INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

MULTI DRUG RESISTANCE PATTERNS AMONG GRAM NEGATIVE BACTERIA IN HOSPITALIZED PATIENTS AND THE ECONOMIC IMPACT IN THEIR TREATMENT

B.V.S Lakshmi, M. Hima bindu, M.Sudhakar, M.Samhitha, S.Manasi*
Malla Reddy College of Pharmacy, Dhulapally, Secunderabad, Telangana-500100 (Affiliated to Osmania University).

ARTICLE INFO

Article history
Received 28/07/2020
Available online
05/09/2020

Keywords
Multidrug Resistance,
Gram Negative Bacteria,
Economic Impact.

ABSTRACT

BACKGROUND: Infections caused by multidrug resistant gram negative bacteria are often corresponded with increased comorbidities, prolonged hospitalization and mortality. These bacteria not only pose a serious threat to global public health but also create a burden to health care systems. The present study was aimed to identify the incidence of Multi drug resistance patterns among gram negative bacteria in hospitalized patients and the economic impact in their treatment. We have also studied the sensitivity and resistance patterns of the isolated gram negative organisms. METHODS: Prospective study was conducted on 165 patients. Relevant data pertaining to demographics characteristics, comorbid conditions, length of stay and costs of antibiotics was taken from the patients. Blood and other samples like swab, sputum, urine, CSF etc were also sent for the culture sensitivity testing. Antimicrobial susceptibility testing was carried out using the Kirby bauer disc diffusion method. RESULTS : The most common multi drug resistant Gram negative bacteria were *E.coli* (33.94%)and *Klebsiella pneumoniae*(12.12%) The multidrug resistance patterns show that E.coli is most resistant to Tetracycline and Amoxyclav , Klebsiella is highly resistant to Ampicillin, Ertapenem & Gentamicin. The economic burden was more in Multidrug resistant cases when compared to sensitive cases. CONCLUSION: There is an increase in multidrug resistance patterns especially in *E.coli & Klebsiella pneumonia* with a significant increase in costs in MDR cases, due to change in their therapy to a more sensitive antibiotic.

Corresponding author
S. Manasi
Pharm D V year.
Malla Reddy College of Pharmacy,
Dhulapally, Maisammaguda,
Secunderabad-5000100, Telangana, India.
08885188645
040-27145588
smanasi97@gmail.com

*Please cite this article in press as **S. Manasi** et al. Multi Drug Resistance Patterns in Gram Negative Bacteria in Hospitalized and the Economic Impact in their Treatment.. Indo American Journal of Pharmaceutical Research.2020:10(08).*

INTRODUCTION

The golden era of antibiotic discovery dates back to 1940-1960 as half of the antibiotic commonly used today were discovered during these years. The first case of penicillin resistance was observed in 1947. [1]The outbreak of multidrug-resistance (MDR) is one of the most considerable clinical and biological phenomena identified over 100 years. [2]The public health is at risk due to the limited treatment alternatives and lack of newly developed antimicrobial medications. Reports by local tertiary care hospitals shows that MDR strains of *E.coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii, Enterobacteriaceae and Stenotrophomonas maltophilia* have become of most concern.[3]

Antibiotic resistance is present in around all parts of the world. New resistance mechanisms emerge and spread rapidly. 80,000 people die across the globe due to antibiotic resistance. The incidence rate of multi drug resistance gram negative bacterial infections was 48 per 100 admitted patients according to a survey conducted in 2017.[4] Bacteria changes in some or the other way in different forms to protect itself from antibiotics and thus antibiotic resistance occurs. The mechanism of bacterial resistance may happen in a number of ways: Bacteria produce enzymes which degrades the antibiotic and then makes it inactive (or) Bacteria can also neutralize the antibiotic before it shows an effect (or) Bacteria also tries to pump the antibiotic out (or) Bacteria could change the site (or) Bacteria can transfer genetic material to other bacteria, or mutate. [5]

The factors which contribute to the existence and widespread of MDR gram-negative bacteria such as : overuse and misuse of existing antimicrobial agents, which has led to the development of adaptive resistance mechanisms by bacteria; a lack of responsible antibiotic handling and improper administration techniques has lead to the cycle of increasing resistance; and a lack of good infection control practices caused other complications in the patients. [6] Usage of multiple antibiotics increase the multidrug resistance and economic burden on patients, by observing the sensitivity and resistance patterns in gram negative bacteria, change of drug or administration of other class of antibiotic can be suggested to overcome this problem. [7]

This study has been taken up to find out the incidence of multidrug resistant organisms and for better understanding of relationship between the microbiological etiology, their sensitivity and resistance patterns to
antibiotics in infected hospitalized patients .We also aimed to study the economic impact.

MATERIALS AND METHODS:

The study was initiated in November 2019 and completed in April 2020 by department of pharmacy practice in Malla Reddy College Of Pharmacy and Malla Reddy Health City.

This study was approved by Institutional Ethics Committee in Malla Reddy Institute Of Medical Sciences. The nature of the study was explained to the patients and their informed consent form was taken.

We studied 165 consecutive patients admitted in various departments in the hospital.

