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Antibiotic Utilization in Patients with Complicated Urinary Tract Infection in the Medicine Wards of a South Indian Tertiary Care Teaching Hospital.

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ABSTRACT

Complicated urinary tract infection (cUTI) is a major issue in the present day because of the wide variety of antibiotics required for its treatment. This study aimed to identify the organisms isolated, sensitivity pattern and utilization of antibiotics in cUTI and the outcome of the therapy. A retrospective cohort study was conducted using medical records of 297 patients diagnosed with cUTI. Patient demography, organisms isolated and their sensitivity pattern, antibiotic regimen used and outcome were recorded and assessed using SPSS 18. The most isolated organisms responsible for cUTI were ESBL *Ecoli* which was found to be very sensitive to cefoperazone-sulbactum, amikacin and to carbapenems and *Ecoli* which was found to be sensitive to most antibiotics. Dual drug regimen was the most preferred treatment. Among the different category of antibiotics used, cephalosporins were the most commonly prescribed. The use of dual drug regimen for the treatment of cUTI was found to produce more significant outcomes than the other regimens. The organisms isolated were found to be most sensitive to cephalosporins, amikacin and carbapenems. Cephalosporins were the most effective antibiotics for the treatment of cUTI. The limitations of this study were small sample size and the unavailability of culture reports for many patients.

Keywords: ESBL *Ecoli*, urinary infections, cephalosporins, sensitivity pattern, risk factors

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INTRODUCTION

Complicated UTI (cUTI) is an infection associated with structural or functional abnormalities of the genitourinary tract or the presence of an underlying disease, which increases the risks of acquiring an infection or of failing therapy [1]. The overall incidence rate of cUTI was estimated to be 18 per 1000 person per year in the general population [2]. *Escherichia coli, Klebsiella, Pseudomonas* and enterococci are the frequently found strains found in cultures. *Enterobacteriaceae* (60-70%) along with *E. coli* are the most common pathogens involved in causing UTI. Pathogens responsible for UTIs are increasingly becoming resistant to antibiotics at a fast rate causing growing concern worldwide. A steady increase of the resistance rate of uropathogens to commonly prescribed antibiotics (amoxicillin, trimethoprim sulfamethoxazole) has been shown in a number of studies carried out in Europe and in the United States, thus proving a reduction in therapeutic possibilities[3-5]. In recent years, the spread of extended spectrum beta-lactamase (ESBL) producing bacteria has resulted in a rise in the number of cUTI related to resistant gram negative organisms causing a number of management problems. Most of these ESBL producers are resistant to the commonly prescribed cephalosporins and penicillins and also to non-beta-lactam agents such as gentamicin, fluoroquinolones and trimethoprim [6]. Treatment for 7-14 days is recommended for most patients but therapy is sometimes prolonged to 21 days in severe infections.

METHODOLOGY

A retrospective study was conducted in a south Indian tertiary care teaching hospital with ethical clearance obtained from the institutional ethical committee. The study was carried out among 297 patients diagnosed with complicated urinary tract infection admitted during the period of January 2011- December 2011. Details regarding predisposing factors responsible for cUTI, complications of cUTI, the organisms isolated, their sensitivity and resistance pattern towards different antibiotics, treatment provided, outcome measures in terms of improved, unchanged and expired and duration of hospitalization were recorded and were analyzed using SPSS 18.0 package. Number of antimicrobial agents prescribed versus outcomes was analyzed using Chi-square test and outcome is represented in terms of improved, unchanged or expired patients. A probability of $P \leq 0.05$ was considered statistically significant.

RESULTS

A total number of 297 patients who were diagnosed with complicated UTI were studied. Among them 54.2% were found to be men. The mean age of the study population was found to be 56.14 ± 14.9 years. The incidence of complicated UTI was predominantly more in the age group of 49-58 years and least in the age group of 18-28 years.

The common clinical symptoms associated with complicated UTI were found to be fever (60.9%), burning micturition (23.2%) and suprapubic pain (21.1%). About 6.7% of the studied population had a documented history of prior or recurrent UTI.

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Diabetes Mellitus was found to be the most common factor responsible for causing complicated UTI (62%).

