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Pharmacist Participation in Antimicrobial Stewardship and Evaluation of Antibiotic Drug Interaction in Hospitalized Patients in A Tertiary Care Center

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ABSTRACT

Antibiotic Stewardship (AS) and AS programs (ASP) have a critical role in promoting judicious antibiotic use. This study describes the need for ASP implementation in a private, large academic tertiary care center in India. The main objective is to monitor the resistance of microorganisms towards antibiotics and to assess the need for the implementation of antibiotic stewardship in the tertiary care hospital. It was a prospective observational study conducted over six months among inpatients in a tertiary care teaching hospital. Samples of all age groups, a total of 71 patients were enrolled in this study following the inclusion criteria from the culture sensitivity tests obtained from the microbiology department. Irrational antibiotic prescribing was found to be a major risk factor to the patients. Proper guidelines follow and an antibiotic treatment regimen is mandatory for the follow-up of proper study. This study confirmed the need to initiate antimicrobial stewardship in a tertiary care hospital to minimize the risks of random antibiotic use It was also found that samples with no growth of bacteria were continued to be treated with antibiotics which leads to unwanted exposure of antibiotics to the organisms aiding them to develop resistance. And these antibiotics may also develop interactions with other drugs.

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INTRODUCTION

Primarily contributing factor to the present rise in resistance includes unregulated access to antimicrobials. Implementing antimicrobial stewardship programs (ASPs) within a hospital setting will help curb inappropriate antibiotic use in India [1]. Antimicrobial stewardship programs (ASPs) are shown to enhance antibiotic use and patient outcomes. Currently, ASPs are rare and that don't follow conventional data models in India. Implementation of an ASP in a large, private tertiary care center can be portrayed in Southern India [2]. Resistance can appear spontaneously due to random mutations. Prolonged use of antimicrobials appears to uplift the selection for mutations which may render antimicrobials ineffective. Preventive measures include the usage of antibiotics when needed, thereby preventing misuse of antimicrobials. Narrow-spectrum antibiotics are preferred over broad-spectrum antibiotics when possible, as effectively and accurately targeting specific organisms is a smaller amount likely to cause resistance, also as side effects.[3] Most stewardship teams include either a communicable disease physician or a pharmacist (with or without specialized training in infectious disease) or both. Sometimes a hospitalist with an interest in communicable disease serves during this role. Engaging hospital leadership will often open doors to good relationships with other physician groups. Therefore, early involvement of thought leaders from hospital administration and therefore the various practitioner groups will improve acceptance and implementation.[4] Cumulated use of antibiotics is crucial to effectively protect patients from harm, treat infections caused by unnecessary antibiotic use, and reduce antibiotic resistance. Antibiotic stewardship programs can help clinicians to enhance better clinical outcomes and minimize harm by improving antibiotic prescription patterns.[5] Combining antibiotics may be a promising strategy for increasing treatment efficacy and for controlling resistance evolution. When drugs are combined, their effects on cells could also be amplified or weakened, that's the drugs may show synergistic or antagonistic interactions. The recent works revealed the underlying mechanisms of such drug interactions by explaining the drugs' joint effects on cell physiology. Moreover, new treatment strategies that use drug combinations to take advantage of evolutionary tradeoffs were shown to affect the speed of resistance evolution in predictable ways. Overall, the technical and conceptual foundation for the rational design of potent drug combinations has been observed to be developing rapidly.[6] An alternative strategy for reducing spontaneous resistance evolution is to

take advantage of evolutionary tradeoffs during which bacteria that evolved resistance to at least one drug become more sensitive to a different. Numerous studies explored such tradeoffs for giant sets of antibiotics.[7] By making antimicrobial stewardship a part of our daily practice, we will improve patient safety and care, reduce the unnecessary use of vulnerable resources, and reduce resistance.[8]

The main aim of our study is to evaluate the development of antimicrobial resistance found among study subjects and to facilitate control by informing the need to improve prescribing patterns and infection control practices.

Primary objectives include the evaluation of resistance of microorganisms towards antibiotics prescribed to the patients and to assess the need for implementation of antibiotic stewardship in the tertiary care hospital. The secondary objective is to analyze and study the severity of drug interactions between the antibiotics with the co-prescribed drugs.

MATERIALS AND METHODS

Study design, study setting, and source of data:

In December 2019 we conducted a prospective observational study on the patients admitted to The Oxford Medical College and Research Centre to evaluate the development of antimicrobial resistance found among study subjects and to facilitate control by informing the need to improve prescribing patterns and infection control practices.

Sampling Size and Technique:

We have done the study on a sample size of 71 patients admitted to the hospital during 6 months through a collection of data from the medical records of the hospital.

The sample size of 71 was calculated using the following sample size equations:

$$X=Z^2P(1-P)/e^2$$

$$n= NX/ X+N-1$$

Patients of all age groups and of both gender that receive antibiotics in the treatment plan and patients showing growth in their culture samples were included. Patients from the outpatient department and with no growth in culture sensitivity tests were excluded.

Collection of Data and Methods of Data Analysis:

1: All the documents which were used in the study were translated to the local language (Kannada).

2: Consent was obtained from the patient through an informed consent form in English and Kannada language.

