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Research Article

ANTIBIOTIC RESISTANCE PATTERN OF UROPATHOGENS, IN A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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ABSTRACT
Background: Urinary tract infections are extremely common in outpatients as well as hospitalised patients. The distribution of uropathogens and their susceptibility pattern to antibiotics varies regionally and over time. Therefore, the knowledge of frequency of causative microorganisms and their susceptibility to various antibiotics are necessary for better therapeutic outcome.
Aim: 1) To study the occurrence and distribution of uropathogens
2) To study their resistance to antibiotics
Material and Methods: A retrospective study was undertaken for a period of one year, from September 2017 to August 2018. The culture and sensitivity data of uropathogens from suspected cases of UTI were collected from the records of the Department of Microbiology for the study period. Urine samples were processed for microscopy and culture as per standard protocol. The organisms were identified by standard methods.
Statistical Analysis: Data was analysed using SPSS version 22. Percentage analysis of the data was given.
Conclusion: The most common uropathogen isolated from urine samples during the study period was *Escherichia coli*. Most isolates show high susceptibility to nitrofurantoin, gentamicin, amikacin, imipenem and meropenem, which can be considered appropriate for empirical therapy of UTI. A large proportion of the isolated organisms show resistance to ampicillin, amoxyclav and third generation cephalosporins and have limited value in the treatment of UTI. Therefore, routine monitoring of the type of uropathogens and their antibiotic resistance will help the clinician to formulate appropriate antibiotic policy and which will help achieve good therapeutic outcome.

Keywords: *antibiotic resistance, susceptibility testing, tertiary care hospital, uropathogen*

INTRODUCTION
Urinary tract infections (UTI) are one among the most common infections encountered in outpatients as well as hospitalized patients. It accounts for 8.3 million hospital visits and more than one million hospitalizations per year around the world (Stamm, 2001). 35% of healthy females suffer from symptoms of UTI at some point of their lives (Haque *et al*., 2015).

UTI is a broad term covering a number of clinical conditions including cystitis, pyelonephritis, bacteriuria and candiduria. The common symptoms of UTI include: burning micturition, urgency, low grade fever, bloody or cloudy urine, pain in the groin and lower abdomen. However, asymptomatic bacteriuria is also frequently seen in clinical practise. Kidney involvement is comparatively less common, but can lead to severe sepsis. Paediatric patients may present with pyrexia of unknown origin, change in the smell or colour of urine, vomiting, fussiness or change in appetite (Sobel, 2000; Mamuye, 2016).

Risk factors for UTI are: a previous episode of UTI, sexual activity(with a new sexual partner), changes in vaginal flora or acidity caused by menopause or use of spermicides, pregnancy, old age, prolonged bed rest or reduced mobility, urinary incontinence or urinary catheterisation, kidney stones, prostate enlargement. UTI is common among women, which is due to the anatomical predisposition and other host factors. An episode of UTI is usually preceded by vaginal colonization with uropathogens. Sexual

activity, pregnancy and obstruction are other factors that lead to the increased occurrence of UTI among women (Stamm, 2005).

Majority of UTI are attributed to gram negative bacteria like *Escherichia coli*, Klebsiella spp., *Proteus mirabilis*, *Pseudomonas aeruginosa*, Acinetobacter spp. and Citrobacter spp. The primary pathogen in both, community acquired and nosocomial UTI is *Escherichia coli* Gram positive organisms like Staphylococcus spp., Streptococcus spp. and Enterococci spp. are also commonly seen (Haque *et al.*, 2015; Somashekhara *et al*., 2014; Mamuye, 2016).

The antibiotics which are used to treat UTI depends on the age, sex, co-morbidities, underlying diseases (like diabetes mellitus), pathogens involved, severity of the infection, and antibiotic susceptibility pattern in that particular region. The Infectious Diseases Society of America (IDSA) guidelines recommend selection of antibiotic agent depending on effectiveness of the agent, resistance rates, risk of adverse effects and the propensity to cause collateral damage. Additionally, physicians should consider cost, availability and host specific factors like history of drug allergy, previous history of antibiotic intake, presence of diabetes mellitus, neurogenic bladder etc. (IDSA guidelines, 2010) (Mamuye, 2016).