Complicated urinary tract infection was found to cause urosepsis in 17.2% of the patients, pyelonephritis in 5.7% of the patients, hydroureteronephrosis in 6.1% of the patients and sepsis in 5.1% of the patients.

Fig.1 illustrates the various organisms responsible for causing complicated UTI.
Table 1 gives the details of the sensitivity and resistance pattern of organisms to different antimicrobial agents.

Table 1: Sensitivity and Resistance Pattern of organisms to different antibiotics

Organisms (n)	Amikacin		Amoxicillin-Clavlulanate		Amoxicillin		Cefotaxime/ Ceftraixone		Cefuroxime		TMP-SMZ		Gentamycin		Netilmycin	
	S %	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%
Ecoli (37)	56.8	0	32.4	16.2	27	18.9	36.1	11.1	37.8	10.8	32.4	16.2	40.5	10.8	55.6	2.8
ESBL *Ecoli* (95)	67.4	14.7	1.1	75.8	1.1	76.8	2.1	75.8	1.1	75.8	16.8	63.2	24.5	54.3	58.9	23.2
Klebsiella (4)	75	0	25	25	0	50	25	25	25	25	25	25	25	25	75	0
Enterobacter (6)	50	16.7	33.3	33.3	50	33.3	33.3	16.7	16.7	33.3	50	50	33.3	50	16.7	16.7
Candida (6)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Acinetobacter (1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MDR *Klebsiella* (5)	0	60	0	80	0	80	20	40	0	60	20	60	0	60	0	60

Organisms	Cefoperazone-Sulbactum		Piperacillin-Tazobactum		Imipenem/ Meropenem		Aztreonam		Cefepime		Ticaricillin-Clavullanate		Norfloxacin	
	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%
Ecoli (37)	48.6	0	40.5	2.7	48.6	0	21.6	8.1	21.6	8.1	21.6	8.1	35.1	5.4
ESBL *Ecoli* (95)	81.1	1.1	58.9	23.2	81.1	3.2	0	71.6	0	72.6	6.3	65.3	3.2	70.5
Klebsiella (4)	50	50	50	0	50	0	0	25	0	25	25	0	25	25
Enterobacter (6)	33.3	0	0	16.7	16.7	0	16.7	0	0	16.7	16.7	0	0	16.7
Candida (6)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Acinetobacter (1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MDR *Klebsiella* (5)	20	40	0	60	20	40	0	60	0	60	0	60	0	60

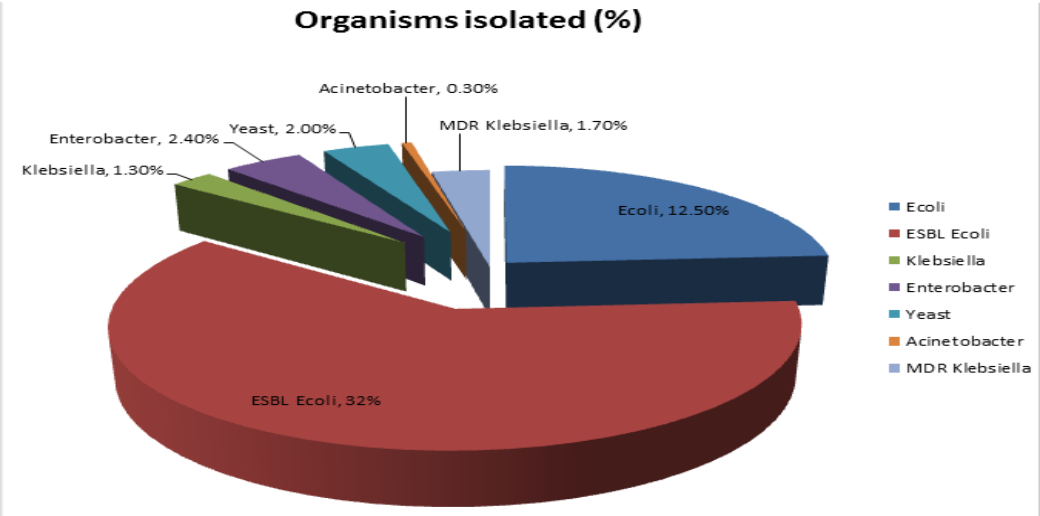

Figure 1: Percentage of different organisms isolated

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From the study it was observed, two drug regimens (38.05%) were the most preferred followed by single drug regimen (31.3%). Patients with co morbidities present were on the three drugs or more regimens.