3: Collected data regarding the demographics of the patient (Name, Age, Sex, I.P.NO, OP.NO, Ward, Height, Weight, DOA, DOD.) and the details regarding the reason for admission, diagnosis, prescribed drugs, past medication history, side effects and drug interactions with antibiotics through the data entry form.

4: Culture sensitivity test reports were examined and collected from the microbiology laboratory.

5: The details obtained were documented in to excel sheet.

6: Comparison of resistivity and sensitivity of the given drugs for all the diseases in the hospital and evaluation of specific side effects of prescribed antibiotics were done.

7: The obtained data were subjected to a suitable statistical tool.

RESULTS AND DISCUSSION

RESULTS

A total of 71 patients were enrolled in this study following the inclusion criteria from the culture sensitivity tests obtained from the microbiology department of the Oxford Medical College Hospital and Research Centre, Bengaluru.

AGE WISE DISTRIBUTION:

Table 1: Distribution of study population based on age

AGE INTERVAL	N=71
00-10	2(2.81%)
11-20	4(5.63%)
21-30	9(12.67%)
31-40	15(21.12%)
41-50	14(19.71%)
51-60	10(14.08%)
61-70	11(15.49%)
>70	6(8.45%)

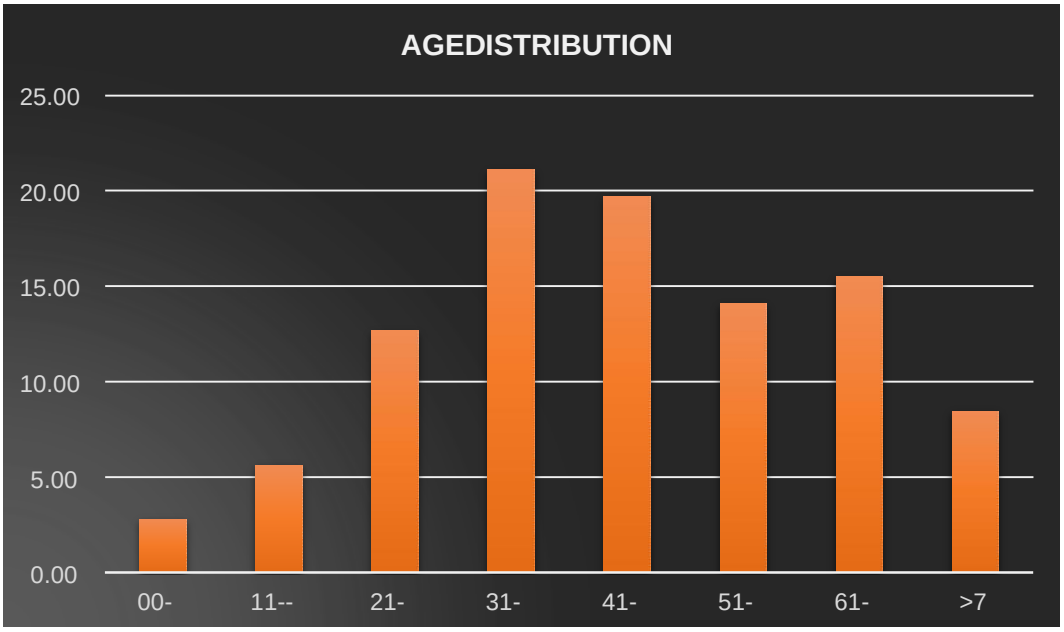

Figure 1: Distribution of study subjects based on age

This result shows that out of 71 culture sensitivity reports of study subjects (both male and female) obtained from the microbiology department, study subjects within the age limit of 31-40 were found to be more frequently prescribed with antibiotics followed by 41-50 years age group respectively.

GENDER WISE DISTRIBUTION

Table 2: Distribution of study subjects based on gender

SEX	N=71
MALE	43(60.56%)
FEMALE	28(39.43%)

