Original Article

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Microbiology Section

Relationship between Antimicrobial Consumption and the Incidence of Antimicrobial Resistance in *Escherichia coli* and *Klebsiella pneumoniae* Isolates

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ABSTRACT

Introduction: Gram negative organisms are one of the major causes of nosocomial diseases. Development of resistance to antibiotics by these organisms increases their risk in clinical treatment of patients. It also affects morbidity and mortality hence needs to be monitored and controlled.

Aim: The aim of the present study was to analyse the correlation between consumption of parenteral antibiotics and the rates of antimicrobial resistance among the *Escherichia coli* and *Klebsiella pneumoniae* isolates collected during Dec 2010 - Jun 2013 from JIPMER hospital.

Materials and Methods: Consumption data of parenteral antibiotics in J01 category of Anatomical Therapeutic Chemical (ATC) in JIPMER was obtained and expressed in Defined Daily Doses (DDD) per 1000 inhabitants. Valid consumption and resistance data during the period Dec 2010 to Jun 2013 were obtained at 6 month intervals and were correlated to draw a relationship between antimicrobial consumption and its impact on drug resistance for *Escherichia coli* and *Klebsiella pneumoniae*.

Results: *Escherichia coli* isolates showed high resistance for increased use of gentamycin and ciprofloxacin. Increase in antibiotic consumption increases the resistance for *Escherichia coli* except for amikacin. Among the *Klebsiella* isolates, meropenem and gentamycin showed high correlations followed by ceftazidime, amikacin, ceftriaxone and ciprofloxacin.

Conclusion: In summary, a statistically significant association was noticed between consumption of the studied antimicrobials and resistance of *Escherichia coli* isolates, except for amikacin and ceftazidime. In the case of *Klebsiella pneumoniae*, there was a statistically significant association between the resistance rates and consumption of gentamycin, ceftazidime and meropenem. Further, a linear relationship was noted between antimicrobial consumption and resistant isolates of *Escherichia coli* and *Klebsiella pneumoniae*, except for *Escherichia coli* resistance to amikacin.

Keywords: Antimicrobial drug resistance, Daily defined doses, Drug utilization, *Escherichia coli, Klebsiella pneumoniae*

INTRODUCTION

Escherichia coli and *Klebsiella pneumoniae* are gram-negative organisms belonging to the *Enterobacteriaceae* family accounting for the majority of hospital and community-acquired UTIs [1]. They are also a frequent cause of nosocomial bloodstream infections, surgical site infections, gastrointestinal infections and community-acquired pneumonia [2-4]. There have been many reports of outbreaks caused by these organisms. These organisms pose resistance to aminoglycosides, fluoroquinolones, carbapenems and cephalosporins. Many studies have been conducted to determine the incidence of development of antibiotic resistance in *Escherichia coli* and *Klebsiella pneumonia* [5-9].

The rates of antibacterial resistance and isolation of resistant bacteria in hospitals are affected by various factors, including selection of antibiotics, dose and duration of treatment and the medical and surgical procedures performed at the hospital [9]. The objective of the present study was to examine the changes in resistance of *Escherichia coli* and *Klebsiella pneumoniae* due to in-patient antimicrobial consumption at JIPMER hospital. Knowledge of these relationships could help in controlling antimicrobial resistance in the hospital setting.

MATERIALS AND METHODS

This retrospective study was conducted at JIPMER, a 1591 bedded tertiary care teaching hospital in Pondicherry, South India. The total number of beds included medical services, surgical beds, ICU, obstetrics, ophthalmology, urology and ENT. The data were collected retrospectively from Pharmacy Stores, Medical Records Department (MRD) and Microbiology Department. The total number of inpatients in the months June and December of 2010-13 were obtained from MRD for calculating the DDD per 1000 patients.