Inclusion criteria included Patients who are willing for study. Patients of age 18 and above, Patients having gram negative bacterial growth in their sample sent to microbiological laboratory. All the patients who had no bacterial growth, gram positive isolates , less than 18years of age and who refused to participate in the study were excluded.

Samples were sent to microbiology lab and based on the culture sensitivity reports the study subjects were divided into 2 groups i.e. Multidrug resistant cases (105) and control group (60).

CRITERIA FOR MULTIDRUG RESISTANCE IN OUR STUDY :

Cases resistant to:

Carbapenems (or) ≥ 1 antimicrobial agent in more then three classes (eg : Penicillins, Macrolides, Aminoglycosides, oxazolidinones) (or) 3rd and 4th Generations of Cephalosporins with carbapenems and other beta-lactam (or) Aztreonam with other classes of antibiotics eg: either carbapenems or beta-lactams or aminoglycosides or fluoroquinolones. [8]

All the patients are subjected to biochemical and haematological tests such as Random blood sugar, complete blood picture, T_3,T_4 and Erythrocyte sedimentation rate.

Detection of Bacterial isolates:

Samples such as swab, sputum, urine, Cerebrospinal Fluid were sent to the microbiological department for the culture sensitivity testing on the advice of the clinician based on the clinical symptoms of the patient. The sample for the culture was inoculated on Mac conkey and blood agar for isolation of microorganisms and incubated at 37˚C over night. The bacterial isolates were confirmed as gram negative bacilli by gram staining and biochemical tests.

Identification of antibiotics sensitivity and resistant patterns for bacterial samples:

Susceptibility and resistance patterns of all the isolates to different antibiotics such as AK- (Amikacin), AMC- (Amoxyclav), AMP (Ampicillin), AZ (Azithromycin), AT (Aztreonam), CPM (Cefepime), CPZ (Cefperazone), CTX (Cefotaxime), CAZ (Ceftazidime), CTR (Ceftriaxone), CXM (Cefuroxime), CIP (Ciprofloxacin), CLR (Clarithromycin), DOR (Doripenem), ETP (Ertapenem), E(Erythromycin), GEN (Gentamicin), IMP (Imipenem), LE (Levofloxacin), MRP (Meropenem), NIT (Nitrofurantoin), OF (Ofloxacin), PIT (Piperacillin-Tazobactam), TE (Tetracycline) were determined by the Kirby Bauer's disc diffusion methods. [9]

Estimation of cost burden:

The medications given before the culture and their costs were noted. Based on the culture report the change of antibiotic was suggested and their costs were noted.

Statistical analysis was done by identifying the significance of differences between variables was examined using t-tests for continuous variables or the Chi-squared test for categorical variables. Paired t- test was performed, considering the level of significance 0.05 for the estimation of differences in the cost of changed and unchanged antibiotics in hospitalized patients. Unpaired t- test was performed considering the level of significance 0.05 for the estimation of differences in the cost of changed vs unchanged antibiotics and MDR vs control.

RESULTS :

Out of the total population of 165, 76 were female which accounts for 46% and 89 were male which accounts for 54%.

Microbiological observations :

Total number of samples collected from various departments including ICUs were 165 and the organisms isolated in all their biological samples were Gram Negative Bacteria. Of the total sample collected, 105 were Multi drug resistant cases and 60 were sensitive cases which were taken as control group. Incidence of the Multi Drug Resistant Bacteria was calculated. The results show that Escherichia coli has the highest incidence of 33.94% with total cases of 56 and Enterobacter cloacae has the lowest incidence of 0.65% with 1 case. (Table 1)

TABLE 1: INCIDENCE OF MULTI DRUG RESISTANT GRAM NEGATIVE BACTERIA.

ORGANISMS ISOLATED	NO. OF CASES (n)	INCIDENCE
Klebsiella pneumonia	20	12.12%
Escherichia coli	56	33.94%
Pseudomonas aeruginosa	17	10.30%
Proteus vulgaris	6	3.64%
Citrobacter freundii	5	3.03%
Enterobacter cloacea	1	0.65%

We have observed that among the Control samples, *Ecoli* is sensitive to Ciprofloxacin (98%) Cefperazone (93%) and Aztreonam (93%) and resistant to Ampicillin (67%) & Erythromycin(67%) and among the MDR samples, E.coli is most resistant to Tetracycline (84.20%) & Amoxyclav (84.20%) and sensitive to Gentamicin (68.40%) & Imipenem. (68.40%) (Table 2)

TABLE: 2 SENSITIVITY AND RESISTANT PATTERNS IN ECOLI.

