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Correlation between antimicrobial consumption and resistance patterns in gram positive organisms over three years in a tertiary care hospital

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Abstract:

Background: Regular assessment of the changing profile of the microbial isolates and their resistance to various antimicrobials in use helps in formulating proper guidelines for the rational use of antimicrobials for the particular bacteria. **Methods:** The present study is an observational, longitudinal, descriptive type of drug utilization studyover the three financial years conducted in a tertiary care hospital in Central India. Antimicrobial resistance pattern and the annual consumption of the antimicrobial agents is obtained from the hospital data & compared by appropriate analytic method using Graph Pad Prism version 5.01 and Epi Info version 3.5 software. **Results:** Total 52,344 biological samples tested for culture positivity, out of which only 10,542 (20%) were showed growth of bacteria. Out of these 10,542 samples 18.8% were Gram positive organisms. The annual consumption of Aminopenicillin and Fluoroquinolone was high as compared to other antimicrobial agents. When the resistance pattern and annual consumption were compared with each other, positive trend was found in Benzyl penicillin, Gentamicin and Cloxacillin group with statistical significance of $p<0.5$. **Conclusion:** The observations of present study can help to improve the rational use of ABAs in indoor patients and also to curtail the economic burden of our tertiary care hospital. Hence, we expect that such type of studies should be done in every hospital to provide a base for formulating the local antibacterial guideline.

Key words: Antibiotic Susceptibility testing; Chi square test for trend; Cloxacillin; Defined daily dose; Occupancy index

Introduction

The discovery and development of antibacterial agents is widely recognized to be one of the most important public health interventions of the last century [1]. Innumerable lives and limbs have been saved by the use of antibacterial agents (ABAs). However, its impact has reduced significantly with the arrival of two shocking trends: the rise of antibacterial resistance and lack of development of new ABAs since in the last 25–30 years only one new family, the oxazolidinones has been introduced [1-4].

It has been found that about 70% of the bacteria that cause infections in hospitals are resistant to at least one of the ABA most commonly used for treatment [5,6]. The recent World Health Organization (WHO) report in June 2010 tried to summarize the world scenario of antibacterial resistance [7]. According to WHO, the worldwide more than 50% isolates of Staphylococcus aureus in hospital settings were Methicillin-resistant [7,8]. The South-East Asia region (SEAR), however had found almost 69% isolates of Streptococcus pneumonia and more than 70% Enterobacteriaceae as Penicillin-resistant [7]. In United states of America (USA), 14% isolates of Pseudomonas aeruginosa were found Imipenem-resistant while the spread of *Klebsiella pneumoniae* producing carbapenemase (KPC) is being increasing in United Kingdom (UK) [8,9].

In India, few studies reported that approximately 50% of isolates of *Staphylococcus aureus* are Methicillin-resistant while the presence of Vancomycin resistant enterococcus ranges from 40 to 53% [4,7]. With the recent discovery of New Delhi Metallo-β-lactamase 1 (NDM-1) in multidrug-resistance Enterobacteriaceae in India, [10] it is time that a national effort is initiated to tackle this problem of antibacterial resistance [3,4].

Recognizing the burden of emerging resistance, WHO made 'Antimicrobial Resistance' an organization-wide priority and the focus of World Health Day 2011[11]. The bacterial resistance is an ecological phenomenon branching from the response of bacteria to the extensive use of ABAs and their consistent existence in the environment [12,13]. Due to indiscriminate use of ABAs, they contribute huge share in institutional pharmaceutical budgets [14].

In developed countries, approximately 10% of the total health budget is spent on antibacterials while in developing countries, it rises up to almost 35% [14,15]. ABAs appear to be used not only in excess but also inappropriately and these account for 20% to 50 % of all antibacterials used [5]. Hence, their use and evaluation for formulary inclusion have important economic implications [14].

The excessive use of ABAs is a well-documented risk factor for the selection of resistant bacteria [15]. It has been observed that some countries like France, Spain are with high per capita antibacterial consumption have the high resistance rates [5,16]. As opposed to this, countries like Netherlands and Scandinavia have reported lower resistance rates by keeping the antibiotic use low by the implication of the restrictive antimicrobial policy, which is attracting a constantly increasing interest from many parts of the world [4,16,17].