Antibiotic Consumption

The antibiotics issued to the hospital were recorded in the pharmacy stores on a monthly basis. Deliveries to the hospital wards were assumed to reflect usage [10]. In the present study, the consumption data of parenteral antimicrobials in the Anatomic Therapeutic Chemical (ATC) Class J01 were obtained for the months June and December of 2010 to 2013 (Dec 2010 to Jun 2013) and expressed in "Daily Defined Doses" (DDD) measuring unit [11]. The gram amounts of antimicrobials were converted to DDD per 1000 in-patients for the top six frequently issued antibiotics i.e. gentamycin, amikacin, ceftazidime, ceftriaxone, ciprofloxacin and meropenem [10]. The number of DDD was calculated by multiplying the quantity issued by the DDD conversion factor [12].

Antimicrobial Resistance

Antibiotic resistance was determined by Kirby Bauer's disc diffusion method according to Clinical Laboratory Standards Institute (CLSI) guidelines. *Escherichia coli* ATCC 25922 was routinely used for the quality control of Kirby Bauer's disc diffusion method [13].

The antimicrobial resistance data during 2010-2013 were collected for the months for which consumption was noted and their consecutive months, i.e. June-July and December-January of the consecutive year [10].

Sl. No.	Antibiotic	Atc Code	Ddd's Per 1000 Patients					
			Dec 2010	Jun 2011	Dec 2011	Jun 2012	Dec 2012	Jun 2013
1	Gentamicin	J01GB03	19.50	24.29	18.95	14.27	12.41[d]	16.02
2	Amikacin	J01GB06	41.65	34.06	36.12	24.50	36.12	45.41
3	Ceftazidime	J01DD02	17.15	15.57[b]	12.10	13.45	15.72	14.43
4	Ceftriaxone	J01DD62	113.62	92.53	92.63	86.41	125.11	111.35
5	Ciprofloxacin	J01MA02	8.44[a]	9.62	8.93	9.99	13.54	12.27
6	Meropenem	J01DH02	15.75	15.09[c]	17.89	9.64	17.96	14.53

[Table/Fig-1]: Consumption of selected Antimicrobials in Group J01 (Anti-infectives for parenteral use) at JIPMER from 2010 to 2013
[a] Stocks were found to be nil from 23-12-2010 to 14-01-2011
[b]Stocks were found to be nil from 31-05-2011 to 07-06-2011
[c] Stocks were found to be nil from 23-06-2011 to 27-06-2011
[d] Stocks were found to be nil from 30-11-2012 to 21-01-2013

STATISTICAL ANALYSIS

Correlations between antibiotic consumption and resistance rates or burden were analysed with the Spearman rank correlation using IBM SPSS Statistics 21. All p-value of less than 0.05 were considered statistically significant.

RESULTS

Antimicrobial Consumption

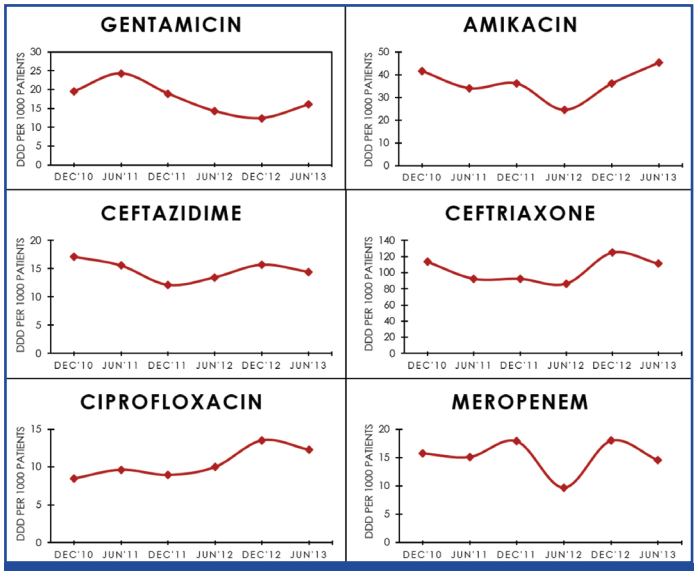
The antimicrobial consumption for the selected parenteral antimicrobials during Dec 2010 - Jun 2013 on a six-month interval was expressed as DDD per 1000 patient as given in [Table/Fig-1]. The data in [Table/Fig-1], show that the consumption of ceftriaxone was highest among all parenteral antimicrobials having a DDD of 113.62 in Dec'10, which decreased drastically to 92.53 with further decrease to 86.41 in Jun'12 and again increased to 125.11. The DDD of gentamycin increased from 19.50 in Dec'10 to 24.29 in Jun'11 and decreased to 12.41 in Dec'12. In the case of amikacin, the consumption decreased from 41.65 to 24.50 in Jun'12 and increased to 45.41 in Jun'13. The consumption of ceftazidime decreased slightly from 17.15 to 12.10 and gradually increased to 15.72 in Dec'12. There was a drastic reduction in consumption of ceftriaxone from 113.62 to 86.41, compared to the mild change in ciprofloxacin consumption from 8.44 in Dec'10 to 13.54 DDD in Dec'12. Meropenem did not show much change in first three intervals and decreased suddenly in June '12 to 9.64 followed by drastic increase in Dec'12 to 17.96 [Table/Fig-2].