The first line of drugs recommended by IDSA includes nitrofurantoin, fosfomycin and trimethoprim or sulphamethoxazole. Second line drugs for management of UTI are fluoroquinolones. The third line drugs for management of UTI include: amoxicillin- clavunate, cefpodoxime and other beta lactams with nitrofurantoin. Fluoroquinolone are used for the empiric therapy of UTI as they have good bacteriological and clinical cure rates. It also has low rates of resistance, among commonly isolated uropathogens (Gupta *et al*., 2002). The extensive use of antibiotics has resulted in the development of antibiotic resistance worldwide. With the rise in antibiotic resistance, treating a case of UTI is a therapeutic challenge for the physician (Kumar *et al*., 2006).

The distribution of uropathogens and their susceptibility pattern to antibiotics varies according to the type of uropathogen isolated, varies according to the region and according to the hospital (primary/ secondary/tertiary/quaternary care hospital). The susceptibility pattern of uropathogens also changes over time. Therefore, the knowledge of the occurrence of the uropathogens and their susceptibility to various antibiotics are crucial to analyse the development of resistance that has occurred over time. It is also helps in the formulation of optimal empirical therapy of UTI (Mamuye 2016, Somashekhara *et al*., 2014). This also helps in establishing the antibiotic policy and good infection control practices in a given hospital.

OBJECTIVES

1) To study the occurrence and distribution of uropathogens.

2) To study the resistance of uropathogens to various antibiotics.

MATERIALS AND METHODS

A retrospective study was undertaken for a period of one year from September 2017 to August 2018. The Institutional Ethical committee approval was obtained before the commencement of the study. The reports of urine culture and sensitivity were collected from the records of Department of Microbiology during the study period. A total of 6046 samples were analysed for culture and sensitivity. Midstream urine samples were collected in sterile containers and processed for microscopy and culture as per standard protocol. Blood agar and Mac Conkey agar were used for culture. The urine sample was inoculated on the above culture plates with a standard loop. These culture plates were incubated overnight at 37^0C. Kass' concept of significant bacteriuria was used to differentiate UTI from contamination. A growth of more than 10^5 colony forming units/ml was considered as significant bacteriuria. The organisms were identified by standard methods (Collee *et al.*, 1996).

Antibiotic susceptibility testing:

Kirby Bauer's disk diffusion method was used for antimicrobial susceptibility testing as prescribed by National Committee for Clinical Laboratory Standards (presently called as Clinical Laboratory Standard Institute, 2009). The antimicrobial disks used for the disk diffusion method were obtained from Hi-Media labs, Mumbai, India. For quality control, *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC 29212, *E. coli* BCC 2132 (ESBL producer), and *E. coli* ATCC 35218 (non-ESBL producer) were used .Different panels of antibiotics were used to test, different groups of uropathogens. The antimicrobial disks used for the disk diffusion method included : amikacin, amoxiclav, ampicillin, aztreonam, cefipime, ceftazidime, cefotaxime, cefoxitin, ceftriaxone, ciprofloxacin, clindamycin, colistin, cotrimoxazole, doxycycline, erythromycin, gentamicin, imipenem, levofloxacin, linezolid, meropenem, netilmycin, nitrofurantoin, norfloxacin novobiocin, oxacillin, piperacillin- tazobactum, teicoplanin tegicycline, tobramycin and vancomycin.

Detection of ESBL by NCCLS phenotypic method

Disk diffusion was done using ceftazidime (30 µg) and ceftazidime – clavulinic (30/10µg) acid. This test was done on Mueller-Hinton agar plate. An increase in the zone of diameter of ceftazidime by ≥ 5-mm, tested with ceftazidime – clavulinic acid versus its zone when tested with ceftazidime only, was considered indicative of ESBL production. For quality control K. *pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 were used.

STATISTICAL ANALYSIS

Data entry was done on Microsoft excel. Data was analysed using SPSS version 22. Percentage analysis of the data was given.