In spite of the well-known importance of antibacterial policy and the periodic recommendations by WHO, only few hospitals in India like Sir Ganga Ram Hospital, have their own hospital antibacterial policy while majority of hospitals lack in formulating the antibiotic policy [18-20]. This is mainly due to the lack of technical infrastructure in larger parts of India to produce useable data on the antibacterial resistance, consumption and expenditure pattern [4]. Hence, as a consequence the economic impact of antibacterial consumption on the emergence of resistance is also deficient here [12]. According to WHO (2001), antibacterial surveillance program at local level is essential [20].

Pharmacological surveillance, in the form of analysis of antibacterial consumption data, is essential for the study and control of the evolution of bacterial resistance [21]. Knowledge of antibacterial consumption trends will facilitate measures to be implemented leading future use, with the aim of avoiding needless healthcare costs and preventing possible ecological effects that might lead to selection of resistance [22].

The enormous potential of antibacterial surveillance study in formulating local antibacterial policy and its non-existence atour hospital were the key drivers to plan this study with the aim to produce the useful data for formulating the hospital antibacterial policy. There are three types of epidemiological studies which can potentially link the antibacterial use with the ecological adverse effects. The first type is case control studies; the second type of study assesses accumulated data on antibacterial use and correlates them with rates of antibacterial resistance and the third type assesses an intervention aimed at limiting the use of an

antibacterial to decrease the resistance to this antibacterial [23].

Our study's design corresponds to the second type of studies which is based on pharmacological surveillance. This study underlines the role of local periodic studies in defined patient cohorts for a finite period to determine the local epidemiology of resistance, associated risk factors and most cost effective antibacterial regimen for infections in our hospital setting.

Materials and Methods

The present study was an observational, longitudinal, descriptive type of drug utilization study restricted to antibacterial agents only. The present study was undertaken in the Government Medical College & Hospital, Nagpur, India from April 2007 to March 2010 (three financial years). The study included retrospective culture sensitivity data from April 2007 to December 2008 and prospective data from January 2009 to March 2010. The data of annual consumption of antibacterials was totally retrospective type which was collected at the end of each financial year (FY). The study group included the indoor patients admitted in the tertiary care centre and comprised of 52,344 different samples of clinically suspected cases of bacterial infections.

Inclusion Criteria: All samples received from wards, operation theatres, surgical and medical intensive care units (ICU) for culture; all culture positive samples; and all antibacterial agents purchased in hospital throughout the study period for which, antibacterial susceptibility testing can be performed in microbiology laboratory of our hospital.

Exclusion Criteria: The samples received from outdoor patient; the samples which do not show culture development; the samples send for testing antibacterial resistance in mycobacteria; the antibacterial agents whose susceptibility testing cannot be performed in Microbiology laboratory of our hospital, like Roxithromycin; the antibacterial susceptibility testing reports obtained from private laboratories; and the preadmission antibacterial susceptibility testing reports of patient.

Microbiology and susceptibility data:

Culture was done on McConkey's medium and Nutrient agar by the standard loop technique after the application of screening tests to various samples. Identification of the bacterial isolates was done on the basis of standard recommended procedures [24].

The various biological samples like urine, pus, sputum, vaginal swab, stool, conjunctival swab, pleural fluid, ascitic fluid, throat swab, cerebrospinal fluid (CSF) etc. of the admitted patients were sent to the clinical microbiology laboratory for antibacterial susceptibility testing (AST). AST was done on Mueller Hinton Agar plates (Hi Media India Ltd., Mumbai) as per the Clinical and Laboratory Standards Institute (CLSI) guidelines [25]. Briefly, Petri dishes containing 20ml of Mueller-Hinton agar were seeded with a 24 hours old broth culture of the bacterial strains. Filter paper discs impregnated with the antimicrobial agent were applied to the seeded plates. After overnight incubation at 37^0C the zone of inhibition around the discs was measured and compared with the standard strains (ATCC *Staphylococcus aureus* 25923) as recommended by the CLSI manual [25]. The results based on the zone size, as compared with the standard strains, were interpreted as Sensitive or Resistant as per the recommendations of the CLSI manual. The choice of the antimicrobial discs used was dictated by the recommendations of the CLSI manual. The Gram positive organisms included *Staphylococcus spp., Streptococcus, Enterococcus* and *Pneumococcus*.