Bacterial Resistance

[Table/Fig-3] provides the number of isolates processed in the corresponding months and percentage resistance for selected antimicrobial agents against gram-negative pathogens, *Escherichia coli* and *Klebsiella pneumoniae.* From the data, it was noted that, the resistance of *Escherichia coli* for ceftriaxone was highest. The resistance patterns of *Escherichia coli and Klebsiella pneumoniae* were almost same for most of the antimicrobial drugs, i.e., the resistance decreases in Jun' 12 and again increases in Dec' 12. The resistance pattern of *Escherichia coli* for amikacin showed a steady increase and that of meropenem was fluctuating.

Correlation Between Antimicrobial Consumption and *Escherichia coli* and *Klebsiella pneumoniae* Resistance Rates (2010-2013)

[Table/Fig-4-6] provide correlation between antimicrobial consumption for selected antibiotics and resistance rate for *Escherichia coli* and *Klebsiella pneumoniae* during the three-year period. Among *Escherichia coli* isolates, high correlations were discovered between



[Table/Fig-2]: Consumption of drugs in group J01 (Anti-infectives for parenteral use) at JIPMER from 2010 to 2013

Organism	Antimicrobial agent	Dec'10 (n=463)	Jun'11 (n=432)	Dec'11 (n=524)	Jun'12 (n=617)	Dec'12 (n=646)	Jun'13 (n=837)
Escherichia coli	Gentamicin	47	60	52	39	36	40
	Amikacin	10	8	12	14	13	13
	Ceftazidime	72	68	65	64	70	59
	Ceftriaxone	82	76	75	75	80	77
	Ciprofloxacin	60	62	58	75	83	81
	Meropenem	8	5	12	4	11	7
Klebsiella pneumoniae	**Antimicrobial agent**	**Dec'10 (n=314)**	**Jun'11 (n=205)**	**Dec'11 (n=226)**	**Jun'12 (n=320)**	**Dec'12 (n=287)**	**Jun'13 (n=306)**
	Gentamicin	52	67	53	38	40	48
	Amikacin	30	24	28	20	26	27
	Ceftazidime	62	64	46	53	60	58
	Ceftriaxone	78	75	72	65	82	66
	Ciprofloxacin	36	58	40	38	52	48
	Meropenem	17	18	21	7	23	16

[Table/Fig-3]: The antimicrobial resistance percentage for *Escherichia coli* and *Klebsiella pneumoniae*

Organism	Drug	Spearman Correlation	Significance
Escherichia coli	Gentamicin	0.943	0.005*
	Amikacin	-0.132	0.803
	Ceftazidime	0.771	0.072
	Ceftriaxone	0.841	0.036*
	Ciprofloxacin	0.943	0.005*
	Meropenem	0.886	0.019*
Klebsiella pneumoniae	Gentamicin	0.886	0.019*
	Amikacin	0.783	0.066
	Ceftazidime	0.829	0.042*
	Ceftriaxone	0.771	0.072
	Ciprofloxacin	0.543	0.266
	Meropenem	0.943	0.005*