RESULTS

From September 2017 to August 2018, 6046 urine samples were examined. No growth was seen in 81.97% (4956/6046) of the urine samples. Mixed growth was seen in 12.52 %(757/6046) of the samples (Figure 1). Only 5.5 % (333/6046) of the urine samples yielded growth.

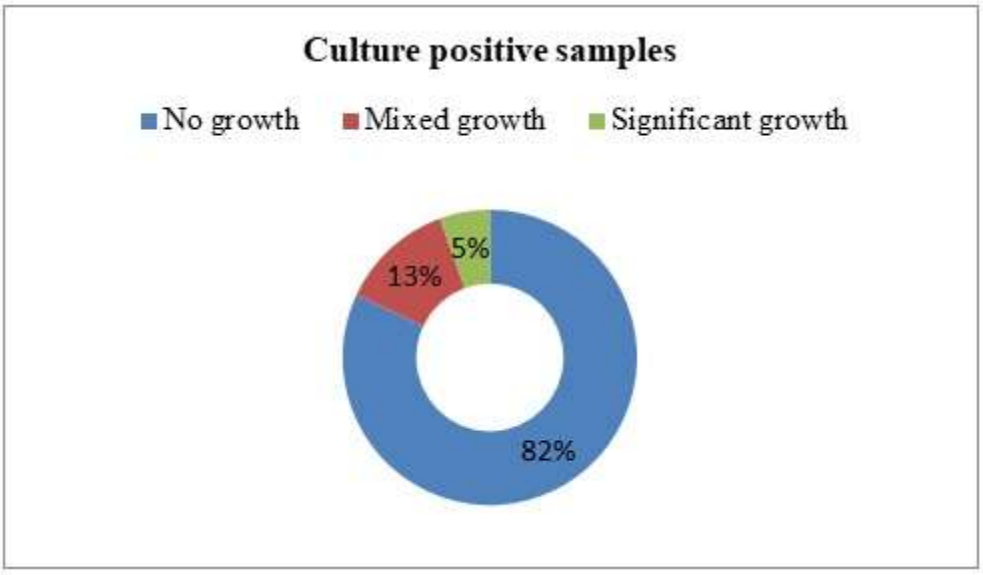

Figure 1: Number of culture positive samples.

Of the 333 samples which yielded growth, 77.17% was constituted by gram negative uropathogens and 22.8% by gram positive uropathogens.

Out of 6046 suspected cases of UTI, 56.36% (3408/6046) were females and 43.63% (2638/6046) were males. (Figure 2)