Among the antibiotics prescribed as shown in Figure 2, cephalosporins were the most commonly prescribed antimicrobial agents (79.1%), followed by extended spectrum penicillins (20.2%) and fluoroquinolones (17.5%). Nitrofurantoins are seldom given as monotherapy; mostly they are given along with third generation cephalosporins.

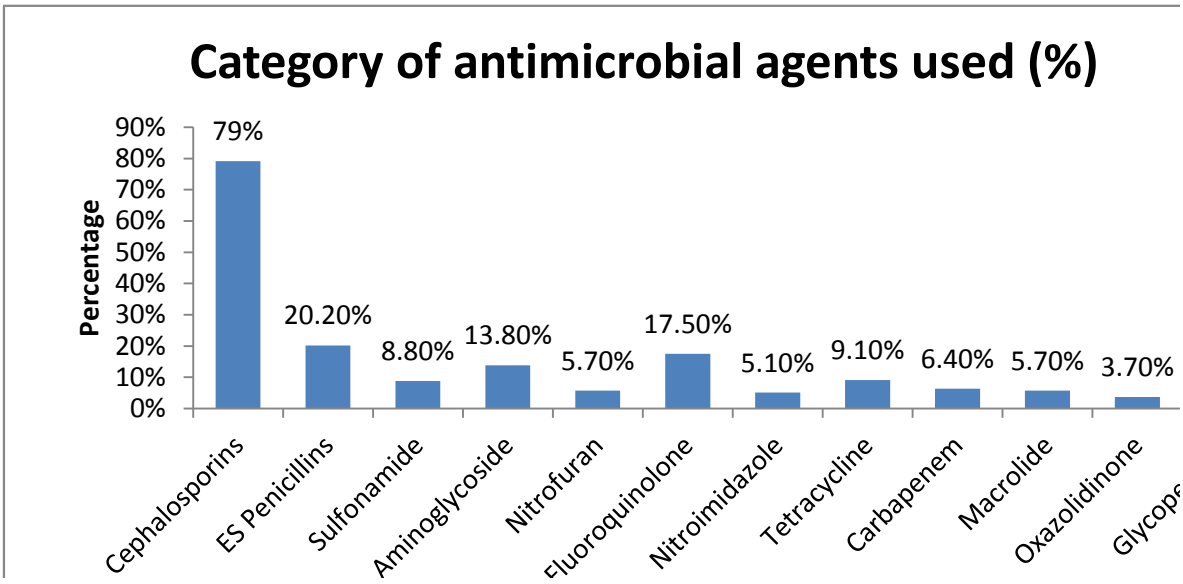

Figure 2: Category of antimicrobial agents used (in percentage) for the treatment of cUTI.

Table 2 indicates the number of antimicrobial agents prescribed. Dual drug regimen was found to have produced a better outcome than single drug regimen or triple or more drug regimens. It was calculated using Chi Square method and the p value was found to be 0.026 which makes it a statistically significant value.

Table 2: Number of Antimicrobial Agents (AMA) prescribed vs. outcome

Number of AMA prescribed	Outcome		
	Improved	Unchanged	Expired
Single drug regimen	79 (84.9%)	14 (15.1%)	0
Dual drug regimen	97 (94.2%)	6 (5.8%)	0
Triple or more drug regimen	89 (89.0%)	8 (8.0%)	3 (3.0%)

Cephalosporins (78.9%) are the most commonly preferred antibiotics for UTI caused by ESBL Ecoli, followed by Aminoglycosides (20%). Extended spectrum penicillins and Fluoroquinoles (13.7%) are prescribed at a same extent, followed by carbapenems (10.5%), Sulfonamides i.e. Trimethoprim-sulfamethoxazole (9.5%), Tetracyclines (8.4%), Nitroimidazoles

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and Nitrofurantoins (5.3%). ESBL Ecoli was found to be most sensitive to Cefoperazome-Sulbactum, carbapenems and amikacin as shown in Figure 3.