[Table/Fig-4]: Spearman correlation between antibiotic consumption and resistance of *Escherichia coli* and *Klebsiella pneumoniae*for the corresponding and next month of antibiotic consumption.
* Significant correlation ($P \leq 0.05$)

the use of gentamycin (r= 0.943, p= 0.005) and ciprofloxacin (r= 0.943, p= 0.005) and the resistance for these agents, followed by meropenem (r=0.886, p= 0.019), ceftriaxone (r= 0.841, p= 0.036) and ceftazidime (r=0.771, p= 0.072). The positive slope of the line in [Table/Fig-5] demonstrated that with an increase in antibiotic consumption, the antibiotic resistance for *Escherichia coli* increases except for amikacin which showed a negative slope (r= -0.132, p= 0.803).

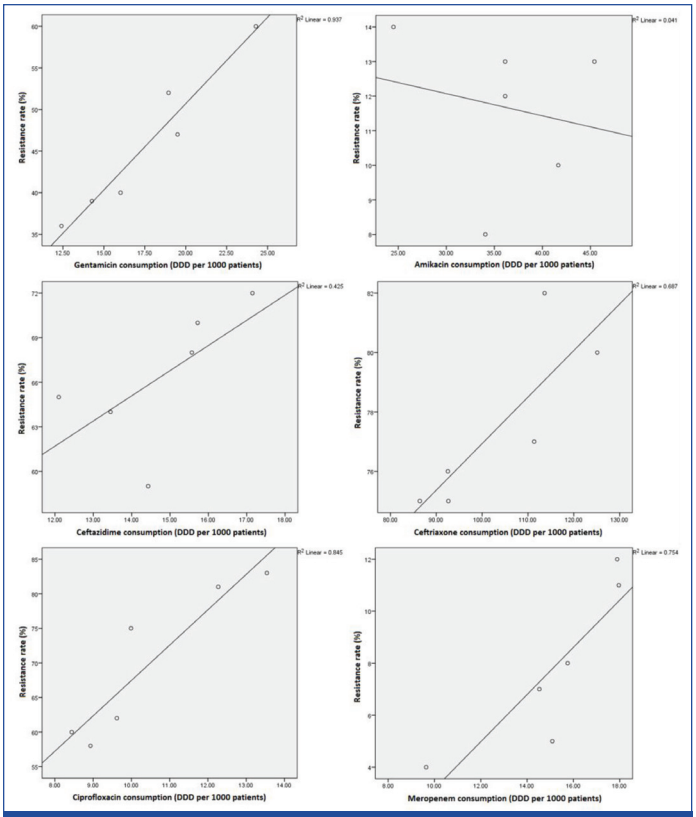
Among the *Klebsiella pneumoniae* isolates, the meropenem (r=0.943, p= 0.005) and gentamycin (r=0.886, p= 0.019) showed high correlations followed by ceftazidime (r= 0.829, p= 0.042), amikacin (r=0.783, p= 0.066), ceftriaxone (r=0.771, p= 0.072) and ciprofloxacin (r=0.543, p= 0.266). [Table/Fig-6] shows a positive slope for all the selected antibiotics, indicating that there was an increase in antibiotic resistance with an increase in antibiotic consumption.