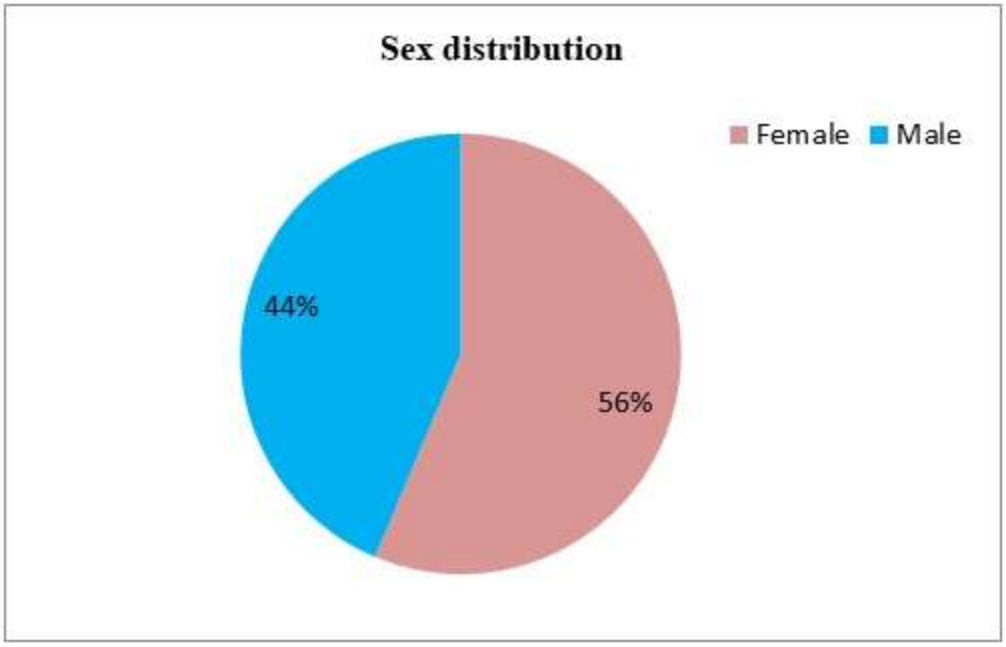

Fig 2: Sex distribution of the study population

The age range was from 1 day to 80 years. Majority (53.47%,3233/6046) in the study population belonged to age group 18-40 years .Middle aged patients constitutes 21.30% (1288/6046)of the study subjects, while elderly (60 years and above) accounted to about 17.78%(1075/6046) of the total patients. Paediatric cases formed 7.44 %(450/6046) of the study group. (Figure 3)

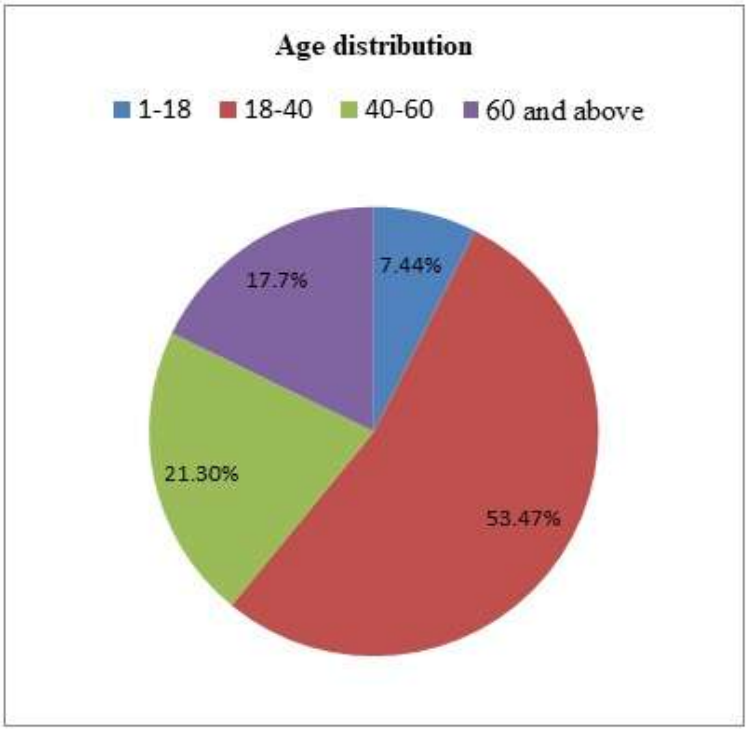

Fig 3: Age distribution of study population

Highest number of suspected UTI cases were reported from the Department of Medicine (2592/6046, 42.87%) followed by OBG (1616, 26.72%) and Surgery (968, 16.01%).6.96 %(421/6046) of the cases were reported from Paediatric department and, 3.98%% (241/6046,) from Orthopaedics. The remaining branches including Venereology, Emergency Medicine, Critical Care Unit, Pulmonology formed 3.44% of the total cases (Figure 4).