ECOLI	ANTIBIOTICS LIST	CONTROL SENSITIVE		CONTROL RESISTANT		MDR SENSITIVE		MDR RESISTANT	
		No.	%	No.	%	No	%	No.	%
	*AK	7	47%	1	7%	26	46%	12	21%
	AMC	7	47%	9	60%	11	19.20%	48	84.20%
	AMP	6	40%	10	67%	6	11%	35	61.40%
	AZ	14	93%	2	13%	8	14%	26	46%
	AT	9	60%	2	13%	2	35%	46	81%
	CPM	11	73%	2	13%	7	12.20%	3	5.20%
	CPZ	14	93%	1	7%	6	11%	33	58%
	CTX	10	67%	2	13%	6	11%	24	42%
	CAZ	8	53%	1	7%	5	9%	24	42%
	CTR	7	47%	1	7%	6	11%	39	68.40%
	CXM	0	-	0	-	4	7%	11	19.20%
	CIP	16	98%	2	13%	11	19.20%	32	56.10%
	CLR	4	27%	2	13%	9	16%	30	53%
	DOR	2	13%	3	20%	41	72%	19	33%
	ETP	3	20%	2	13%	44	77%	22	39%
	E	8	53%	10	67%	8	14%	27	47.30%
	GEN	11	73%	2	13%	39	68.40%	18	32%
	IMP	2	13%	2	13%	39	68.40%	19	33%
	LE	13	87%	2	13%	17	30%	46	81%
	MRP	4	27%	1	7%	32	56%	18	32%
	NIT	10	67%	4	27%	24	42%	19	33%
	OF	8	53%	2	13%	15	26.30%	21	37%
	PIT	5	33%	5	33%	22	39%	30	53%
	TE	1	7%	6	40%	28	49%	48	84.20%

We have observed that among the Control samples, *Pseudomonas aeruginosa* is sensitive to Ceftriaxone (93%) and resistant to Tetracycline (47%) and among the MDR samples, it is highly resistant to Tetracycline (72%), Erythromycin (72%) & Doripenem (72%) and sensitive to Piperacillin-Tazobactam (20%), Meropenem (13%) & Ertapenem .(20%) (Table 3).

TABLE 3: SENSITIVE AND RESISTANCE PATTERNS IN *PSEUDOMONAS.*

PSEUDOMONAS	ANTIBIOTICS LIST	CONTROL SENSITIVE		CONTROL RESISTANT		MDR SENSITIVE		MDR RESISTANT	
		No.	%	No.	%	No.	%	No.	%
	*AK	11	73%	1	7%	8	44%	7	39%
	AMC	12	80%	2	13%	6	33%	8	44%
	AMP	12	80%	2	13%	3	17%	13	72%
	AZ	10	67%	2	13%	3	17%	6	33%
	AT	2	13%	1	7%	9	50%	12	66%
	CPM	9	60%	2	13%	4	22%	3	17%
	CPZ	12	80%	1	7%	6	33%	4	22%
	CTX	8	53%	2	13%	8	44%	6	33%
	CAZ	10	67%	3	20%	5	28%	11	61%
	CTR	14	93%	2	13%	8	44%	7	39%
	CXM	12	0.8	1	0.07	3	17%	6	33%
	CIP	13	87%	3	20%	2	11%	13	72%
	CLR	13	87%	2	13%	2	11%	9	50%
	DOR	9	60%	2	13%	13	72%	13	72%
	ETP	7	47%	3	20%	12	66%	7	39%
	E	12	80%	2	13%	2	11%	13	72%
	GEN	13	87%	2	13%	11	61%	7	39%
	IMP	11	73%	2	13%	15	83%	9	50%
	LE	12	80%	1	7%	3	17%	7	39%
	MRP	12	80%	2	13%	12	66%	10	55%
	NIT	12	80%	1	7%	5	28%	5	28%
	OF	9	60%	1	7%	5	28%	5	28%
	PIT	13	87%	3	20%	14	78%	4	22%
	TE	3	20%	7	47%	10	55%	13	72%

We have observed that among the Control samples, *Proteus Vulgaris* is sensitive to Cefepime (90%) and resistant to Nitrofurantoin (40%) and among the MDR samples, it is highly resistant to Ampicillin (98%), Amoxyclav (98%) and sensitive to Meropenem (98%). (Table 4)

TABLE 4: SENSITIVE AND RESISTANCE PATTERNS IN PROTEUS VULGARIS.

PROTEUS	ANTIBIOTICS LIST	CONTROL SENSITIVE		CONTROL RESISTANT		MDR SENSITIVE		MDR RESISTANT	
		No.	%	No.	%	No.	%	No.	%
	*AK	6	60%	1	10%	3	50%	3	50%
	AMC	3	30%	2	20%	4	67%	7	98%
	AMP	3	30%	3	30%	2	33%	7	98%
	AZ	8	80%	1	10%	1	17%	2	33%
	AT	2	20%	3	30%	4	67%	5	83%
	CPM	9	90%	2	20%	2	33%	1	17%
	CPZ	8	80%	1	10%	2	33%	2	33%
	CTX	6	60%	2	20%	2	33%	1	17%
	CAZ	8	80%	3	30%	2	33%	3	50%
	CTR	8	80%	3	30%	2	33%	3	50%
	CXM	8	0.8	2	20%	2	33%	1	17%
	CIP	8	80%	2	20%	1	17%	2	33%
	CLR	7	70%	2	20%	1	17%	4	67%
	DOR	4	40%	1	10%	3	50%	1	17%
	ETP	5	50%	1	10%	4	67%	2	33%
	E	3	30%	1	10%	1	17%	3	50%
	GEN	6	60%	1	10%	1	17%	4	67%
	IMP	4	40%	1	10%	4	67%	3	50%
	LE	7	70%	3	30%	1	17%	2	33%
	MRP	4	40%	1	10%	7	98%	2	33%
	NIT	3	30%	4	40%	1	17%	2	33%
	OF	7	70%	2	20%	1	17%	4	67%
	PIT	5	50%	3	30%	2	33%	3	50%
	TE	3	30%	3	30%	1	17%	2	33%

