Original Article

Temporal association between antibiotic use and resistance in Gram-negative bacteria

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Abstract

Background: The present investigation has attempted to enhance the understanding of the occurrence of interaction at a time between antibiotic usages with resistance ability of antimicrobial pathogens. **Methods and materials:** The collection of data on prescription and consumption of antibiotics and database on susceptibility covering isolation rate of resistance potential per quarter was collected. **Results:** The prescription rate of third-generation cephalosporins and Fluoroquinolones has shown an increased annual resistance rate of gram-negative bacterial strains. The results showed a positive significant correlation between two quarterly lagged numbers of BLBLIs that indicated increased susceptibility to the resistance potential of the strains, whereas levofloxacin and meropenem exhibited no association with resistance to the infections. **Conclusion:** The usage of BLBLIs showed promising results against infections, still, it required a cautious planning and wide understanding of acquiring and sustaining resistance to BLBLIs and its associated antibiotics at the clinical level.

Keywords: Piperacillin/Tazobactam, Ceftazidime, Klebsiella pneumoniae, B-Lactam/ B-lactamase inhibitors

INTRODUCTION

The emergence of B-lactam-hydrolysing enzyme, B-lactamases has been known to be a remarkable threat and considered to be a clinical challenge as its virulent capability in responding to environmental inputs [1]. The enhancing rate of infections caused by Extended-Spectrum B-lactamase (ESBL) producing organisms is regarded as a global alarm due to its acquiring capacity in the hydrolytic activity of B-lactam antibiotics [2, 3]. These strains were conferring resistance to the B-lactam antibiotics such as cephalosporins and Fluoroquinolones [4-6]. As a result of worst outcomes, prolonged stays in hospital, ineffective treatment results and morbidity are prevalent in many countries caused by ESBL producing gram-negative bacteria than other strains [7, 8]. To date, more than 150 ESBL, were identified and described [4]. These B-lactamases have emerged from various genera of *Enterobacteriaceae and Pseudomonas aeruginosa.* To conquer this problem, alternate to Carbapenem which is being used as an effective treatment for ESBL infections in clinical practices, B-lactam/Lactamase inhibitors (BLBLIs) were instigated. Carbapenem usage and choice of antibiotics for the treatment of ESBL produced infections were based on in vitro activity and animal experiments [9, 10].

Outcomes of the treatments were subjected to conflict and highly debatable. According to Ofer *et al.,* 2015 an increased use of carbapenems contributed to the strains by opening many resistance pathways covering point mutation to acquire the ability to hydrolyze carbapenems [11]. This led to the quest of producing effective B-Lactam antibiotics against ESBL producing pathogens. To add up the effectiveness of B-Lactam BLBLIs synergists' administration was recommended in the clinical medication [12]. Although they were believed to be effective, ESBL producing strains hydrolyze BLBLIs combination drugs also; the rate of resistance ability differs from the antibiotics such as ampicillin/Sulbactam and Piperacillin/Tazobactam against the infections [13].

Therefore, it is known that emerging challenges in conferring resistance to ESBLIs related infections against

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BLBLIs attracted the attention of many researchers and physicians worldwide. A recent study report revealed that equally efficacious alternate antibiotic agents undergo hydrolytic process against third-generation cephalosporins, specifically, Ceftriaxone and Cefotaxime were directly implied that prescribed and consumed antibiotics were unsuited for the treatment of ESBL associated infections. [2]. In an earlier study, it was reported that the use of BLBLIs combination has altered its molecular point resulted mutant for developing susceptibility in antibiotic resistance to the inhibitors [14]. Wong-Beringer *et al.,* 2002 stated that ceftazidime treatment was unsuccessful in treating ESBL producing pathogens. Besides, increased use of carbanemes against ESBL-EK infections was occurred, simultaneously; the emergence of carbonemes resistance developed in associated other pathogens [15].

However, there are close association existing between prescribed consumption of antibiotics and antimicrobial resistance to the prevalent ESBL producing pathogens, is still not understood obviously. The present study was carried out with an objective of wide understanding of the association between usage of antibiotics and resistance rate to BLBLIs, third-generation cephalosporins, all Fluoroquinolones, against prevalent pathogens of ESBLIs such as *K.Pneumoniae, Acinetobacter, and Pseudomonas aeruginosa* species

Materials and Methods

Collection of Data on Prescription of Antibiotic

Before starting data collection, ethical approval was obtained from the ethics research committee with a registration number GURP/2019/43 reviewed by the institutional review board of Gulbarga University, Karnataka, India. The date on consumption and prescription of antibiotics for a tenure of 2014 – 2017, was collected from the public health department database. It is a predominant database pool that includes 98% of prescription details to the patients of Karnataka State, India. Coding for the antibiotics was followed by WHO and anatomical therapeutic chemical classification (ATC) [16]. As the mechanism of antibiotics against bacteria is considered to be the same in all classes. Hence, ATC classification has been accepted and used to analyze the relationship between the occurrence of prevalence isolates resistance efficacy and on the different antibiotic exposure [17, 18]. In the present study, data on the prescription of antibiotics specifically to BLBLIs treatment choice (ATC code JOICR) covering 3rd generation Cephalosporins and Fluoroquinolones were added for the analysis.