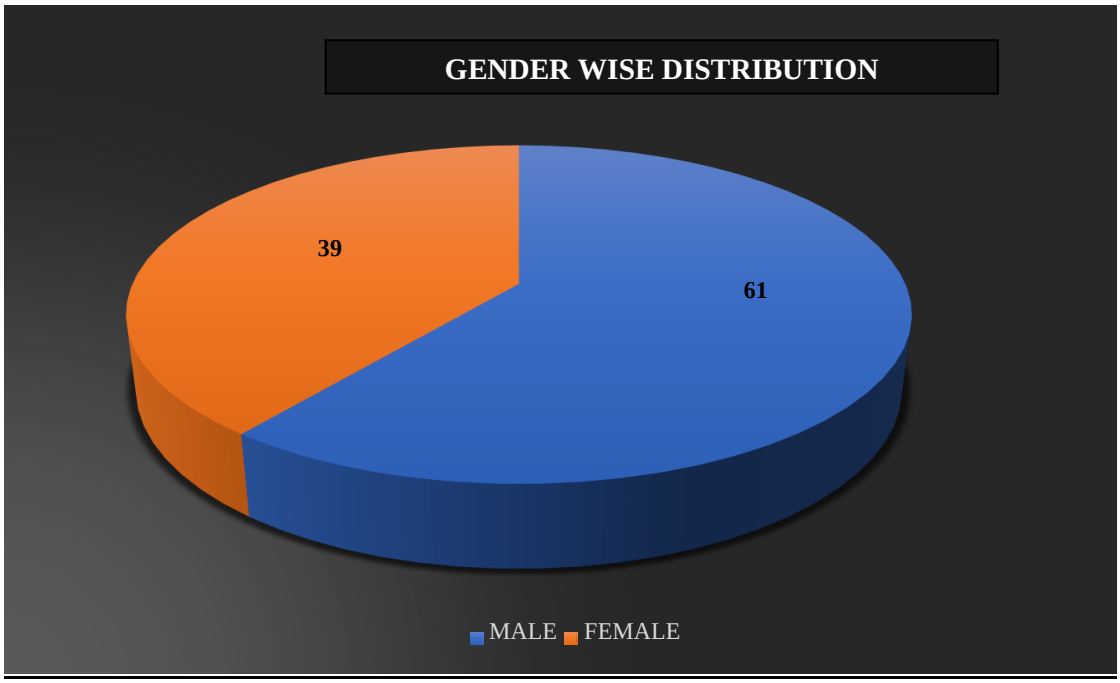

Figure 2: Distribution of study subjects based on gender

This result shows that out of 71 culture sensitivity reports of study subjects (both male and female) obtained from the microbiology department; male patients were more frequently prescribed antibiotics when compared to female patients. This data also indicates that male patients were more prone to infections when compared to female patients.

DEPARTMENT WISE CLASSIFICATION

Table 3: Distribution of study subjects based on department

WARD	NO.OF PATIENTS
GS	33(47%)
GM	20(28%)
PAED	2(3%)
DERMO	2(3%)
OBG	6(8%)
ORTHO	3(4%)
OTHERS (ICU, ENT, PULMO, CASUALITY,)	5(7%)

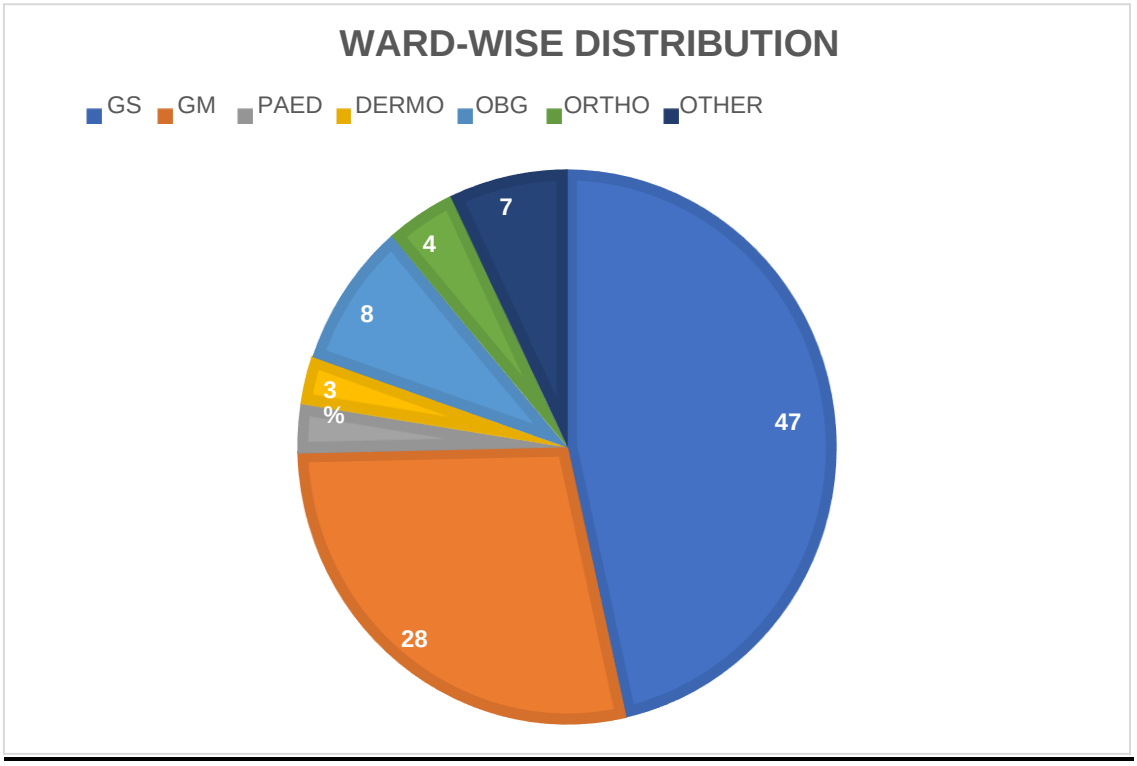

Figure 3: Distribution of study subjects based on department

This result shows that out of 71 culture sensitivity reports of study subjects obtained from the microbiology department, the majority of samples were procured from General Surgery Department (47%), followed by General Medicine Department (28%), OBG(8%), Other Departments (ICU, ENT Pulmonology, Casualty) (7%), Orthopaedics (4%) and finally Paediatrics and Dermatology coming to (3%). This indicates that patients were under the surgery department.