Antibacterial usage from hospital medicine store:

The data on annual antibacterial consumption was collected of the three financial years (April 2007-March 08, April 2008- March 09 & April 2009- March 10). The total quantity of particular antibacterial agent given to indoor patients and its strength were obtained by checking the purchased and dispensed records maintained in the medicine store.

The antibacterials which were purchased as per hospital list and whose susceptibility test can be done in our institution were only considered for the analysis. The six antibacterials are namely Ampicillin, Benzyl penicillin, Cloxacillin, Gentamicin, Amikacin and Ciprofloxacin. Ampicillin can be used to represent Amoxicillin for resistance, thus if the organisms that are resistant to Ampicillin are also considered resistant to Amoxicillin [26]. As both these antibacterials were purchased in our hospital, instead of Ampicillin, Aminopenicillin group used to consider them together.

In our study we employed the Anatomical Therapeutic Chemical (ATC) classification to categorize different antibacterials, by which we could maintain the uniformity for comparing the national and international studies on the antibacterial

utilization data [27,28]. The ATC codes of the various antibacterials were obtained from the ATC index- WHO collaborating centre for drug statistics methodology: Version 2010 [1,29].

Defined daily doses (DDD):

The consumption of different subclasses of antibacterials was expressed as defined daily doses (DDD) per 1000 patient- year (PY), calculated by the following formula:[1,30]

DDD/1000 PY=

Number of packets or vials consumed x Number of tablets or vial/ packet x strength of tablet or vial x1000

Standard DDD x Number of beds x Occupancy index x Number of years

The ATC / DDD classification from the WHO, version 2010, was used to calculate the number of DDD of the various antibacterials [26]. In our 1400 bedded hospital the occupancy index was 0.76, 0.72 and 0.74 for the three financial years 2007-08, 2008-09 and 2009-10 respectively; which was obtained from medical record section and calculated by using the following formula:

Occupancy Index=

Summation of bed occupancy in a service day in a FY

1400 x Total service days in that FY

This study was approved by the Institutional Ethics Committee of Government Medical College and Hospital, Nagpur. Since it was an observational study and did not possess any intervention hence the consent part was waived.

Statistical analysis:

The antibacterial resistance was explained in terms of percentage and recorded in tabular form, while to estimate the comparison between resistance patterns from one year to another the Chi-square test was performed with degree of freedom (df) of one with the help of Graph pad prism version 5.01 software. The statistical significance was considered when p value <0.05. The annual consumption of ABA throughout the three years was shown by the simple line diagrams. The trend between the relationships of antibacterial consumption with the percentage resistance of different micro-organisms were analysed by Chi square for trend with EpiInfo version 3.5 software. The trend was considered statistical significant when p value <0.05.

Results

During the three financial years, total 52,344 patients' biological samples were received in clinical microbiology laboratory for the AST. Out of 52344 samples, total 10542 (20%) samples were found culture positive and undergone into AST as per the protocol. Out of the 10542 culture positive samples, 1990 (18.8%) had shown the growth of Gram positive organisms which were included for the further analysis.

Table 1 shows the comparison of resistance patterns in Gram positive cocci in the three financial years. There were 744, 675 and 571 biological samples found Gram positive cocci as the isolated organism in year 2007-08, 2008-09 and 2009-10 respectively. When resistance in FY 2008-09 was compared with the 2007-08, it showed statistical significant decrease in resistance to Cloxacillin (χ^2= 11.6, df=1, p<0.001) and Gentamicin (χ^2= 5.3, df=1, p<0.05). However, when resistance in FY 2009-10 was compared with 2007-08, showed statistical significant decrease in resistance to Benzyl Penicillin (χ^2= 46.83, df=1, p<0.001), Cloxacillin (χ^2= 6.92, df=1, p<0.01) and Gentamicin (χ^2= 29.77, df=1, p<0.001) . Similarly, when FY 2009-10 was compared with FY 2008-09, it showed statistical significant decrease in resistance to Benzyl Penicillin (χ^2= 34.28, df=1, p<0.001) and Gentamicin (χ^2= 10.79, df=1, p<0.01).