Among the Control samples, *Klebsiella pneumoniae* is sensitive to Ceftriaxone (73%) and resistant to Ciprofloxacin (40%) & Tetracycline (33%) and among the MDR samples, it is highly resistant to Ampicillin (85%), Ertapenem (85%) & gentamicin (85%) and sensitive to Piperacillin-Tazobactam (70%) & Amikacin (70%). (Table 5)

TABLE 5 : SENSITIVE AND RESISTANCE PATTERNS OF KLEBSIELLA.

KLEBSIELLA	ANTIBIOTICS LIST	CONTROL SENSITIVE		CONTROL RESISTANT		MDR SENSITIVE		MDR RESISTANT	
		No.	%	No.	%	No.	%	No.	%
	*AK	11	73%	1	8%	14	70%	6	30%
	AMC	10	67%	2	13%	4	20%	16	80%
	AMP	10	67%	2	13%	6	30%	17	85%
	AZ	8	53%	2	13%	1	5%	5	25%
	AT	5	33%	3	20%	5	25%	16	80%
	CPM	12	80%	2	13%	5	25%	3	15%
	CPZ	12	80%	1	8%	2	10%	16	80%
	CTX	14	93%	2	13%	7	35%	7	35%
	CAZ	12	80%	1	8%	11	55%	16	80%
	CTR	11	73%	3	20%	6	30%	11	55%
	CXM	10	0.67	3	20%	6	30%	8	40%
	CIP	13	87%	6	40%	5	25%	15	75%
	CLR	8	53%	2	13%	2	10%	4	20%
	DOR	7	47%	3	20%	8	40%	2	10%
	ETP	6	40%	5	33%	13	65%	17	85%
	E	5	33%	3	20%	3	15%	7	35%
	GEN	8	53%	1	8%	5	25%	17	85%
	IMP	6	40%	3	20%	13	65%	8	40%
	LE	12	80%	2	13%	11	55%	16	80%
	MRP	6	40%	4	27%	14	70%	8	40%
	NIT	8	53%	1	8%	5	25%	6	30%
	OF	10	67%	1	8%	9	45%	2	10%
	PIT	9	60%	2	13%	14	70%	14	70%
	TE	2	13%	5	33%	6	30%	9	45%

Among the Control samples, *Citrobacter freundii* is sensitive to Erythromycin (77%) & Gentamicin (77%) and resistant to amoxyclav (66%) and among the MDR samples, it is highly resistant to Ceftriaxone (100%), followed by ampicillin (80%) and sensitive to Gentamicin (100%).(Table 6)

TABLE 6 : SENSITIVE AND RESISTANCE PATTERNS IN CITROBACTER.

CITROBACTER	ANTIBIOTICS LIST	CONTROL SENSITIVE		CONTROL RESISTANT		MDR SENSITIVE		MDR RESISTANT	
		No.	%	No.	%	No.	%	No.	%
	*AK	5	55%	1	11%	3	60%	2	40%
	AMC	2	22%	6	66%	1	20%	3	60%
	AMP	2	22%	4	44%	1	20%	4	80%
	AZ	6	66%	2	22%	2	40%	2	40%
	AT	7	77%	2	22%	2	40%	4	80%
	CPM	4	44%	2	22%	1	20%	3	60%
	CPZ	6	66%	2	22%	1	20%	1	20%
	CTX	5	55%	3	33%	2	40%	3	60%
	CAZ	5	55%	2	22%	2	40%	3	60%
	CTR	5	55%	1	11%	2	40%	5	100%
	CXM	5	55%	1	11%	1	20%	3	60%
	CIP	8	88%	1	11%	3	60%	3	60%
	CLR	7	77%	3	33%	1	20%	1	20%
	DOR	6	66%	1	11%	3	60%	1	20%
	ETP	6	66%	1	11%	4	80%	2	40%
	E	7	77%	3	33%	2	40%	2	40%
	GEN	7	77%	3	33%	5	100%	1	20%
	IMP	5	55%	1	11%	1	20%	2	40%
	LE	6	66%	1	11%	3	60%	4	80%
	MRP	6	66%	1	11%	3	60%	3	60%
	NIT	5	55%	1	11%	3	60%	2	40%
	OF	5	55%	4	44%	3	60%	1	20%
	PIT	4	44%	3	33%	2	40%	3	60%
	TE	3	33%	1	11%	3	60%	2	40%

*AK- Amikacin, AMC- Amoxyclav, AMP- Ampicillin, AZ- Azithromycin, AT- Aztreonam, CPM- Cefepime, CPZ- Cefperazone, CTX- Cefotaxim, CAZ-Ceftazidime, CTR-Ceftriaxone, CXM-Cefuroxime, CIP- Ciprofloxacin, CLR- Clarithromycin, DOR-Doripenem, ETP-Ertapenem, E-Erythromycin, GEN-Gentamicin, IMP-Imipenem, LE-Levofloxacin, MRP-Meropenem, NIT-Nitrofurantoin, OF-Ofloxacin, PIT-Piperacillin-Tazobactam, TE- Tetracycline.

