The post-pandemic era resulted in a decrease in AMR due to significant changes in antibiotic prescribing patterns. This report may guide future antibiotic prescribing.

Keywords: Antimicrobial resistance pattern, Antibiogram, Anti-infective therapy, COVID-19, Empiric therapy

INTRODUCTION

Antibiotics have revolutionized medicine by creating breakthroughs in a wide variety of clinical fields, such as safer childbirth, surgical procedures, organ transplantation, and myeloablative chemotherapy regimens. Antimicrobial resistance (AMR), on the other hand, threatens to subvert and even reverse some of this development.[1]

AMR is the ability of microorganisms to evolve mechanisms that make them immune to drugs widely used to treat associated infections, allowing for the transmission of resistant genetic traits to the population. New mechanisms of resistance have recently resulted in the simultaneous production of resistance to many antibiotic groups, resulting in extremely dangerous multidrug-resistant bacterial strains, some of which are referred to as "superbugs." Antibiotic resistance and various genetic mechanisms (e.g., co-selection and compensatory mutations) have been shown to influence bacterial virulence and fitness in recent studies.[2]

In Pakistan, AMR has rendered certain antimicrobial agents inactive against some agents used in empiric therapy. The factors due to AMR in Pakistan are nearly like the rest of the world. Few exceptions include the uncontrolled self-medication of antibiotics by the general public and non-compliance of patients to complete antimicrobial therapy.[3]

Our study is based on analyzing the antimicrobial susceptibility data of tertiary care hospitals before and after the pandemic to guide the clinicians in their antibiotic prescribing for infectious diseases.

MATERIAL AND METHODS

This retrospective study was based on antibiogram data of different tertiary care hospitals (Civil Hospital, Aga Khan University Hospital, and Jinnah Postgraduate Medical Centre) obtained from Pakistan AMR Network from January 2016 to December 2020.

The antibiogram data obtained are a yearly average of antimicrobial susceptibility, that is, conjugation of the antibiotic sensitivity test conducted over a year. The data observed are qualitative (percentage resistivity or percentage sensitivity) which included the Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus* spp., while Gram-negative organism includes *Escherichia coli*, *Enterobacter* Spp., *Proteus mirabilis*, *Klebsiella pneumoniae,* and *P. aeruginosa*.

In addition, antimicrobial susceptibility literature survey was conducted using the keywords "Antimicrobial Sensitivity," "Antimicrobial Susceptibility," "Antimicrobial Resistance," "Tertiary care," and "Pakistan" on an online research database such as Google Scholar and PubMed. Most of the publications observed were organism-specific antimicrobial susceptibility or sensitivity reports, while other reports were disease and/or patient conditions specific.[4-9]

The antimicrobials commonly tested in every antibiogram and literature review were tabulated and analyzed. For Gram-positive bacteria, antimicrobials included Oxacillin, Clindamycin, Erythromycin, Vancomycin, and Cotrimoxazole. While for Gram-negative bacteria, Amikacin, Ciprofloxacin, Ceftriaxone, Piperacillin/Tazobactam, and Cotrimoxazole were observed.

The susceptibility reports analyzed on IBM SPSS version 23 included a sample size of 24,523 Gram-positive organisms and 75,145 Gram-negative organisms from different tertiary care hospitals in Karachi between January 2016 and December 2019. The sample size of bacterial isolates is variable among different hospitals. The ethical committee waived off the ethical consideration of this study as this does not directly involve patients or any confidential data.

Table 1: Antimicrobial resistance %age Resistivity of Gram-positive bacteria pre- and post-pandemic.

	Gram-positive organisms	Ampicillin	Ciprofloxacin	Gentamicin	Vancomycin	Clindamycin	Cotrimoxazole	Erythromycin	Oxacillin
Pre-pandemic	*Staphylococcus aureus*	57	71	49	19.5	-	-	-	-
Post-pandemic	*Staphylococcus aureus*	50	81	61	17.33	-	-	-	-
Pre-pandemic	*Enterococcus* sp.	-	-	-	0	24	19.66	44.3	63.5
Post-pandemic	*Enterococcus* sp.	-	-	-	0	14	21	57.5	80.5

Table 2: Antimicrobial resistance %age Resistivity of Gram-negative bacteria pre- and post-pandemic.