In present study, we categorized ABA into three groups for the analysis as 0 - 1000 DDD/1000PY (less consumed); 1,000 – 1,00,000 DDD/1000PY (moderately consumed) and 1,00,000 - 5,00,000 DDD/1000PY (highly consumed). Figure 1 shows year wise comparison of consumption of less consumed antibacterials (DDD ranging from 0 to 1000 DDD/1000 PY) which included Amikacin. Figure 2 shows year wise comparison of consumption of moderately consumed antibacterials (DDD ranging from 1000 to 100000 DDD/1000 PY). This group consisted of Benzyl penicillin, Cloxacillin and Gentamicin. The Cloxacillin (15876, 8882, 9769 DDD/1000 PY) showed decrease in consumption in FY 2008-09 and slight increase in FY 2009-10, while all other ABA showed progressive decrease in consumption with time. Figure 3 shows year wise comparison of consumption of highly consumed antibacterials (DDD ranging from 100000 to 500000 DDD/1000 PY). This group consisted of Aminopenicillin and Ciprofloxacin. The Aminopenicillin (421760, 424465, 423396 DDD/1000 PY) showed peak rise in consumption in FY 2008-09 and slight fall in FY 2009-10, while

Ciprofloxacin (131981, 158125, 160421 DDD/1000 PY) showed progressive increase in consumption with time.

Figure 1: Line diagram showing year wise comparison of consumption of less consumed antibacterials (DDD range: 0-1,000 DDD/1000 patient- year)

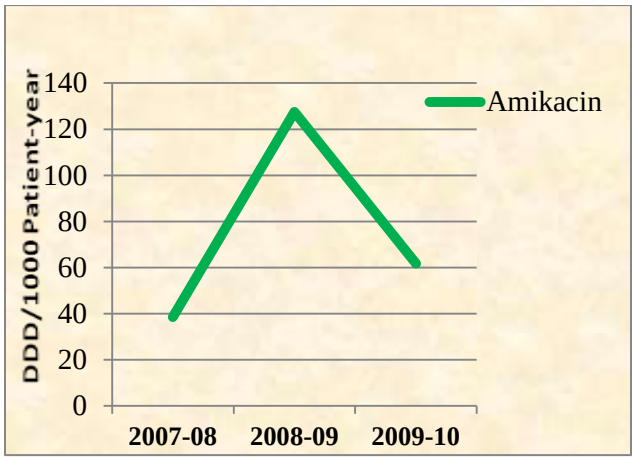


Figure 2: Line diagram showing year wise comparison of consumption of moderately consumed antibacterials (DDD range: 1000-100000 DDD/1000 patient- year)

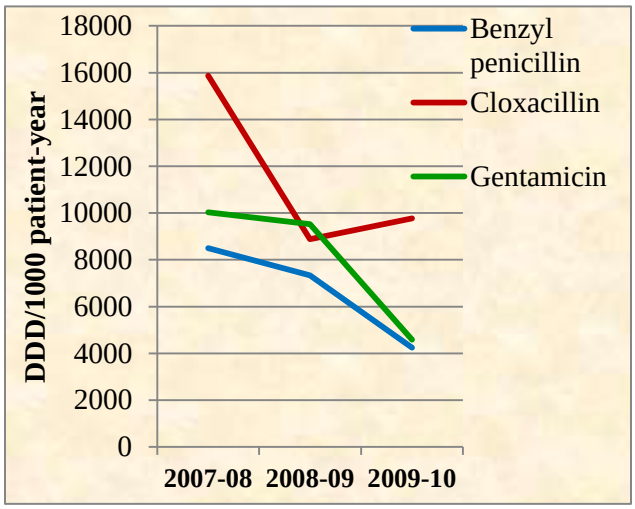


Figure 3: Line diagram showing year wise comparison of consumption of highly consumed antibacterials (DDD range: 1,00,000 - 5,00,000 DDD/1000 patient- year)