Estimation of economic impact:

It was observed that Control group i.e., patients sensitive to antibiotics stay for lesser time (Equal to or less than 10 days), when compared to patients with Multi drug resistance, a substantial number of patients (39 cases) stayed beyond 10 days (11-15days).

Taking into consideration the length of stay of multidrug resistant patients taken, the total average costs were calculated. The average total costs of subject samples before and after their culture sensitivity test was also taken as a main aspect to compare cost burden on multidrug resistant patients. Based on the culture sensitivity report, among the 105 MDR patients, the antibiotics prescribed were changed in about 68 subjects and in the rest 37 subjects it remained unchanged.

The average total costs of 68 patients was calculated, the pre culture average costs and post culture average costs was calculated based on their length of stay in the hospital. From the graph (Fig 1) suggests that the post culture average costs was more , when compared to the average costs of pre culture.

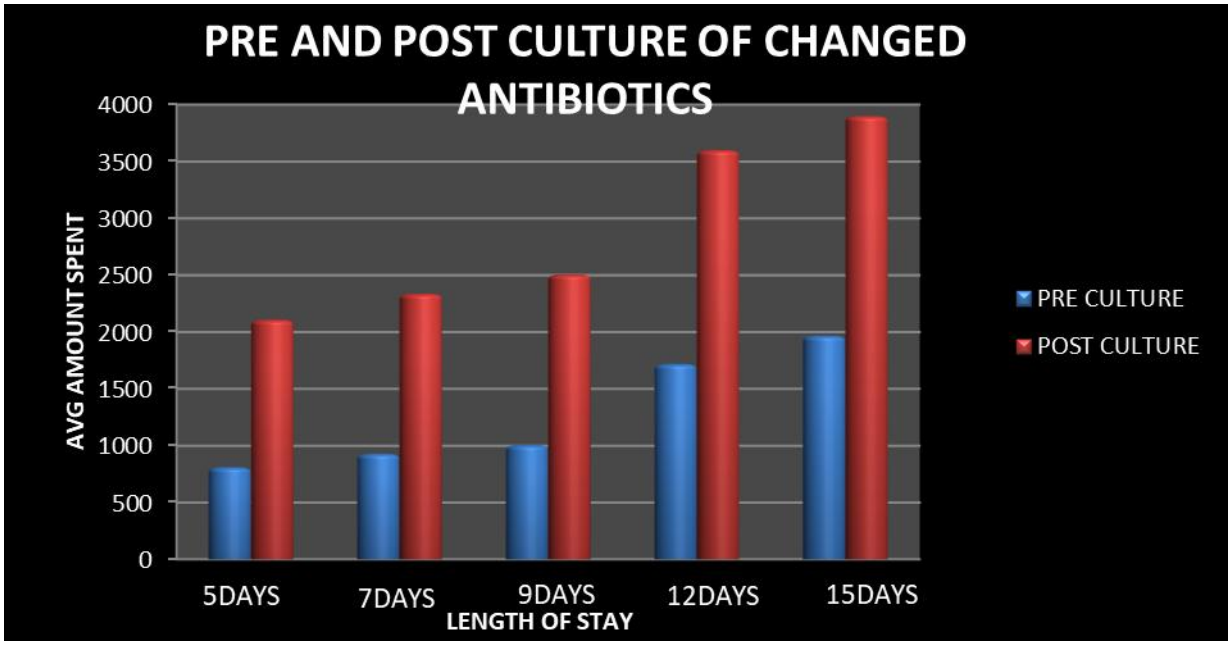

FIGURE 1 : GRAPH SHOWING COSTS OF CHANGED ANTIBIOTICS PRE AND POST- CULTURE IN MDR CASES BASED ON PATIENT'S LENGTH OF STAY.

The average total costs of 37 patients was calculated, the pre culture average costs and post culture average costs was calculated based on their length of stay in the hospital. From the graph (fig 2) suggests that the post culture average costs was more, when compared to the average costs of pre culture. The average total costs of unchanged antibiotics and changed antibiotics were compared based on the average length of stay. The average total cost was higher in changed antibiotics, when compared to unchanged antibiotics.