	Gram-negative organism	Amikacin	Ceftriaxone	Ciproloxacin	Cotrimoxazole	Piperacillin/Tazobactam
Pre-pandemic	*E. coli*	20.5	84	74.5	74	35.5
Post-pandemic	*E. coli*	12	78.66	76	66.5	31
Pre-pandemic	*K. pneumoniae*	34.5	81	70.5	66	46
Post-pandemic	*K. pneumoniae*	28	66.33	59.33	48	54
Pre-pandemic	*Enterobacter* sp.	28	72	62.75	59.3	38
Post-pandemic	*Enterobacter* sp.	21	60.33	54.33	39	31.33
Pre-pandemic	*P. mirabilis*	26	81	59.5	66	8.66
Post-pandemic	*P. mirabilis*	27.3	49.33	59.33	61	9.66
Pre-pandemic	*K. pneumoniae*	20.5		33		15.5
Post-pandemic	*K. pneumoniae*	19.6		31.66		21.6

E. coli: Escherichia coli, K. pneumonia: Klebsiella pneumonia, P. mirabilis: Proteus mirabilis, K. pneumoniae: Klebsiella pneumoniae

RESULTS

Among the Gram-positive organisms, *S. aureus* showed a decrease in resistance against Oxacillin and Erythromycin after the COVID pandemic while showing an increase in resistance of 37.17% and 13.5% for Oxacillin and Erythromycin from 2016 to 2019, respectively. Vancomycin showed negligible resistance against *S. aureus* while clindamycin showed an increase in resistance after the pandemic from 14% to 24%. The resistivity of Cotrimoxazole was considerably unaffected by the pandemic [Table 1]. In the case of *Enterococcus* spp., Ampicillin, Gentamicin, and Ciprofloxacin showed an increasing pattern of resistance from 2016 to 2019. After the pandemic, only the resistance of Ampicillin was decreased while Ciprofloxacin and Gentamicin were decreased to 81% and 61%, respectively. The resistance against Vancomycin was variable throughout the years and only decreased to 17.33% after the pandemic [Figure 1].

Against the Gram-negative organisms, Ceftriaxone showed the highest resistivity against *E. coli*, *Enterobacter* spp., *K. pneumoniae,* and *P. mirabilis* with the highest resistivity reported against *E. coli* with a 12.32% increase in resistance between 2016 and 2019. Ceftriaxone showed the highest resistance in 2019 against the mentioned organism which substantially decreased after the advent of the COVID pandemic in 2020 [Figure 2]. Ciprofloxacin showed an increase in resistance against *E. coli* with no change in resistivity after the pandemic. While a decrease in resistivity was observed against *Enterobacte*r Spp. and *K. pneumonia*e against all tested antibitics after the COVID pandemic. Resistance of Ciprofloxacin against *P. mirabilis* was increased by 14.6% from 2016 to 2019 and was unaffected by the spread of COVID-19 in 2020.

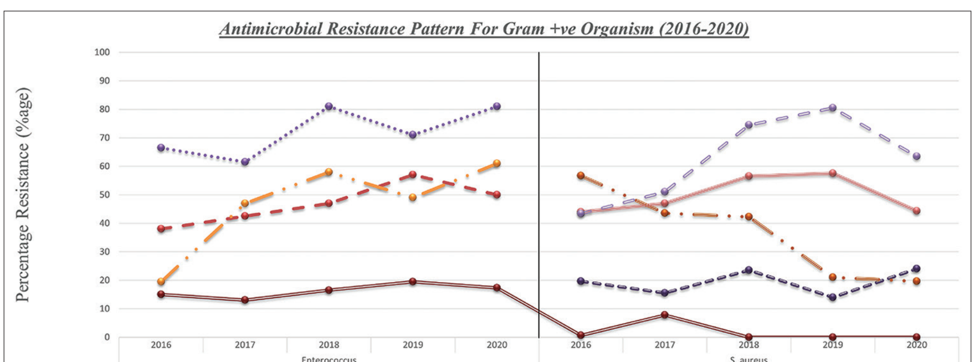
Cotrimoxazole showed a decreasing pattern of resistance after the pandemic against *E. coli*, *Enterobacter* spp., *K. pneumoniae,* and *P. mirabilis* with the highest resistance against *E. coli*, 66% in 2020. Resistance to Cotrimoxazole was increased in all said organisms from 2016 to 2019 but showed a decrease in resistance after the COVID pandemic in 2020. Piperacillin/Tazobactam followed by Amikacin showed the least resistance against the Gram-negative organism with the highest resistance against *K. pneumoniae* and *Enterobacter*. Both drugs showed a decrease in resistance after the pandemic against *E. coli*, *Enterobacter* spp., and *K. pneumoniae*. *P. aeruginosa* showed the lowest and most variable resistance against Ciprofloxacin, Piperacillin/Tazobactam, and Amikacin [Table 2].