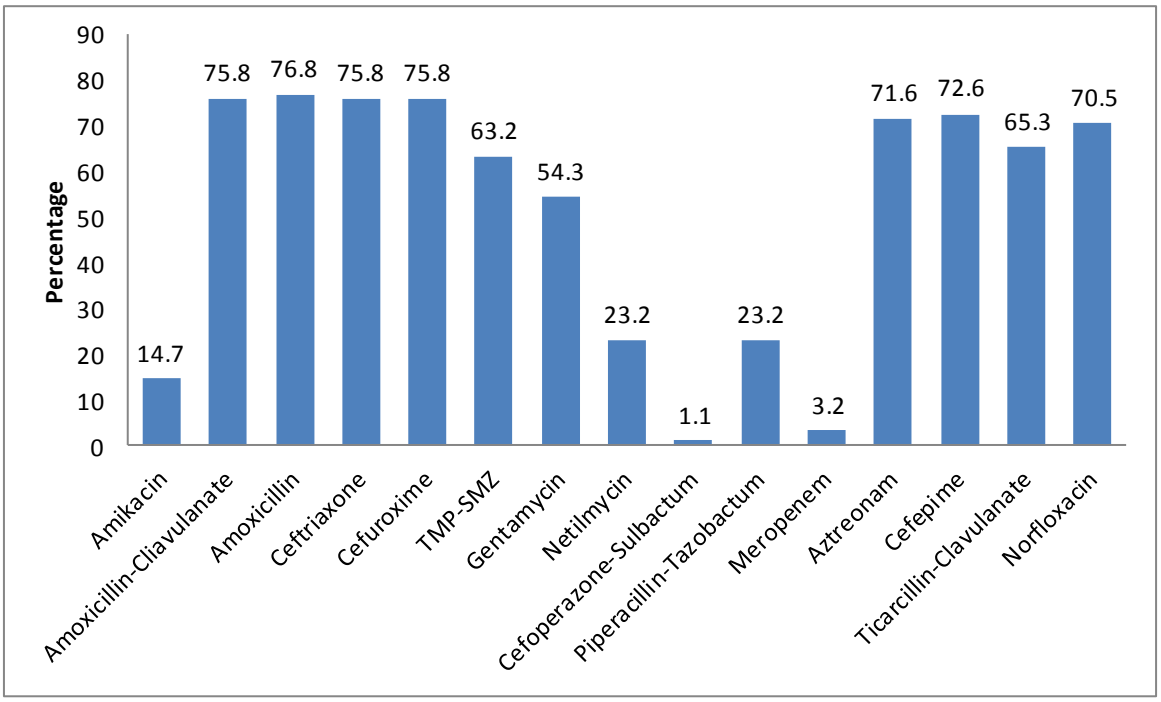

Figure 3: A diagrammatic representation of the percentage resistance of ESBL Ecoli to different antimicrobial agents.

For the treatment of ESBL *E coli*, dual drug regimen was the most preferred regimen and showed maximum improvement in outcome (97.2%) followed by single drug regimen (89.7%).

DISCUSSION

The study was done retrospectively by reviewing the medical records of all patients admitted under medicine unit at Kasturba Hospital, Manipal with a diagnosis of complicated urinary tract infection, during the year 2011 (Jan 2011 to Dec 2011).

Mean age of our study population was found to 56.1±14.9 years. The probability of the occurrence of complicated UTI was found to be higher in the age group of 49-58. This may be probably due to the increase in proportion of Diabetes Mellitus in this age group (66.7%). The age group most affected by cUTI in this study was found to be similar to the study conducted by Sushma Muraraiah *et al* [7] and an Indian study on complicated UTI conducted by Mohan J et al[8], in which the average age group was found to be 41-60 years. In our study population, 54.2% were found to be males; which is controversial to studies done by KC. Arul Prakasam et al[15] in which females were found to be more susceptible to cUTI. This may be because pregnant females with complicated UTI who were admitted in the OBG department were excluded from our study.

Hospital admission is required for patients with complicated UTI, because of the requirement of IV antibiotics. Our study revealed that the average days of hospitalization for patients with complicated UTI were 10.72±5.2 days.