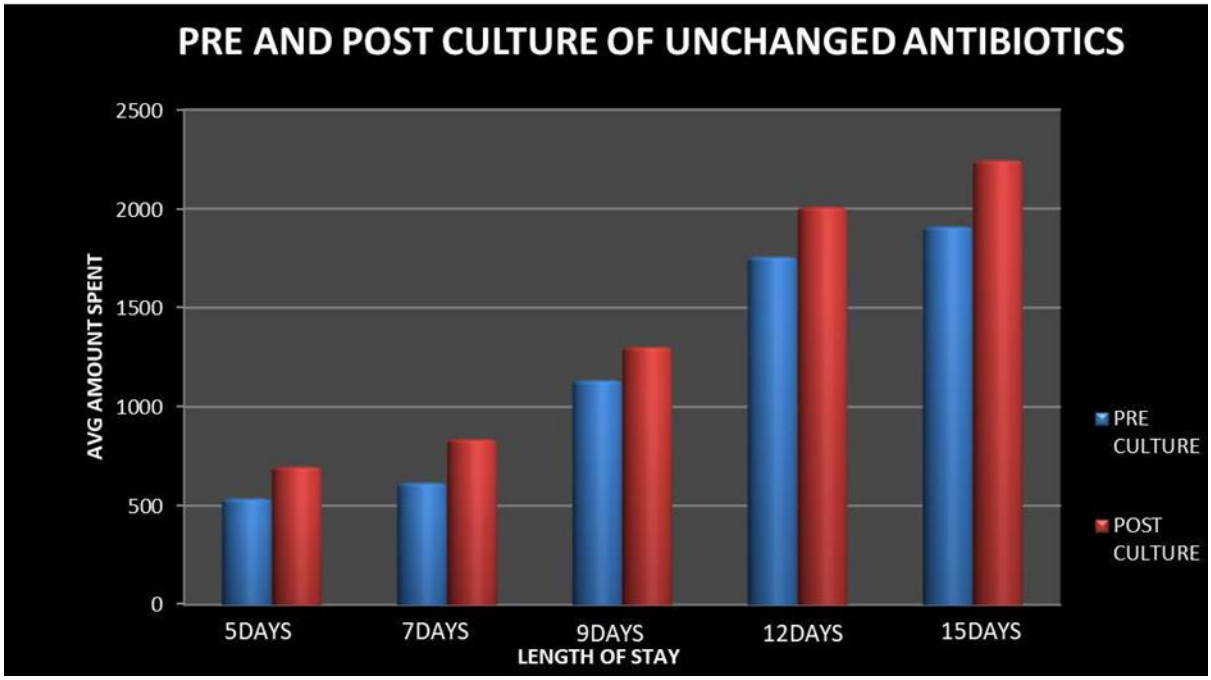

FIGURE 2: GRAPH SHOWING COSTS OF UNCHANGED ANTIBIOTICS PRE AND POST-CULTURE IN MDR CASES BASED ON PATIENT'S LENGTH OF STAY.

From the graph (Fig 3) we can say that as the length of stay increased the average total costs also increased. The average total costs of Multidrug resistant cases and control cases were compared based on the average length of stay.

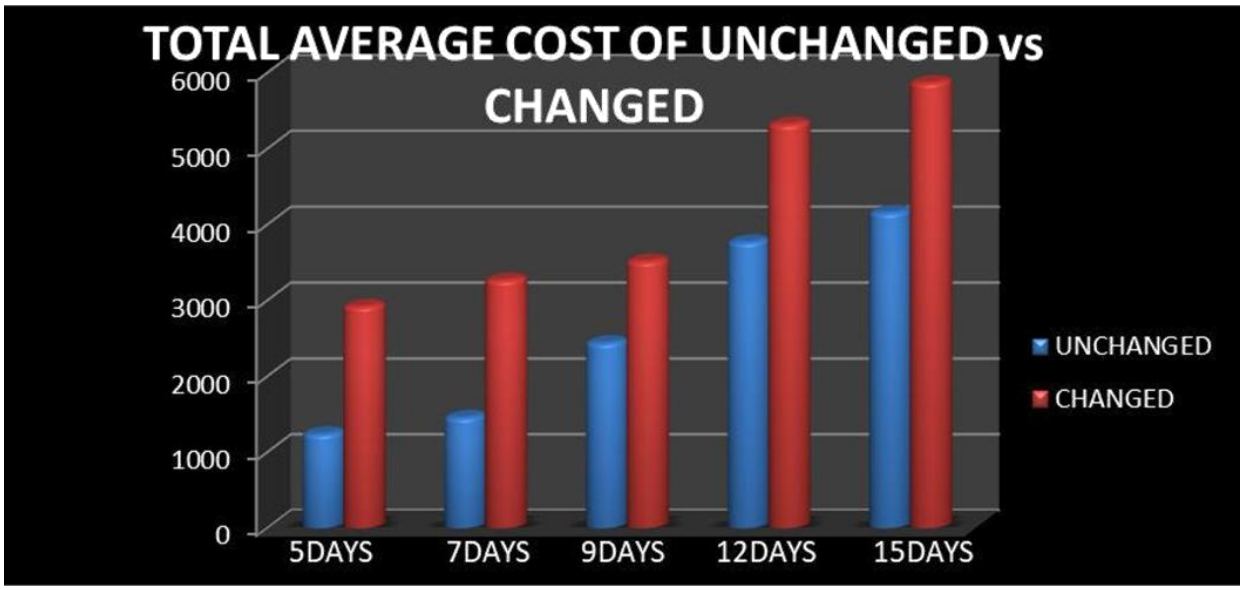

FIGURE 3: GRAPH SHOWING THE AVERAGE TOTAL COSTS OF CHANGED AND UNCHANGED ANTIBIOTICS IN MDR CASES BASED ON LENGTH OF STAY.