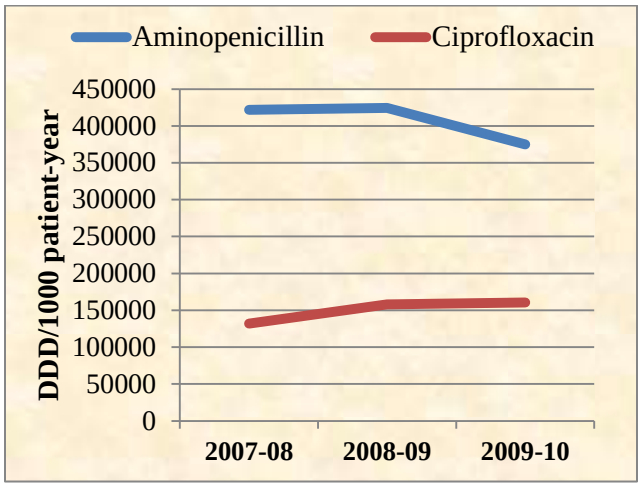
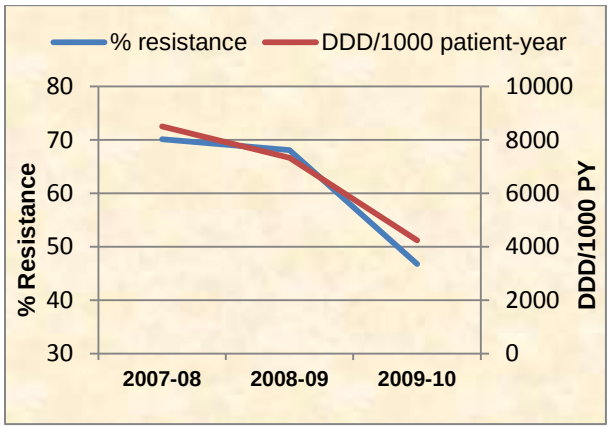


Figure 4 and 5 show the trend of resistance to Benzyl penicillin and Gentamicin in Gram positive cocci with respect to its annual consumption expressed in DDD/1000 PY respectively. It was observed that when consumption of Benzyl penicillin and Gentamicin were decreased from FY 2007-08 to 2009-10 (8503 to 4239 DDD/1000PY and 10027 to 4584DDD/1000PY respectively), the resistance to it were also reduced and the trend was found statistically significant with χ^2=55.1 for Benzyl penicillin and χ^2=26.2 for Gentamicin with p value <0.001 in both.

Figure 6 shows trend of resistance to Cloxacillin in Gram positive cocci with respect to its annual consumption expressed in DDD/1000 PY. It was observed that with the fall in consumption of Cloxacillin from FY 2007-08 (15876 DDD/1000PY) to 2008-09 (8882 DDD/1000PY), the resistance to it was also reduced from 90.32% to 79.24%. While with the increase in its consumption from 2008-09 (8882 DDD/1000PY) to 2009-10 (9769 DDD/1000PY) there was increase in resistance from 79.24% to 81.61% and the trend was found statistically significant with χ^2=11.4 and p value <0.001. In all other ABA also the trend was same but not statistically significant.

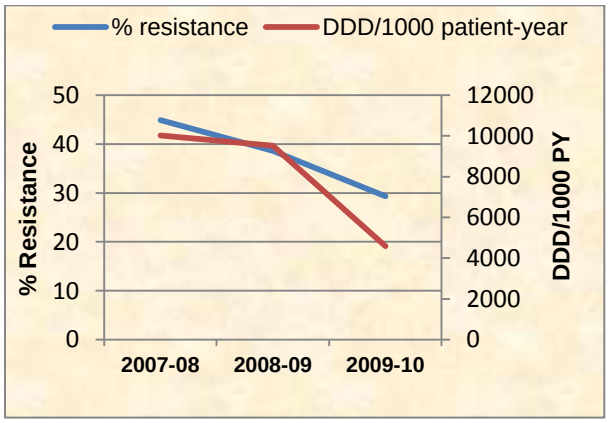
Figure 4: Trend of resistance to Benzyl penicillin in Gram positive organisms with respect to its annual consumption in DDD/1000 patient –year (PY)