In our study, risk factors like Diabetes Mellitus (62%), renal failure (20.6%), Benign Prostatic hypertrophy (8.8%), Urolithiasis (7.7%) are associated with Complicated UTI. In a similar study conducted by, Sushma Muraraiah et al [7], Type 2 Diabetes mellitus, followed by structural abnormality of genitourinary tract and chronic kidney disease, were the commonly observed conditions for complicated UTI. Whereas in a study conducted by KC. Arul Prakasam et al[9], smoking appears to be the predominant risk factor followed by Diabetes (34.3%) and BPH (17.1%) for UTI in males. 6.7% of the cases were presented with recurrent UTI in our study. In a similar study by Mahesh E et al [13], 8.7% of the cases had presented with recurrent UTI.

In our study, the most frequently observed organism was found to be *Ecoli* (43.8%), followed by ESBL *Ecoli* (31.3%), *Klebsiella* (3.0%) and *Enterobacter* (2%). This collaborates with studies conducted in many other regions. According to the study conducted by Arslan et al [10], *E coli* were the causative agent in 78% of cUTI, 12% of those being ESBL *E coli*. In the study conducted by Chen et al [11] in Taiwan, *E coli* were found to be one among the most common uropathogens. Similar results were obtained in a review conducted by Lindsay E. Nicolle [12], in Canada, in which *Ecoli* (21%-54%) was found to be the most prevalent organism causing cUTI worldwide, followed by *Klebsiella* (1.9-17%), and *Staphylococcus aureus*. In one other similar study conducted by Mahesh E et al [13], in an Indian setting, *Ecoli* (65.7%) was the most frequently isolated organism followed by *Klebsiella* (15.9%) and Pseudomonas (11.4%).

According to our study, *Ecoli* was found to be highly sensitive to, Cefoperazone-Sulbactum, followed by Amikacin, Imipenem/Meropenem in all cases. In a similar study conducted by Sushma Muraraiah et al [7], the antimicrobial sensitivity pattern showed the maximum susceptibility of *Ecoli* to Piperacillin-Tazobactum, followed by cefoperazone-sulbactum and amikacin. In this study, *Ecoli* was found to be most resistant to Amoxicillin-Clavulanate(16.2%), Cotrimoxazole (16.2%) and Cefuroxime (10.8%).

ESBL *Ecoli* was found to have varying degrees of resistance to different antibiotics but was mostly sensitive to cefoperazone-sulbactum (1.1% resistant) and imipenem/meropenem (3.2% resistant). In this study, the higher proportion of ESBL *Ecoli* strains resistant to amoxicillin (76.8%), amoxicillin-clavulanate(75.8%) and gentamycin(54.3%) is similar to what was reported by Aboderin and coworkers [14]. Similarly, in the study conducted by Mahesh E et al[13], all the ESBL E coli isolates were highly sensitive to carbapenems, and 52% of the ESBL *Ecoli* strains were resistant to first generation fluoroquinolones, amikacin, gentamicin and nitrofurantoin. The resistance to third generation cephalosporins ,i.e, ceftriaxone (75.8%), cefuroxime (75.8%), cefepime(72.6%) was also significantly high which collaborates with the study conducted by Randrianirina and coworkers [15] which reports an increasing resistance rate to third generation cephalosporins in their study. Resistance to trimethoprim-sulphamethoxazole (63.2%) in this study was similar to the results obtained from other studies conducted in United

States and worldwide [16,17] which indicate the emergence of trimethoprim-sulphamethoxazole resistance in a significant percentage (>20%) of community acquired UTI isolates. The findings of this study indicate that beta-lactams, trimethoprim-sulphamethoxazole, nitrofurantoin should not be used as empirical treatments of cUTI due to their high rates of resistance.