TYPE OF INFECTIONS AND DISEASES

Table 4: Type of infections and diseases that occurred in patients

INFECTIONS	PATIENTS (71)
RESPIRATORY INFECTIONS	8(11.10%)
RENAL INFECTIONS	5(6.90%)
ABDOMINAL AND UTERINE ABNORMALITIES	13(18.05%)
ULCERATIONS, ABSCESS AND SKIN LESIONS	26(37.0%)
CANCER	2(2.27%)
PYREXIA	7(9.72%)
OTHERS	10(13.88%)

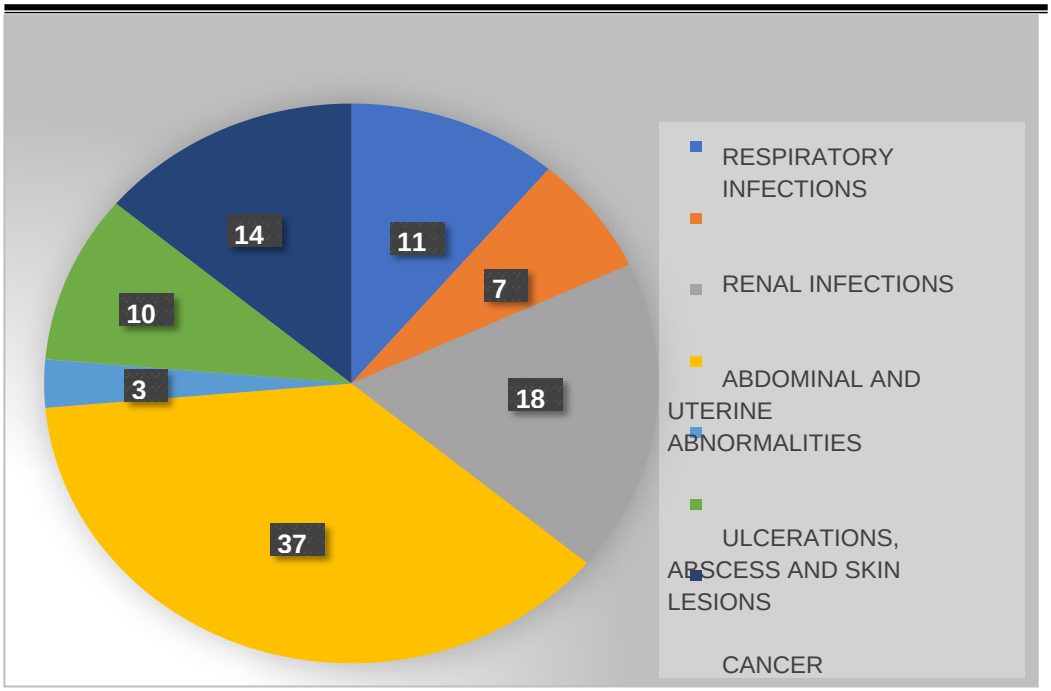

Figure 4: Type of infections and diseases that occurred in patients

From the above graph, which shows the type of infections and disease conditions observed in study subjects, it was found that out of 71 patients majority of patients were affected with Ulcerations, Abscess and Skin Lesions (37%) followed by Abdominal and Uterine infections (18%) and Respiratory infections which showed 14% of the total sample size.

ISOLATED ORGANISMS WHICH CAUSED INFECTIONS IN STUDY SUBJECTS

Table 5: Distribution of study subjects based on the isolated organism with which they were infected

ORGANISMS	N=71
CITROBACTER SPECIES	1(1.4%)
E COLI	13(18.3%)
ENTEROCOCCI	4(5.6%)
K OXYTOCA	7(9.8%)
K PNEUMONIAE	7(9.8%)
KLEBSIELLA	2(2.8%)
MR CONS	1(1.4%)
MRSA	6(8.4%)
MSSA	5(7%)
NFGNB	1(1.4%)
NO GROWTH	12(16.9%)
P AERIGINOSAE	3(4.2%)
P VULGARIS	2(2.8%)
PROTEASE	3(4.2%)
S EPIDERMIDIS	1(1.4%)
PSEUDOMONAS	2(2.8%)
S PYOGENES	1(1.4%)