Collection of Data on Antimicrobial Resistance Efficacy:

The database on microbial culture was derived from the above-designated specialty hospital and complied with to evolve a quarterly estimate for the antimicrobial resistance (ARN). It is noteworthy that data derived hospital has been declared as an "Antimicrobial resistance monitoring focal point" by the WHO during 1988 with 2200 beds. The required microbial specimens were received from both outpatient and inpatient departments and further identification and susceptibility tests were also carried out in electronic Automated system (Vitek, bioMerieux) or else disk diffusion tests were performed followed by clinical laboratory standards institute (CLSI) guidelines (ARN). To represent BLBILs 3rd generation Cephalosporins and Fluoroquinolones, drugs such as Piperacillin/Tazobactam and Ceftazidime were applied respectively. In the collection of the database on resistance, duplicates isolates and intermediate susceptible samples were avoided in this study. The rate of resistance was calculated by applying the following formula as the number of resistance isolates divided by the number of tests in each annum.

Statistical analysis

To analyze and identify the trends of antibiotic prescriptions and resistant ability was carried out by applying regression analysis. If P-value showed less than 0.05 with R square values greater than 0.3 are considered to be statistically significant [19]. To assess the association between a quarterly number of antibiotic prescription and quarterly isolation rate of antibiotic susceptibility, a cross-correlation was executed [20]. The Box-Jenkins method was also performed to analyze time-series data on autoregressive moving average models [21, 22]. Outcomes were evaluated using the Dickey-Fuller test applied to find out if spurious correlations to be ruled out. Akaike information criterion test portmanteau tests were also carried out [23]. All statistical analysis was performed in R version 3.2.4.

Results

During the study period (2014-17) mean value of annual antibiotic prescription was recorded as 16,127 with a range of 3782-51469 numbers covering all BLBLIs, third-generation Cephalosporins, fluoroquinolones, Aminoglycosides, Carbapenems, and Macrolides. The average number of prescription and consumption of all BLBLIs was found to be 41,107 with (34768-51469 range). Third generation Cephalosporins, Fluoroquinolones and Aminoglycosides annual averages are recorded as 27599 with a range of (24646-37426), 16,917 with a range of (9707-25858) and 24,664 numbers with a range of (14668-31549) respectively. Similarly, average annual numbers of prescription rate on Carbapenems and Macrolides were found to be 18087 with a range of (14456-27491) and 9454 range from (9707-15858) respectively. It was noticed that no remarkable deviation was observed in the prescription rate throughout the study period (**Table 1**).

Annual Mean Value of rate of resistance of major pathogen, *K. Pneumoniae* to the antibiotic Piperacillin/Tazobactam, Ceftazidime, Levofloxacin, Ciprofloxacin, Gentamicin, and Meropenem was found to be 38.2%, 29.3, 27.17, 57.8, 53.5

and 5.02% respectively. Whereas Azithromycin value was not determined (NA). The average value of yearly resistance rate of *Acinetobacter* to the prescribed antibiotics was recorded such as Piperacillin/Tazobactam (42.02%, Ceftazidime (32.24%), Levofloxacin (29.7%), Ciprofloxacin (63%), and Gentamicin (59.6%) Meropenem (5.4%) and Azithromycin was observed and showed as 21.15%. Similarly, the value of *Pseudomonas Aeruginosa* resistance rate was recorded as 46.2%, 35.46, 32.87, 69.6, 64.94 and 6.07% to the respective antibiotics such as Piperacillin/Tazobactam, Ceftazidime, Levofloxacin, Ciprofloxacin, Gentamicin, and Meropenem, whereas Azithromycin value was also N.D. (Not Determined) (**Table 2**).