Based on the calculations and results the average total costs of pre culture and post culture of MDR samples were higher than that of average total cost of pre culture and post culture of control samples.(Fig 4)

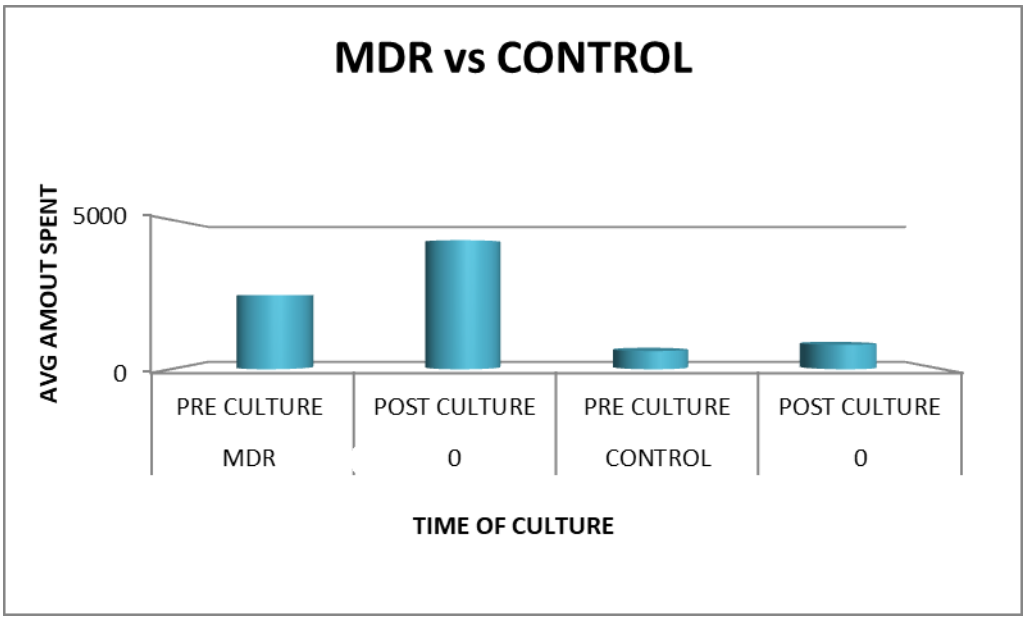

FIGURE 4 : GRAPH SHOWING AVERAGE TOTAL COSTS OF PRE AND POST CULTURES OF MDR AND CONTROL CASES RESPECTIVELY.

DISCUSSION

In our study, Incidence was calculated based on the statistical formula, it was also observed that among the different Gram Negative bacteria isolated E.coli (33.94%) has more incidence and Enterobacter (0.61%) has less incidence and a study conducted by Deena E. Sutter, et al concluded that the most common gram-negative bacteria were Escherichia coli (53% were MDR), Acinetobacter (9% were MDR), Klebsiella (63% were MDR) and enterobacter (17% were MDR) [10]

In our study, mainly among the MDR samples, E.coli is highly resistant to Tetracycline & Amoxicillin and sensitive to Gentamicin & Imipenem, Pseudomonas is highly resistant to Tetracycline, Erythromycin & Doripenem and sensitive to Piperacillin-Tazobactam, Meropenem & Ertapenem, Proteus vulgaris is highly resistant to Ampicillin and sensitive to Meropenem, Klebsiella is highly resistant to Ampicillin, Ertapenem & gentamicin and sensitive to Piperacillin-Tazobactam & Amikacin, Citrobacter is highly resistant to Ceftriaxone and sensitive to Gentamicin and among the control samples, Ecoli is sensitive to Ciprofloxacin & Cefperazone and resistant to Ampicillin & Erythromycin, Pseudomonas is sensitive to Ceftriaxone and resistant to Tetracycline, Proteus vulgaris is sensitive to Cefepime and resistant to Nitrofurantoin, Klebsiella is sensitive to Ceftriaxone and resistant to Ciprofloxacin & Tetracycline, Citrobacter is sensitive to Erythromycin & Gentamicin and resistant to amoxicillin and study conducted by Nicholas Agyepong et al concluded that the isolates showed high resistance to ampicillin (94.4%), trimethoprim/sulfamethoxazole (84.5%), cefuroxime (79.0%) and cefotaxime (71.3%) but low resistance to ertapenem (1.5%), meropenem (3%) and amikacin (11%) [11]

In our study, patient's length of stay plays a crucial role on the cost burden for multidrug resistant patients. Based on the data above, most of the multidrug resistant patients stayed for longer time (i.e. ≥ 12 days) when compared to the control group (i.e.≤ 7days).

Taking this into consideration, costs were compared based on the patient's length of stay and it was noticed that due to the multidrug resistance the cost burden was increased in such patients where as a study conducted by Christian G. Giske, et al concluded that multi drug resistant microorganisms in hospitalized patients are associated with longer duration of hospital stay and increased costs. [12]

To prove our above theory of Cost being higher for Multi Drug resistant cases, we have followed the below steps:
We have divided the MDR cases (105 cases) into Changed (68 cases) and Unchanged (37 cases) Categories. We further split the Total cost into Pre and Post Culture costs for both the Changed and Unchanged costs.