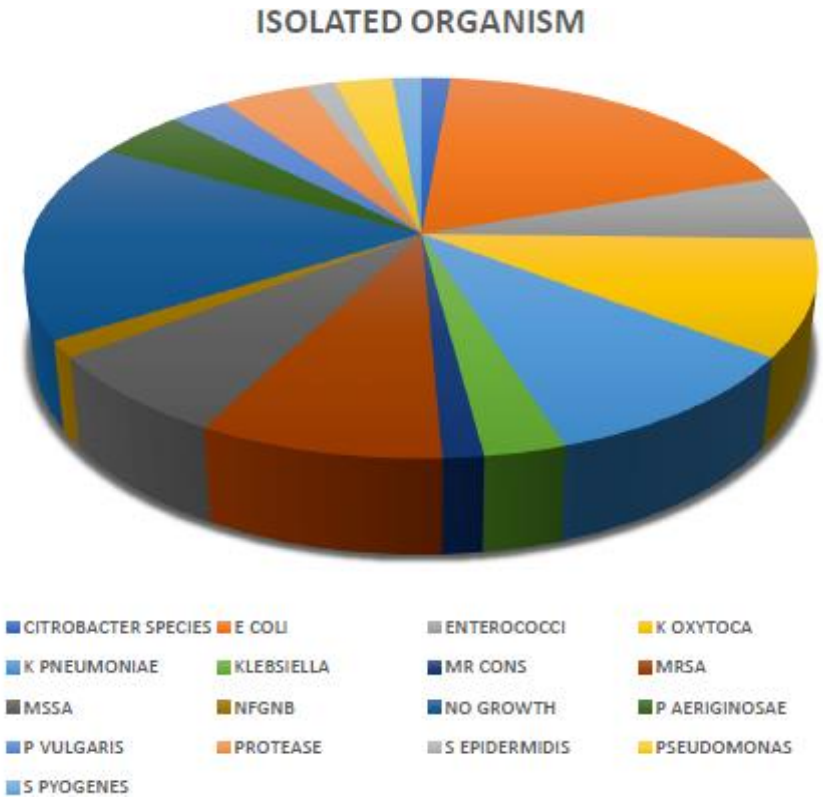

Figure 5: Distribution of study subjects based on the bacterial organism with which they were infected

From the isolated organisms obtained from 71 study subjects, it was revealed that there was more incidence of infections caused by E. coli (18%) in the study sample in which antibiotics were prescribed when compared to other isolated organisms. Surprisingly, the second largest group that is: samples with no growth (16.9%) were also continued to be prescribed antibiotics.

CLASSIFICATION OF ANTIBIOTICS PRESCRIBED

Table 6: Distribution of antibiotics prescribed among the study population

ANTIBIOTICS	PRESCRIBED
CEFTRIAXONE	37(25.6%)
CEFOTAXIME	29(20.1%)
AMOXICLAV	5(3.4%)
PIPERACILLIN TAZOBACTUM	15(10.4%)
CIPROFLOXACIN	7(4.8%)
LEVOFLOXACIN	1(0.69%)
AMIKACIN	14(9.7%)
GENTAMICIN	2(1.3%)
NITROFURANTOIN	3(2%)
CLINDAMYCIN	2(1.3%)
LINEZOLID	8(5.5%)
AZITHROMYCIN	10(6.9%)
NORFLOXACIN	2(1.3%)
CEFEPIME	3(2%)
CEFEXIME	4(2.7%)
DOXYCYCLINE	2(1.3%)

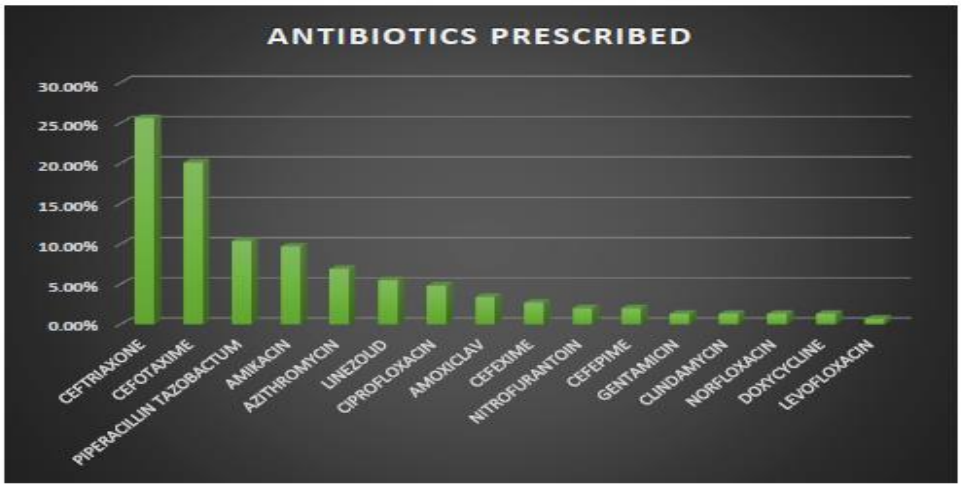

Figure 6: Distribution of antibiotics prescribed among the study population

The above graph depicts the antibiotics that are prescribed in the tertiary care teaching hospital and it is found that the most frequently prescribed antibiotics were Ceftriaxone (25.6%), Cefotaxime (20.1%), Piperacillin Tazobactum (10.4%), Amikacin (9.7%) respectively.

RESISTANCE AND SENSITIVITY DISTRIBUTION

Table 7: Resistance and sensitivity status of antibiotics prescribed

ANTIBIOTICS	NO.OF PATIENTS	SENSITIVE	RESISTANT
AMPICILLIN	46	8(2.3%)	38(12.17%)
PENICILLIN	19	2(0.57%)	17(5.44%)
AMOXICLAV	42	11(3.17%)	31(9.93%)
AMIKACIN	43	26(7.51%)	17(5.44%)
CLINDAMYCIN	14	9(2.6%)	5(1.60%)
CIPROFLOXACIN	21	8(2.31%)	13(4.16%)
COTRIMOXAZOLE	18	11(3.17%)	7(2.24%)
CEFTAZIDIME	33	15(4.33%)	18(5.76%)
CEFTRIAXONE	29	9(2.6%)	20(6.41%)
CEFUROXIME	19	2(0.57%)	17(5.44%)
CEFAZOLINE	21	7(2.02%)	14(4.48%)
CEFIXITINE	24	9(2.6%)	15(4.80%)
CEFOTAXIM	21	8(2.31%)	13(4.16%)
CEFEPIME	37	17(4.91%)	20(6.41%)
DOXYCYCLINE	5	5(1.44%)	0
ERYTHROMYCIN	14	7(2.02%)	7(2.24%)
GENTAMICIN	36	20(5.78%)	16(5.12%)
GENTAMICIN 120	6	4(1.15%)	2(0.64%)
IMIPENAM	33	31(8.95%)	2(0.64%)
LEVOFLOXACIN	12	10(2.89%)	2(0.64%)