DISCUSSION

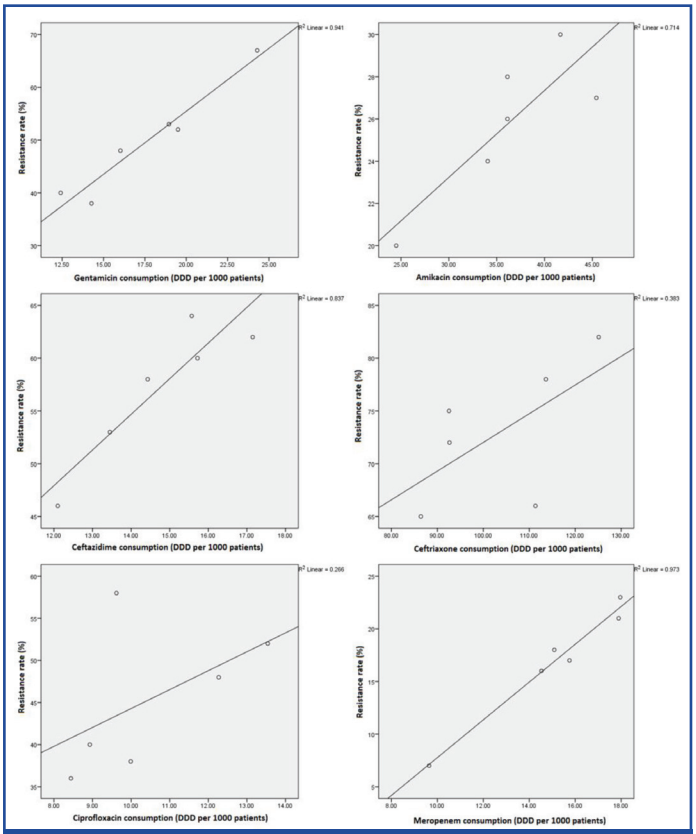
Antimicrobial consumption analysis is a critical task which is based on the parameter used for quantifying [14]. The parameter for drug consumption in our study is DDD, defined by the WHO Collaborating Centre for Drug Statistics Methodology. DDD is most widely used method for measuring the consumption in drug utilization research. However, it is emphasized by WHO that the Defined Daily Dose is a statistical measurement of average dose of drug utilisation per day and does not necessarily represent the recommended therapeutic dose or actual Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations [11]. A study concluded that, DDD methods are useful for benchmarking purposes and do not imply the number of Days of Therapy (DOTs) or relative use for many antibacterial drugs [14]. Also, many studies demonstrated the use of DDD for measuring the Antibiotic consumption [12,15-18].