Year	DDD/1000PY	R	S
2007-08	8503	355	151
2008-09	7336	269	126
2009-10	4239	161	183

R- Resistance, S- Sensitive
Chi square for trend= 52.112
p Value=<**0.001*****

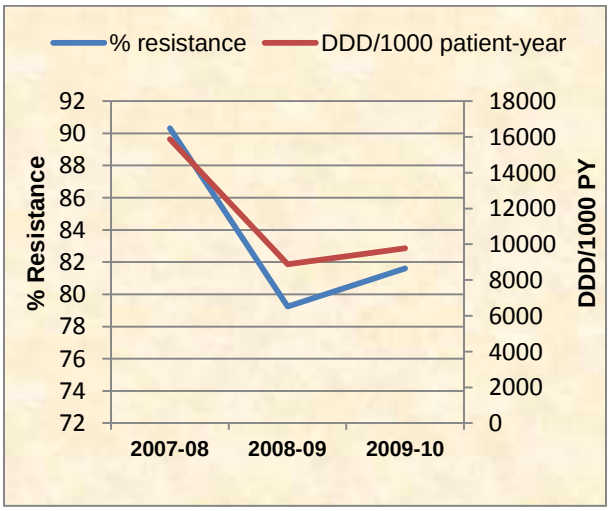
Figure 5: Trend of resistance to Gentamicin in Gram positive organisms with respect to its annual consumption in DDD/1000 patient –year (PY)



Year	DDD/1000PY	R	S
2007-08	10027.63	312	383
2008-09	9526.45	250	397
2009-10	4584.39	147	354

R- Resistance, S- sensitive
Chi square for trend= 26.17, p Value=<**0.001*****

Figure 6: Trend of resistance to Cloxacillin in Gram positive organisms with respect to its annual consumption in DDD/1000 patient –year (PY)



Year	DDD/1000PY	R	S
2007-08	15876	168	018
2008-09	8882	443	116
2009-10	9769	262	059

R-Resistance, S- Sensitive
Chi square for trend= 11.417
p Value=<**0.001*****

Table 1: Comparison of resistance patterns in Gram positive organisms in the three financial years

Antibacterial group	ABA Ψ	ATC code	2007-08 (n=744)			2008-09 (n=675)			2009-10(n=571)		
			Total tested	Resistant		Total tested	Resistant		Total tested	Resistant	
				No.	%		No.	%		No.	%
Aminopenicillin	**A**	J01CA01	179	141	**78.77**	260	209	**80.38**	254	202	**79.52**
Acid resistant Penicillin	**Pn**	J01CE01	506	355	**70.15**	395	269	**68.10**	344	161	**46.80*****^###
Penicillinase resistant penicillin	**Cx**	J01CF02	186	168	**90.32**	559	443	**79.24*****	321	262	**81.61****
Aminoglycoside	**G**	J01GB03	695	312	**44.89**	647	250	**38.63***	501	147	**29.34*****^##
	Ak	J01GB06	519	89	**17.14**	326	60	**18.40**	182	32	**17.58**
Fluoroquinolone	**Cf**	J01MA02	511	263	**51.46**	371	193	**52.02**	279	146	**52.32**

Chi square test applied, df=1, p value <0.05 (significant)

* p value<0.05

** p value<0.01

*** p value<0.001

When compared with the 2007-08 resistance

p value<0.01

p value<0.001

When compared with the 2008-09 resistance

Ψ(ABA= Antibacterial agent, A= Ampicillin, Pn=Benzyl Penicillin, Cx= Cloxacillin, G= Gentamicin, Ak= Amikacin, Cf=Ciprofloxacin)

Discussion

In present study out of 52,344 biological samples received, only 10,542 (20%) had shown presence of bacteria, thus, remaining 41,802 (80%) samples found sterile on culture. This was probably due to previous antibacterial therapy or being non-bacterial samples (protozoal, viral or fungal origin) or being non-representative samples. Similar findings were reported by Veenakumari et al [31]. The majority of biological samples from which bacterium was isolated were consisted of urine (35.65%), pus (25.30%) and sputum (11.30%) indicating that urinary tract infection (UTI), wound infection and lower respiratory tract infection (LRTI) are the common causes of morbidity in the local population and hospital visits. Javiya VA et al [32] stated similar findings in their study.In present study, Gram positive organisms constituted 19% of all the isolates. This finding was similar to that noted by Sonavane A et al [33] and Kader AA et al [22].