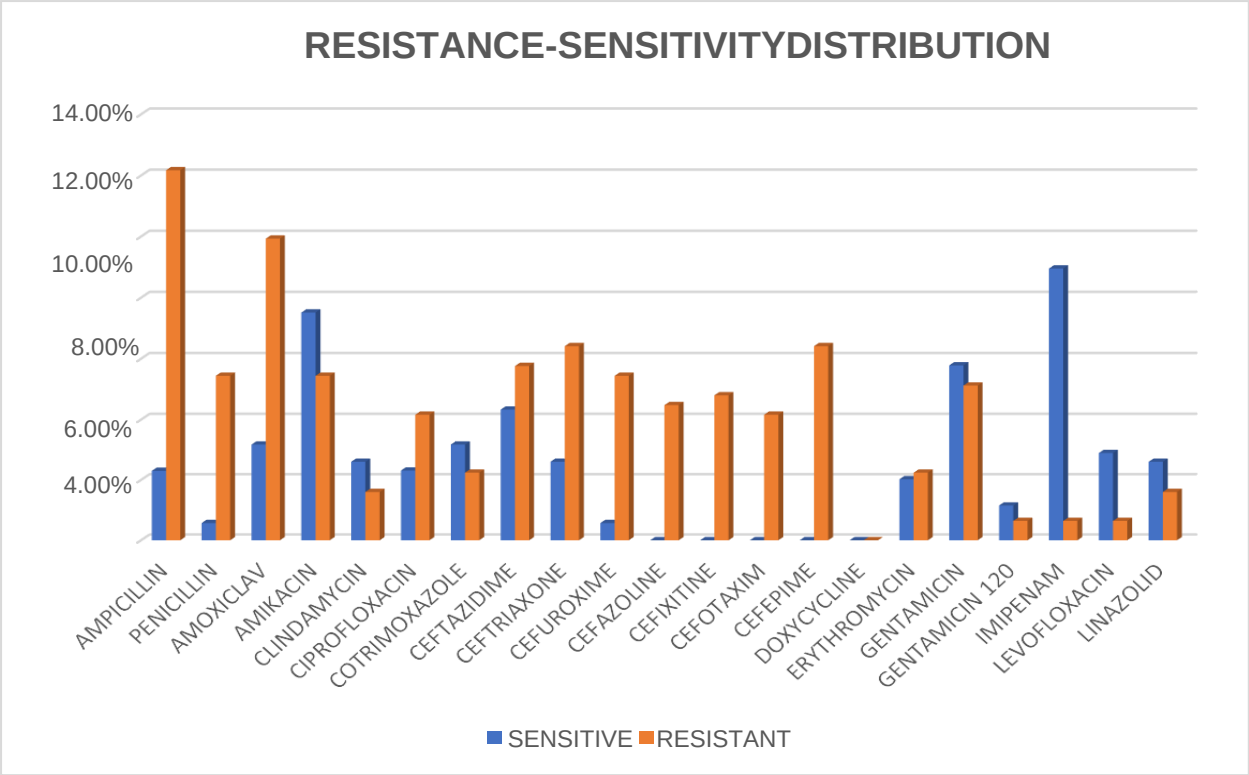

Figure 7: Resistance and sensitivity status of the antibiotics prescribed to the study population

From the above graph resistance and the sensitivity of various organisms towards the antibiotics are depicted above. The graph portrays most of the drugs are resistant and very few organisms are sensitive to antibiotics. Antibiotic showing more resistance is ampicillin 38(12%) and lower class of antibiotic showing sensitivity in most of the cases is Imepenam 31(8.95%).

CLASSIFICATION BASED ON GRAM STAINING

Table 8: Classification of isolated microorganisms based on gram staining found in the samples of the study population

ORGANISMS	GRAM STAINING
CITROBACTER SPECIES	GRAM NEGATIVE
ESCHERICHIA COLI	GRAM NEGATIVE
ENTEROCOCCI	GRAM POSITIVE
K OXYTOCA	GRAM NEGATIVE
K PNEUMONIAE	GRAM NEGATIVE
KLEBSIELLA	GRAM NEGATIVE
MRCoNS	GRAM POSITIVE
MRSA	GRAM POSITIVE
MSSA	GRAM POSITIVE
NFGNB	GRAM NEGATIVE
P AERIGINOSAE	GRAM NEGATIVE
P VULGARIS	GRAM NEGATIVE
S EPIDERMIDIS	GRAM POSITIVE
PSEUDOMONAS	GRAM NEGATIVE
S PYOGENES	GRAM POSITIVE