As a result of bivariate analysis on the major antibiotic resistance, *K. Pneumoniae* showed a positive significant correlation with two quarterly lagged numbers of BLBLIS such as piperacillin/Tazobactam (β=0.56;p<0.05), ceftazidime (β=0.62;p=0.05) and ciprofloxacin (β=0.56 ; p <0.05) whereas levofloxacin (β=0.40;p =0.01) and meropenem (β= -0.250; p =0.01) showed no correlation. Moreover, the lagged quarterly number Cephalosporins prescription was also significantly correlated with *K.Pneumoniae* resistance to Ceftazidime (β=0.54;P<0.05) in two-quarter Levofloxacin (β=0.59; P<0.03) and Meropenem (β=0.39; P=0.055) One quarter lag number. However, all fluoroquinolones prescription to *K.pneumoniae* resistance had no association to ceftazidime (β=0.24;p<0.01) two-quarter lags, ciprofloxacin, meropenem, levofloxacin, and their values were found to be (β=0.26; P=0.02); (β=0.07; P=0.05) and (β=0.27; P=0.35) respectively (**Table 3**).

Table 1: Prescription rate throughout the study period

Antibiotics	The annual mean number of antibiotics prescriptions				
	2014	2015	2016	2017	
β-lactam/β-lactamase inhibitors	41,344 (33,799–50,123)	43,635 (33,556–4,568)	42,937 (38,660–6,667)	38,183 (27,001–50,628)	41,107 (34,768–51,469)
Third-generation cephalosporins	37,982 (30,586–50,543)	38,870 (30,248–7,164)	30,947 (24,663–4,567)	23,404 (22,789–36,510)	27,599 (24,646–37,426)
Fluoroquinolones	17,580 (16,353–23,003)	18,973 (15,910–5,796)	16,549 (11,090–5,856)	15,540 (12,446–22,029)	16,917 (09,707–25,858)
Aminoglycosides	24806 (23,099–30,126)	26181 (13,656–4,580)	25761 (18,696–6,637)	22909 (17,901–30,642)	24664 (14,668–31,549)
Carbapenems	18191 (10,866–20,453)	19199 (10,845–7,445)	18892 (14,396–4,777)	16800 (12,859–26,160)	18087 (14,456–27,496)
Macrolides	9509 (6,353–13,903)	10036 (5,910–15,576)	9875 (8,090–15,656)	8782 (7,446–12,029)	9454 (9,707–15,858)

Table-2a: Antibiotic resistance rate to Klebsiella pneumoniaethroughout the study period

Antibiotics	**Isolation rate (%) of antibiotic-resistant *Klebsiella pneumoniae***			
	2014	**2015**	**2016**	**2017**
Piperacillin/Tazobactam	36.9	38.25	36.25	41.4
Ceftazidime	25.875	34.65	24.3	32.4
Levofloxacin	23.625	26.1	29.25	29.7
Ciprofloxacin	53.66	56.343	59.16015	62.1181575
Gentamicin	49.66	52.143	54.75015	57.4876575
Meropenem	4.66	4.893	5.13765	5.3945325
Azithromycin	ND	ND	ND	ND

Table-2b: Antibiotic resistance rate to Acinetobacter baumanniithroughout the study period

Antibiotics	**Isolation rate (%) of antibiotic-resistant *Acinetobacterbaumannii***			
	2014	2015	2016	2017
Piperacillin/Tazobactam	40.59	42.075	39.875	45.54

Ceftazidime	28.4625	38.115	26.73	35.64
Levofloxacin	25.9875	28.71	32.175	32.67
Ciprofloxacin	59.026	61.9773	65.076165	68.32997325
Gentamicin	54.626	57.3573	60.225165	63.23642325
Meropenem	5.126	5.3823	5.651415	5.93398575
Azithromycin	21.66	22.96	22.11	19.15

Table-2c: Antibiotic resistance rate to Pseudomonas aeruginosathroughout the study period

Antibiotics	Isolation rate (%) of antibiotic-resistant *Pseudomonas aeruginosa*			
Piperacillin/Tazobactam	44.649	46.2825	43.8625	50.094
Ceftazidime	31.30875	41.9265	29.403	39.204
Levofloxacin	28.58625	31.581	35.3925	35.937
Ciprofloxacin	64.9286	68.17503	71.5837815	75.16297058
Gentamicin	60.0886	63.09303	66.2476815	69.56006558
Meropenem	5.6386	5.92053	6.2165565	6.527384325
Azithromycin	ND	ND	ND	ND

Table-3: Antibiotic-resistant Klebsiella pneumoniae

	Antibiotics				
	Piperacillin/Tazobactam	Ceftazidime	Levofloxacin	Ciprofloxacin	Meropenem
β-lactam/β-lactamase	0.56	0.62	−0.40	0.56	−0.250
inhibitors	p < 0.05	p = 0.05	p = 0.01	p < 0.05	p = 0.01
	2 quarters lag	2 quarters lag	2 quarters lag	2 quarters lag	2 quarters lag
Third-generation	−0.11	0.54	0.59	−0.19	0.39
cephalosporins	p = 0.35	p < 0.05	p = 0.03	p = 0.61	p = 0.055
	-	2 quarters lag	1 quarter lag	-	1 quarter lag
Fluoroquinolones	0.36	0.24	0.27	0.26	0.07
	p = 0.19	p < 0.01	p = 0.35	p = 0.22	p = 0.05
	-	2 quarters lag	-	-	-