According to WHO, "Antimicrobial resistance (AMR) is resistance developed in microorganism, for one or multiple antimicrobial agents, to which it originally was sensitive. Resistant microorganisms are able to combat effect of antimicrobial medicines, making standard treatments ineffective and long persistence of infections, increasing their risk of spread to others." Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness, greater risk of death and higher costs [19]. Many studies have evaluated the relationship between antimicrobial use and resistance in clinical isolates, and different results have been reported [10,20-25]. A study was conducted to determine the correlation between consumption of imipenem and β-Lactam resistance in *Pseudomonas aeruginosa* and it was found that imipenem utilisation was the major component associated with carbapenem and β-lactam resistance in endemic *P. aeruginosa*. Also, extensive use of imipenem was linked with a significant increase in their resistance [10]. In the present study also, we observed a significant correlation between the use of meropenem and its resistance rates. Another study was conducted to investigate the relationships between rates of antimicrobial consumption and the prevalence of antimicrobial resistance in *Staphylococcus aureus* and *Pseudomonas aeruginosa* isolates. From the data obtained from 47 French hospitals, it was concluded that a statistically significant relationship existed between the rate of fluoroquinolone consumption and the resistance rates among *S. aureus* and *P. aeruginosa* isolates [20]. The MYSTIC programme in North America evaluated the antimicrobial usage and resistance relationships for *Enterobacteriaceae* and *P. aeruginosa* over a period of three years (1999–2001) in 10–15 medical centres and many significant trends were identified in the prevalence of resistance among *P. aeruginosa* and *Enterobacteriaceae*. Firstly, increased use of ciprofloxacin was accompanied by a higher resistance among *Enterobacteriaceae*, and secondly a correlation existed between resistance rates of ciprofloxacin classes and levels of resistance to other antimicrobial classes in *P. aeruginosa* [21]. We also observed that the resistance rates of ciprofloxacin showed a significant correlation with its consumption. Similarly, in a recent study from India, a decreasing trend in the resistance rates was seen in *P. aeruginosa* to ciprofloxacin, ceftazidime, meropenem and imipenem. The authors have suggested that the decline in the use of ciprofloxacin could be the probable reason for the decline in the resistance rate [22]. Consumption of ciprofloxacin is known to upregulate MexEF-OprN efflux system and decrease the levels of outer membrane porin protein OprD, thereby mediating resistance to fluoroquinolones, as well as carbapenems [26,27]. Another study conducted at a tertiary hospital in India stresses the startling increase in resistance and antibiotic use. Further, they suggested that, in *Klebsiella pneumoniae,* evolution of pan-resistance could be due to the production of carbapenemases and the mechanism of resistance in *Escherichia coli* is by virtue of ESBL production [28]. Researchers in Finland examined the association between consumption of macrolide and its regional resistance rates in *Streptococcus pyogenes* during 1997–2001. In order to explain their association, a linear mixed model for repeated measures was used and it was found that a statistically significant association existed between regional resistance rates of erythromycin in *S. pyogenes* and the consumption of macrolides; however their association with azithromycin use alone was not found [23]. In Spain, researchers assessed the evolution of *Streptococcus pneumoniae* resistance to penicillin and erythromycin in relation to β-lactam and macrolide consumption over a 19-year period (1979-1997). In this study, a causal relationship could not be established between antibiotic consumption and development of resistance, but the study proposes that overuse of certain specific antibiotics is related to an increase in drug-resistant strains strains of *S. pneumonia* [24]. Another study was conducted in 20 hospital districts, in Finland, to explore the relationship between the antimicrobial consumption of Out-patients and their resistance in *Escherichia coli* during 1997-2005. Interestingly, only a few associations were found between antimicrobial consumption and its resistance. Including the association between consumption of fluoroquinolone and its resistance, the majority of the associations studied were not significant [25]. Most of the research discussed above showed a linear relationship between the rate of antimicrobial use and drug resistance.

In our study, only parenteral antibiotic used was analysed and oral ciprofloxacin, which was prescribed at out-patient clinics were not considered which may also account to antibacterial resistance.



[Table/Fig-5]: Correlation of antimicrobial use and incidence of resistance for *Escherichia coli* the corresponding and next month of antibiotic consumption.



[Table/Fig-6]: Correlation of antimicrobial use and incidence of resistance for *Klebsiella pneumonia* the corresponding and next month of antibiotic consumption

Researchers from India reviewed the need to adopt and reinforce an antimicrobial policy to restrain antimicrobial resistance at community and hospital level in India [29]. An antibacterial policy was developed in JIPMER for containment of antimicrobial resistance. The first version of the antibiotic policy was introduced in January 2012 following which there was a decrease in the antibiotic resistance in June 2012. Similarly, the revised version was introduced in January 2013, following which the resistance rates decreased again. Antibiotic prescription policy of the hospital will have a significant impact on bacterial resistance rates. There are studies, supporting the concept that an antibiotic policy which optimises the consumption of various antibiotic classes may influence the microbial sensitivity patterns of hospitals [10,30].

CONCLUSION

In conclusion, we found that a statistically significant association prevail between consumption of the studied antimicrobials and resistance of *Escherichia coli* isolates except amikacin and ceftazidime. In the case of *Klebsiella pneumonia* isolates, gentamycin, ceftazidime and meropenem show statistically significant association between their consumption and resistance. The data from the above study showed a linear trend in the relationship between antimicrobial consumption and resistance exhibited by *Escherichia coli* and *Klebsiella pneumoniae* isolates, except *Escherichia coli* resistance for amikacin. The present study provides an important input in controlling the development of resistant strains of *Escherichia coli* and *Klebsiella pneumoniae* to ensure effective treatment and a better perception can be obtained to make necessary changes in antibiotic rotation.

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