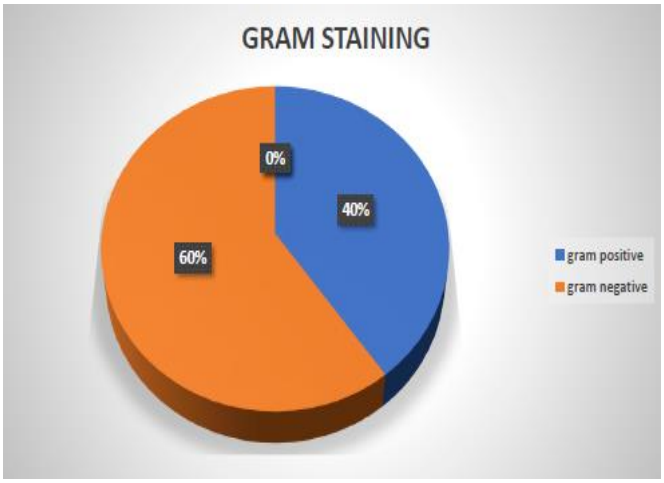

Figure 8: Classification of isolated microorganisms based on gram staining found in the samples of the study population

From the above graph Gram-Negative Bacteria (60%) such as E.coli, K. oxytocca, Klebsiella, Pseudomonas, etc were found to be causing more infections in the study subjects when compared to Gram-Positive Bacteria (40%).such as Enterococci, MRSA, S.epidermidis, etc.

DISTRIBUTION OF MICROORGANISMS BASED ON ANTIBIOTIC SENSITIVITY AND RESISTANCE

ANTIBIOTICS		ISOLATED BACTERIA										
		E.coli (13)	Pseudomonas (2)	Klebsiella (2)	K.oxytoca (7)	K.pneumoniae (7)	P.aeriginosae (3)	Protease (3)	Enterococci (4)	MRSA (6)	MSSA (5)	MR CONS (1)
Penicillins	Ampicillin	R-13 S-0	R-0 S-1	R-2 S-0	R-7 S-0	R-5 S-1	R-1 S-1	R-3 S-0	R-3 S-0	R-1 S-1	R-0 S-2	R-0 S-1
	Amoxiclav	R-10 S-2	R-1 S-0	R-1 S-1	R-6 S-1	R-5 S-2	R-1 S-1	R-0 S-3	R-0 S-3	R-2 S-0	R-0 S-1	R-1 S-0
	Penicillin	R-1 S-0	–	–		–	–	R-2 S-0	R-2 S-0	R-6 S-0	R-4 S-0	R-0 S-1
	Piperazin-Tazobactum	R-0 S-9	R-1 S-1	–	R-1 S-4	R-0 S-7	R-1 S-1	R-1 S-2	R-1 S-2	R-0 S-1	R-1 S-0	R-0 S-1
Fluro-quinolones	Ciprofloxacin	R-4 S-0	R-0 S-1	R-2 S-0	R-2 S-1	R-3 S-2	–	R-0 S-2	R-0 S-2	R-1 S-0	R-1 S-1	R-0 S-1
	Levofloxacin	R-0 S-1	–	–	R-0 S-2	–	–	R-0 S-1	R-0 S-1	R-0 S-2	R-1 S-2	–
Macrolides	Erythromycin	R-0 S-1	R-1 S-0	R-1 S-0	–	–	–	R-1 S-0	R-1 S-0	R-2 S-3	R-1 S-2	–

Table 9: Classification of antibiotics based on their sensitivity and resistance status in the study population

ANTIBIOTICS		E.coli (13)	Pseudomonas (2)	Klebsiella (2)	K.oxytoca (7)	K.pneumoniae(7)	P.aeriginosae (3)	Protease (3)	Enterococci (4)	MRSA (6)	MSSA (5)	MR CONS (1)
Cephalo sporins	Ceftriaxone	R-10 S-1	R-1 S-0	R-0 S-1	R-3 S-2	R-4 S-1	R-0 S-1	R-0 S-2	R-0 S-2	–	–	R-0 S- 1
	Cefotaxim	R-7 S-0	R-0 S-0	R-0 S-0	R-3 S-2	R-0 S-3	R-0 S-1	R-0 S-0	–	R-1 S-1	–	R-1 S- 0
Amino Glycosides	Amikacin	R-5 S-8	R-1 S-1	R-0 S-1	R-6 S-1	R-2 S-5	R-0 S-3	R-0 S-3	R-0 S-3	–	R-0 S-2	R-1 S- 0
	Gentamycin	R-6 S-5	R-1 S-1	R-1 S-1	R-3 S-3	R-2 S-5	R-0 S-2	R-0 S-1	R-0 S-1	–	–	R-0 S- 1
Nitrofurans	Nitrofurantoin	R-0 S-7	R-0 S-1	R-1 S-0	–	R-1 S-0	–	R-0 S-1	R-0 S-1	R-0 S-1	–	–
Lincosamides	Clindamycin	–	–	R-0 S-1	–	–	R-0 S-1	–	–	R-3 S-3	R-0 S-3	R-1 S- 0

The above table represents the resistance rates of the isolated organisms to commonly used antimicrobials in the hospital. The numbers shown in the table enumerate the samples containing microorganisms that exhibit Resistance (R) and Sensitivity (S) towards the specific antibiotics prescribed. From the above data, it is evident that most of the samples were resistant to the most prescribed antimicrobials.