Table 4: Percentage of the rate of Isolation of antibiotic-resistant against ESBL producing pathogens

Antibiotic	*Klebsiella*	*Acinetobacter*	*Pseudomonas*
Piperacillin/Tazobactam	88.2	42.02%	46.23
Ceftazidime	29.3	32.24%	35.46
Levofloxacin	27.17	29.7	32.87
Ciprofloxacin	57.8	63.5	69.95
Gentamicin	53.5	59.6	64.74
Meropenem	5.02%	5.4	6.078
Azithromycin	ND	21.15	ND

Discussion

The increasing rate of production of ESBL producing strains such as *K.Pneumoniae, Acinetobacter* and *Pseudomonas* species were limiting the clinical therapeutic practices [7, 10, 24]. BLBLIs such as Piperacillin/Tazobactam, Third generation Cephalosporins are recognized as an alternate antibiotic choice against infections [25]. Even though Carbapenems is believed to be effective, it is evident that consumption has led to the unsuccessful results in the

treatments of ESBL producing pathogens and outcomes of treatment has been debatable. However, all the evidence showed that BLBLIs have equal efficacy comparing with Carbapenems and known to be an alternate antibiotic agent to Carbapenem drugs [26].

To develop an appropriate protocol for BLBLIs, as other options for Carbapenem, it is mandatory to test the association between BLBLIs and resistance capability of antimicrobial pathogens. Similar earlier studies have focused on the association/correlation between seasonality and antibiotic usages [17, 18, 27]. In the present investigation, a significant association was observed between all prescribed and consumed BLBLIs showed the greatest at a time occurrence of association to the Piperacillin/Tazobactam, Ceftazidime, Levofloxacin, Ciprofloxacin and Meropenem resistance in *K.Pneumoniae.* Whereas Third generation Cephalosporins and Fluoroquinolones showed insignificant correlation. This may be attributed to the selection of pressure of antibiotic usage on the predominant of resistance isolates strains [28]. Our study results were agreed with the findings of Lai et *al.,* 2011 found that a significant correlation between Piperacillin/Tazobactam usage and its resistance ability [29]. Our investigation has also revealed that one of the antibiotics administered ceftazidime resistance in *K.Pneumoniae* showed a positive correlation with entire BBLIs, Third generation Cephalosporins and Fluoroquinolones statistically. In Klebsiella, the maximum annual mean resistance rate was observed to the ciprofloxacin (57.87%) followed by gentamicin (53, 5%) whereas the minimum rate was recorded as (29.3%) to the ceftazidime. In Acinetobacter, the Annual maximum resistance rate was found to be (63%) to the ciprofloxacin followed by gentamicin (63%) with minimum value to the meropenem (5.4%). Similarly, *Pseudomonas* species showed a maximum value of annual resistance rate exhibited to the ciprofloxacin ((69.9%) followed by gentamicin (64.74%) and minimum to meropenem and recorded as (6.007%).

An earlier report on *Klebsiella* species showed a significant positive correlation with BBLIs Cephalosporins and fluoroquinolones in clinical investigation [30]. This may be presumed that Fluoroquinolone resistance might have attributed to the transferable plasmid within ESBL producing strains [31]. Overall that correlation may be due to the potential of providing resistance to all classes of antibiotics [28]. No correlation was observed in Levofloxacin resistance in *K. Pneumoniae* in the present study. It also indicated all BLBLIs consumption was positively correlated while Levofloxacin showed negatively associated. This finding may due to the instability of a quarterly number of Fluoroquinolones advised and consumed.

Conclusions

In the present investigation, a remarkable association was identified between BLBLIs medication and piperacillin/Tazobactam resistance was found to be an increasing trend to the *K.pneumoniae, Acinetobacter* and particularly to *Pseudomonas* pathogenic strains. Our results suggested that to maintain the potential of resistance of the strains not to develop, usage of BLBLIs has been recommended to minimize clinical practices. The intervention of An alternate possible choice has been appreciated and it is considered to be the eleventh hour. Moreover, as a result of our study, it is to opine that prolonged prescription and usage of BLBLIs against tested pathogenic strains has indicated the emerging of resistance ability. Although several studies were emphasized to these inhibitors, inconsistent results were observed in our investigation. We further argued that a focus intervention is necessary to avoid perpetuation of resistance power to the BLBLIs.

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