After the pandemic in December 2019, the antibiotic resistance of most antibiotics was reduced which included Oxacillin, Erythromycin, Cotrimoxazole, Ampicillin, Vancomycin for Gram-positive organisms, and Ceftriaxone, Ciprofloxacin, Cotrimoxazole, and Piperacillin/Tazobactam for Gram-negative organisms.

DISCUSSION

In this study, retrospective antimicrobial susceptibility data are analyzed from different tertiary care hospitals in Pakistan over a timeline from 2016 to 2020. This is the first comprehensive report to predict the resistivity pattern of the most common Gram-positive and Gram-negative bacteria observed in the locality. Gram-negative isolates were more prevalent compared to Gram-positive isolates. Among the Gram-negative isolates, *E. coli* and Gram-positive isolates, *S. aureus* predominates in their respective group.

According to a study conducted by Khan *et al.*[10] regarding most commonly prescribed antibiotics for in-patients, Cephalosporins (Ceftriaxone and Cefoperazone), Quinolone (Ciprofloxacin and Moxifloxacin), Metronidazole, Penicillin (Ampicillin), Penicillin + Enzyme inhibitors (Coamoxiclav



	2016	2017	2018	2019	2020	2016	2017	2018	2019	2020
	Enterococcus					S. aureus				
Ampicillin	38	42.5	47	57	50					
Ciprofloxacin	66.5	61.5	81	71	81					
Gentamicin	19.5	47	58	49	61					
Vancomycin	15	13	16.5	19.5	17.33	0.66	7.75	0	0	0
Clindamycin						19.66	15.5	23.5	14	24
Co-Trimoxazole						56.66	43.5	42.25	21	19.66
Erythromycin						44	47	56.5	57.5	44.3
Oxacillin						43.33	51	74.5	80.5	63.5

Figure 1: Antimicrobial resistance pattern for Gram-positive organism.

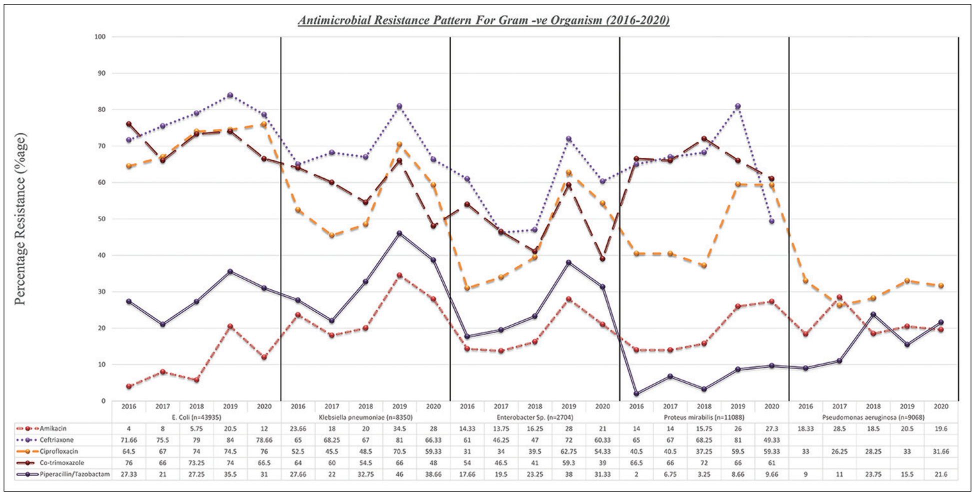


Figure 2: Antimicrobial resistance pattern for Gram-negative organism.

and Piperacillin/Tazobactam), Aminoglycosides (Amikacin), and Glycopeptide antibiotics (Vancomycin) are generally utilized antibiotics in tertiary care hospitals. Among these antibiotics, the agents being tested for antimicrobial susceptibility testing are Oxacillin, Clindamycin, Erythromycin, Cotrimoxazole, Vancomycin, Ampicillin, Ciprofloxacin, and Gentamicin for Gram-positive organisms which establishes the fact that this study can be the basis of guidelines for empiric therapy against infectious organisms.