DRUG INTERACTIONS BASED ON SEVERITY

Table 10: Drug interactions classified based on the severity

DRUG INTERACTION	OCCURRENCE
MAJOR	41(58%)
MODERATE	83(117%)
MINOR	14(18%)

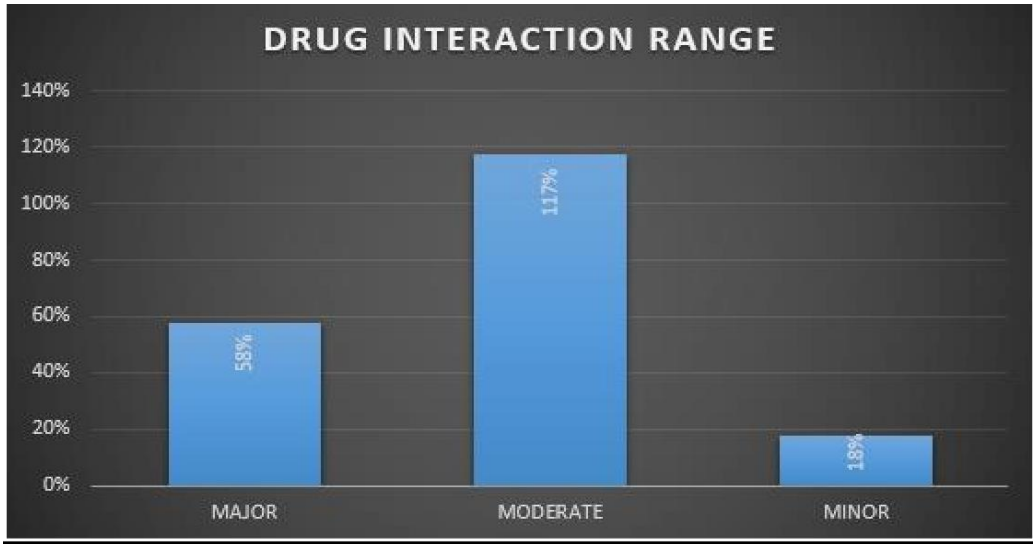

Figure 9: Drug interactions classified based on the severity

The above graph shows the percentage of the severity of drug interactions between antibiotics and other prescribed drugs to the study subjects.

DISCUSSION

The demographics and prescribing patterns of antibiotics provided to our study population were similar to the reports of other studies on the Antimicrobial Stewardship Program. A total number of 71 patients were involved in this study.

A study was conducted by **Y. Tagashira**[9]***et al.***, that showed considering the age group, the majority of the number of patients was in age around 40 years and above followed by 50 to 60 years age group patients. A similar article was found with a study done by **Leah M. Feazel1**[10]***et al.,*** where they did the survey and study of all the wards of the hospital. They had 1% of the patients from geriatrics departments and other major departments had patients of about 88% and other minor wards had 11%.In a study done by **Leah M. Feazel*et al.,*** antibiotic drugs were evaluated in the study and found that the cephalosporin class of drugs and fluoroquinolones respectively were included in the majority of drug regimens. Similarly, a study was done by **Nebyu Daniel Amaha**[11]***et al.,*** that shows 79% of hospitalizations had at least one antibiotic prescribed, and on average 1.29 antibiotics were prescribed per hospitalization. Lower classes of antibiotics showed major resistance like ampicillin 38(12.17%), amoxiclav 31(9.93%), and other classes of antibiotics like cephalosporins eg. ceftriaxone and cefepime which are more frequently prescribed for various infections were found to be showing high levels of resistance. Drugs that showed sensitivity towards the

organisms were higher-class drugs. Very few drugs are sensitive to microorganism infections and hence have to be preserved for future aid. A study conducted by Taher Azimi[12]***et al.,*** shows that among the bacterial pathogen isolated from clinical specimens, 55% (n=622) were GNB and 45% (n=508) were GPB. The prevalent gram-negative bacteria isolates were Pseudomonas aeruginosa, Klebsiella spp., Acinetobacter baumannii, Escherichia coli, Enterobacter spp., and Citrobacter spp., Among GPB, Enterococcus spp. was found to have low levels of resistance and CoNS was having the most frequent resistance to linezolid. In GNB, most P. aeruginosa and A. baumannii were ceftriaxone resistant.

CONCLUSION

Results from the study confirm that as we go from lower classes of antibiotics to higher classes majority of the organisms exhibited resistance towards and lower class antibiotics and sensitivity were exhibited by only a few higher classes of antibiotics. It was also found that samples with no growth of bacteria were continued to be treated with antibiotics which leads to unwanted exposure of antibiotics to the organisms aiding them to develop resistance. This study showed that frequently prescribed antibiotics such as ciprofloxacin which showed major interactions and metronidazole and linezolid which showed moderate interactions were the most repeated drugs which showed interactions with other drugs. Antibiotic drug monitoring and pharmacist participation to follow up the need of monitoring of proper antibiotic drug use is severely necessary. It was concluded that good practice of proper antibiotic use at the right time and right frequency to the right patient is mandatory in a stewardship program for preserving the antibiotics we have. As no newer antibiotics classes were discovered since 1998 it is a serious responsibility of Health Care Professionals to maintain rational use of antibiotics for treatment.

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