To maintain the uniformity in our comparison, we considered the Average Costs of Pre and Post Culture based on the length of stay. The MDR patients stayed for 5, 7,9,12 & 15 days which were used to calculate the average costs in both Changed and Unchanged categories which implies that the post culture costs were higher due to the longer stay which in turn was because of the patients having MDR.. The resultant outcome was of higher costs in the Changed category when compared to the Unchanged category due to the following reasons: Post receiving the result of the culture sensitivity test, the prescription of the drug was modified to a drug the patient was more susceptible to.

In substantial number of patients, more number of antibiotics were prescribed post the result. In nearly half of the patients, higher classes of antibiotics were prescribed post the results. Certain patients had Comorbid conditions like Diabetes, hypertension which increases the chances of the patient contracting an infection, which might lead to a longer duration of stay. The Average total cost is significantly higher in the MDR cases when compared to Control cases and the Average total cost of Post culture is higher compared to the Pre culture in Control cases as well, however, this increase is due to the additional number of days stayed and not due to Multi Drug Resistance.

CONCLUSION

E.coli is the most common pathogen followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Citrobacter freundii*. Gram negative bacteria from the study sample had high rates of antimicrobial resistance. Patients experiencing complex trauma and prolonged hospital stays likely contribute to the presence of MDR bacteria in this facility. However, many of these patients had community-acquired cases, which implies high rates of colonization prior to hospital admission.

Current evidences suggest that economic burden on the patients with multi drug resistance increase with the change of antibiotics after the culture sensitivity report and increased length of stay. as there was a shift of the antimicrobials to a more sensitive one which was most of the time more expensive patients with multidrug resistance had more number of hospital days compared to the patients without multidrug resistance which also added to their economic burden. Our agenda is to reach out to the pharmacists and pharmacologists of the infection control committee of our hospital and discuss with them about the significance of the research and the impact it would have on patients if relevant antibiotics are given.

The main drawback in our study was that the sample size was small, future studies can include a larger sample size to make a significant impact to the Hospital Infection Committee for an effective antibiotic policy.

ACKNOWLEDGEMENTS

We thank the management of Malla Reddy Health City, the Principal of Malla Reddy College Of Pharmacy, the Dean of Malla Reddy Institutes Of Medical Sciences, all participating pharmacists, faculty of pharmacology, technicians and faculty of the Microbiology Department, General surgeons and patients for their collaboration in this study.

Funding
The study was not funded by any grant.

Conflicts of Interest

No conflicts of interest have been declared.

REFERENCES

1. Clardy, J.; Fischbach, M.A.; Currie, C.R. The natural history of antibiotics. Curr. Biol. 2009, 19, 437–441.
2. Elizabeth J. Klemm, Vanessa K. Wong, and Gordon Dougan Emergence of dominant multidrug-resistant bacterial clades: Lessons from history and whole-genome sequencing. 2018, 115(51): 12872–12877.
3. Emily R. M. Sydnor and Trish M. Perl Hospital Epidemiology and Infection Control in Acute-Care Settings 2011 , 24(1): 141–173.
4. Mechanisms for the Horizontal Spread of Antibiotic Resistance Among Bacteria,Antibiotics and Antibiotic Resistance, 2011,167-186.
5. Sagar, S., Kaistha, S., Das, A. J., & Kumar, R.. Intrinsic Antibiotic Resistance Mechanism in Bacteria. Antibiotic Resistant Bacteria: A Challenge to Modern Medicine, 2019, 69-85.
6. Butaye, P. Mobile genes coding for efflux-mediated antimicrobial resistance in Gram-positive and Gram-negative bacteria. International Journal of Antimicrobial Agents, 2003, 22(3), 205-210.
7. Pollack, M., Nieman, R., Reinhardt, J., Charache, P., Jett, M., & Hardy, P. Factors Influencing Colonisation And Antibiotic-Resistance Patterns Of Gram-Negative Bacteria In Hospital Patients. The Lancet, 1972, 300(7779), 668-671.
8. Poole, K.. Multidrug resistance in Gram-negative bacteria. Current Opinion in Microbiology, 2001,4(5), 500-508.
9. Hedges, A. J. The influence of factors affecting the `critical population density of inocula on the determination of bacterial susceptibility to antibiotics by disc diffusion methods. Journal of Antimicrobial Chemotherapy, 1999 ,43(2), 313-313.
10. Deena E Sutter , Linda U Bradshaw et al High incidence of multidrug-resistant gram-negative bacteria recovered from Afghan patients at a deployed US military hospital ,2011;32(9):854-60.
11. Nicholas Agyepong , Usha Govinden et al Multidrug-resistant gram-negative bacterial infections in a teaching hospital in Ghana 2018 , 7:37.
12. Christian G. Giske, Dominique L. Monnet et al Clinical and Economic Impact of Common Multidrug-Resistant Gram-Negative Bacilli,2008; 52(3): 813–821.

5487847845**1200211**