The pathogen *S. aureus* has been identified as a significant pathogen linked to inpatient and community infections.[11] The resistivity pattern of *S. aureus* for Oxacillin indicated a critical increase in resistance infers to the prevalence of Methicillin-resistant Staphylococcus aureus strains of the organism which may render penicillin ineffective for empiric therapy in infectious diseases. A significant decrease in resistance toward Cotrimoxazole may contribute to less frequent prescribing as empiric therapy, which led to desensitization to the agent. Over 5 years, Clindamycin and Vancomycin showed no considerable variation in resistance.

Among the Gram-negative organisms, a substantial increase in resistivity pattern toward Ceftriaxone, Ciprofloxacin, and Cotrimoxazole is observed. This may provide a signal to the prescribing physician not to use these agents for empiric therapy against suspected infection as it may escalate the resistance of these agents. This will render these agents ineffective soon for treating any infectious disease.

According to the American College of Clinical Pharmacy; Ceftriaxone, Cotrimoxazole, and Ciprofloxacin are recommended in UTIs caused by *E. coli*.[12] Our study has shown a mean resistance of 77%, 70%, and 72%, respectively, for these antimicrobials suggestive of controlled use of these agents empirically UTIs. Amikacin and Piperacillin/Tazobactam remain a more efficacious choices of the drug for treating UTIs due to their lower resistivity.

K. pneumoniae is associated with diseases such as community-acquired pneumonia, UTI, and nosocomial infections.[13] According to the guidelines, Ciprofloxacin monotherapy, Ceftriaxone, and Cotrimoxazole are useful for treating such infections. Our study suggests an increase in resistance toward these agents which may render the treatment strategy ineffective. Aminoglycosides (Amikacin) or Penicillin/enzyme-inhibitor complex (Cotrimoxazole) have shown greater sensitivity and are recommended for the treatment of such conditions.

P. mirabilis is common among Gram-negative causes of bacteremia with the most cases secondary to UTI and often associated with urinary catheters. Quinolone, Cephalosporin, and Cotrimoxazole are generally recommended for empiric therapy for Proteus suspected UTI.[14] The antibiogram data suggested an elevation in resistance toward these agents over the 4 years. Piperacillin/Tazobactam and amikacin remain the least resistant agents against such organisms.

P. aeruginosa showed no change in resistivity pattern over the years toward the tested antibiotics. On the other hand, *Enterobacter* showed a significant increase in resistance pattern over the years toward Piperacillin/Tazobactam, Ciprofloxacin, and Amikacin with the highest resistance observed in Ceftriaxone.

With the outbreak of coronavirus starting in February in Karachi, antibiotic prescribing patterns were shifted from traditional empiric therapy protocols. According to Akhtar *et al*., the azithromycin prescription rate was 88.6% followed by Ceftriaxone at 23.6% and Cefixime at 0.5% for the year 2020.[15] The spike in usage of azithromycin due to its role in COVID-19 in some preliminary trials resulted in an overall decrease in AMR of other antibiotics. A similar study conducted by Saini *et al*.[16] which also shows a similar transition from resistivity to the susceptibility of some antimicrobial agents. This also shows the lowering in the occurrence of some bacterial organisms in tertiary care hospitals. These transitions in antimicrobial susceptibility may mostly be due to the influence of antibiotic prescribing patterns but due to the lack of prescribing data in Pakistan, this could not be compared. Further studies involving antibiotic prescribing patterns should be conducted to obtain a clear image of this scenario.

CONCLUSION

The retrospective study revealed an overall increase in every antimicrobial agent observed before the COVID-19 outbreak. The post-pandemic antibiotic resistance pattern was greatly altered due to changes in the antibiotic prescribing pattern. Few exceptions were there due to minimal prescribing of the agent. More studies should be conducted to assess the activity of oral antimicrobial agents for the treatment of infectious diseases as this study revealed Piperacillin/Tazobactam (for Gram-negative organism) and Cotrimoxazole (for Gram-positive organism) to be the most effective agents.

Declaration of patient consent

Patient consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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