In the present study, a high resistance was observed in Gram positive cocci to Cloxacillin (90%), Ampicillin (80%), Benzyl penicillin (70%) and Ciprofloxacin (52%) with a statistical significant ($p<0.001$) decrease in resistance to Cloxacillin, Gentamicin and Benzyl penicillin from FY 2007-08 to 2009-10 (Table 1). Similar findings were reported by Tyagi A et al [34]. The resistance to Aminoglycoside was relatively low (Gentamicin: 29% and Amikacin: 18%) in Gram positive cocci. This retained sensitivity was probably due to lack of use of Aminoglycoside by the physicians for treating infections caused by Gram positive cocci as it is known to be ineffective against *S. pyogenes* and *S. pneumoniae* when administered alone and inhibits *S. aureus* only in high doses [25]. Study done by Sonavane A et al [33] in 2008 gave relatively positive presentation in this aspect.

In present study, the ABA were categorized into three groups as 0-1000 DDD/1000PY (less consumed); 1,000-1,00,000 DDD/1000PY (moderately consumed) and 1,00,000-5,00,000 DDD/1000PY (highly consumed). The less consumed group comprised of Amikacin. Moderately consumed group included Benzyl penicillin, Cloxacillin and Gentamicin; while Aminopenicillin and Ciprofloxacin were in the highly consumed group. Kotwani et al [12], Cars O et al [16], Jankovic SM et al [35] and Vaccheri A et al [26] stated similar findings in their studies. When the pattern was observed from first to third year, then it was found that in, there was progressive increasing trend seen in Ciprofloxacin while decreasing trend seen in Benzyl penicillin and Gentamicin. These findings were similar to that noted by Liem TYB et al [36] and Vaccheri A et al [26].

In Gram positive cocci the statistical significant ($p<0.001$) trend of resistance and consumption was observed for Gentamicin (Figure 5), Benzyl penicillin (Figure 4) and Cloxacillin (Figure 6). All these findings indicate that the increasing use of antibacterial and corresponding increase in resistance in above mentioned bacteria-antibacterial pairs go hand in hand in the local setting.

In the present study, the assumption that only antibacterial consumption accounts for resistance may be criticized, since other potential or even not yet well-identified factors like clonal spread and clonal turnover that may play a role have not been considered. However, while it is certain that such factors may be important, in the light of the high determination coefficients obtained, they do not seem as crucial as antibacterial use.

The expected outcomes of the implementation of the effective antibacterial guideline at local level can lead to earlier administration of effective antibacterial agent to the patient, leading to early recovery and decrease in the hospital stay. This will also help in the optimal utilization of health service resources thus, decreasing the unnecessary economic burden of hospital. Besides, the patient's infectivity will also reduce dramatically which will subsequently lower the danger of transmission of resistant organisms to the community.

However, in the present study the consumption of ABAs was determined by using the aggregate method, while the individually prescribed (prescription method) ABAs to indoor as well as out-patient departments were not evaluated. Hence, the further studies including these factors can be done to estimate the rational utilization of the ABAs. The possibility of reducing resistance by controlling the use of antibacterials is a logical approach, but the implementation of effective guidelines has proved difficult in most situations. However, a combined approach of antibiotic restriction, effective surveillance and good infection control practices is essential if antibiotic resistance is to be overcome.

Conclusion

The rational use of antibacterials can only be expected if the prescriber is aware of the local antibacterial guideline which generally based on the knowledge of commonest bacteria and the possible

susceptible antibacterial agent in that local setting. Thus, our observations can help to improve the rational use of ABAs in indoor patients and also to curtail the economic burden of our tertiary care hospital. Hence, we expect that such type of studies should be done in every hospital to provide a base for formulating the local antibacterial guideline.

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Conflict of Interest: None.

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