In our study, most of the patients were treated with a single drug regimen (31.3%) or a dual drug regimen (38.03%). Patients with co morbidities present were on the three drugs or more regimens. In our study, dual drug regimens were shown to have more significant outcomes as compared to other drug regimens. According to our study, no difference between the prescribing patterns for males and females was found and cephalosporin (79.1%) comprise of the most commonly prescribed AMA followed by extended spectrum penicillin (20.2%). A study conducted by Chowta M. et al [17] also showed similar prescribing patterns. In our study it was also found that, nitrofurantoins are seldom given as monotherapy, mostly they are given along with third generation cephalosporin and oxazolidinones and glycopeptides are the least prescribed antibiotics for complicated UTI. They are usually given if other co morbid conditions are present along with UTI like sepsis, endocarditis, pneumonia or abscesses whereas penicillin and cephalosporin constituted 57.73% and 42.27% respectively as highlighted in a similar study conducted by Sachidananda Adiga MN et al[18].

Out of the 297 patients enrolled in our study, 89.6% of the patients responded to the treatment and showed complete improvement, whereas, for 9.4% of the study population, the condition was unchanged and 1% expired due to failure of therapy.

CONCLUSION

A drug utilization pattern of antibiotics for cUTI in about 297 inpatients above 18 years was carried out. Diabetes Mellitus followed by renal failure was found to be the most common predisposing factors responsible for cUTI and urosepsis was found to be the most common complication associated with cUTI. Among the different organisms isolated, *Ecoli* and ESBL *Ecoli* were the most commonly found organisms. The antibiotic sensitivity profile of microorganisms causing cUTI showed that *Ecoli* was sensitive to majority of the antibiotics and ESBL Ecoli was most sensitive to cefoperazone-sulbactum followed by amikacin and carbapenems. Dual drug regimen was the most preferred for the treatment of cUTI when compared to single and three or more drug regimens. Among the different category of antibiotics, cephalosporins were majorly prescribed and macrolides were the least prescribed antibiotics. The broader outcome of this study would be the potential utility of this data in designing strategies both at the level of physicians and the administrators for rational prescribing and policy decisions respectively. The limitations of this study were small sample size and the unavailability of culture reports for many patients.

REFERENCES

[1] Nicolle LE. Can J Infect Dis Med Microbiol 2005;16(6): 349-60.

[2] Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Infection 2007;35(3):150–53.
[3] Zhanel GG, Hisanaga TL, et al. Int J Antimicrob Agents 2006;27: 468 –75.
[4] Gupta K, Scholes D, Stamm WE. JAMA 1999;281: 736 – 738.
[5] Livermore DM, Canton R, Gniadkowski M et al. J Antimicrob Chemother 2007; 59: 165–74.
[6] Introduction to Drug Utilization Research/WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistic methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, *World Health Organization*, 2003, Oslo, Norway.
[7] Mohan J, Gopal KM, Meganathan M, Sasikala P, Gowdhaman N, Balamurugan K et al. Global J Pharmacol 2011;5(1): 01-03.
[8] Prakasam AKC, Kumar DKG and Vijayan M. Int J Res Pharm Biomed Sci 2012;3(3):1125-130.
[9] Arslan H, Azap OK, Ergonul O, Timurkaynak F. J Antimicrob Chemother 2005;56: 914 – 918.
[10] Chen SS, Chen KK, Lin AT, Chang YH, Wu HH, Hsu TH, et al. Zhonghua Yi Xue Za Zhi (Taipei). 1998;61(11):651-6.
[11] Nicolle LE. J Infect Dis 2001;183(1):S5–8.
[12] Mahesh E, Ramesh D, Indumathi VA, Punith K, Kirthi Raj and Anupama HA. Al Ameen J Med Sci 2010; 3(2):120-27.
[13] Aboderin OA, Abdu AR, Odetoyin BW, Lamikanra A. J Natl Med Assoc 2009;101:1268 – 73.
[14] Randrianirina F, Soares JL, Carod JF, Ratsima E, Thonnier V, Combe P et al. J Antimicrob Chemother 2007;59: 309-12.
[15] Akram M, Shahid M, Khan AU. Ann Clin Microbiol Antimicrob 2007;6: 4 .
[16] Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. Antimicrob Agents Chemother 2002;46:2540–45
[17] Mukta N. Instasci J Med Sci Clin Res 2011;1(1):13-19.
[18] Adiga MN, Alwar MC, Pai M, Adiga US. Online J Health Allied Sci 2009;8(4):10