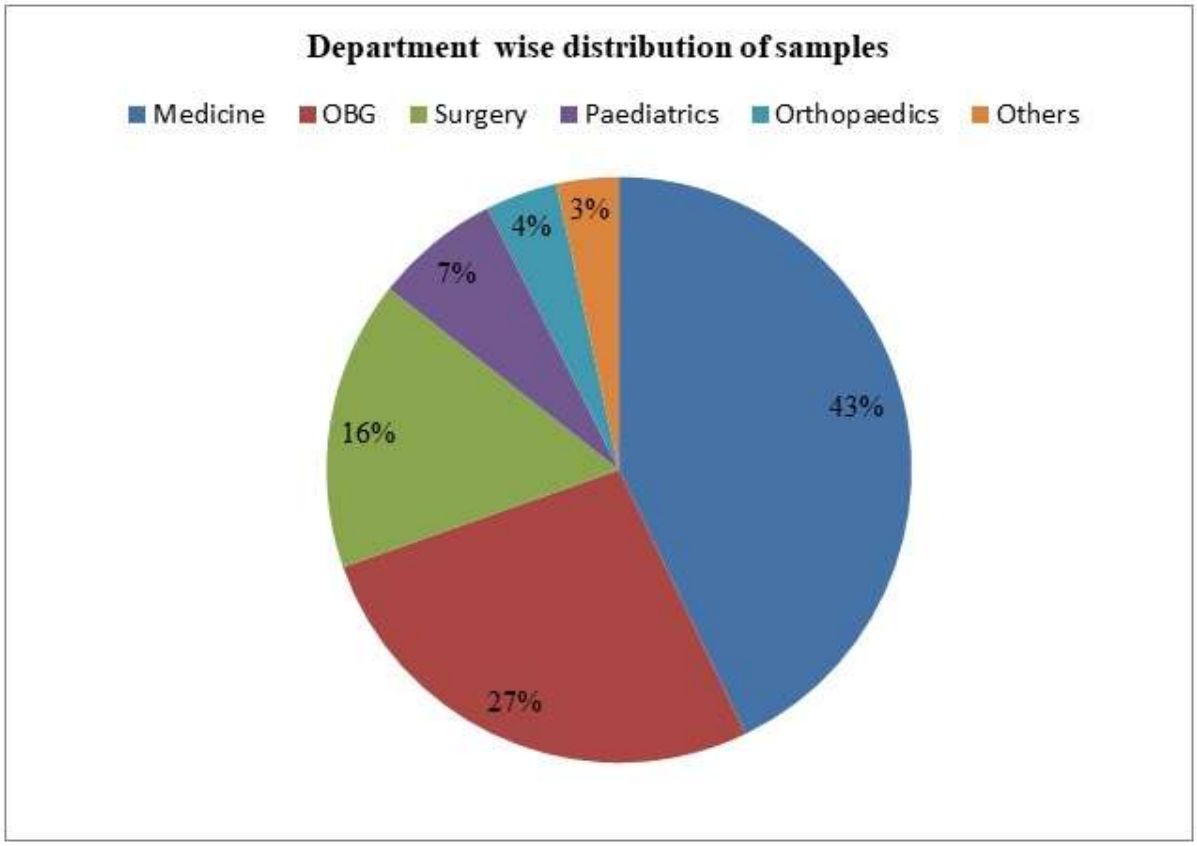

Fig 4: Department wise distribution of samples

Out of the total isolates (n=333), the predominant pathogen was *Escherichia coli* (177/333, 53.15%).It was succeeded by Klebsiella species (53 /333, 15.92%) and *Staphylococcus aureus* (50/333, 15.02 %).4.5% (15/333) isolates were Enterococci spp. and 3 % (10/333) of the isolates were *Citrobacter freundii*. *Proteus mirabilis* and *Pseudomonas aeruginosa* isolates were found in 9 (2.70%) and 7 (2.10%) isolates respectively. 8 (2.40%) isolates were identified as Candida spp. Streptococcal spp. (0.90%, 3/333) and Acinetobacter spp. (0.30%, 1/333) were identified in less than 1% of the samples (Figure 5).

ANTIOBIOTIC SUSCEPTIBILITY TESTING

Escherichia coli was the predominant uropathogen found in this study. It constituted for 53% of the total isolates. Resistance was seen to amoxicillin- clavulanic acid (88.71%), ampicillin (79.84%), cefotaxime (76.61%), ceftriaxone (75.00%), ceftazidime (72.58%), and ciprofloxacin (54.84%). It was susceptible nitrofurantoin (84.68%), meropenem (81.45%), gentamicin (80.65%), amikacin (78.23%), imipenem (66.94%) and cotrimoxazole (54.03%) (Figure 6). Among the 177 *Escherichia coli* isolates, 53 (29.94%) were ESBL producers.

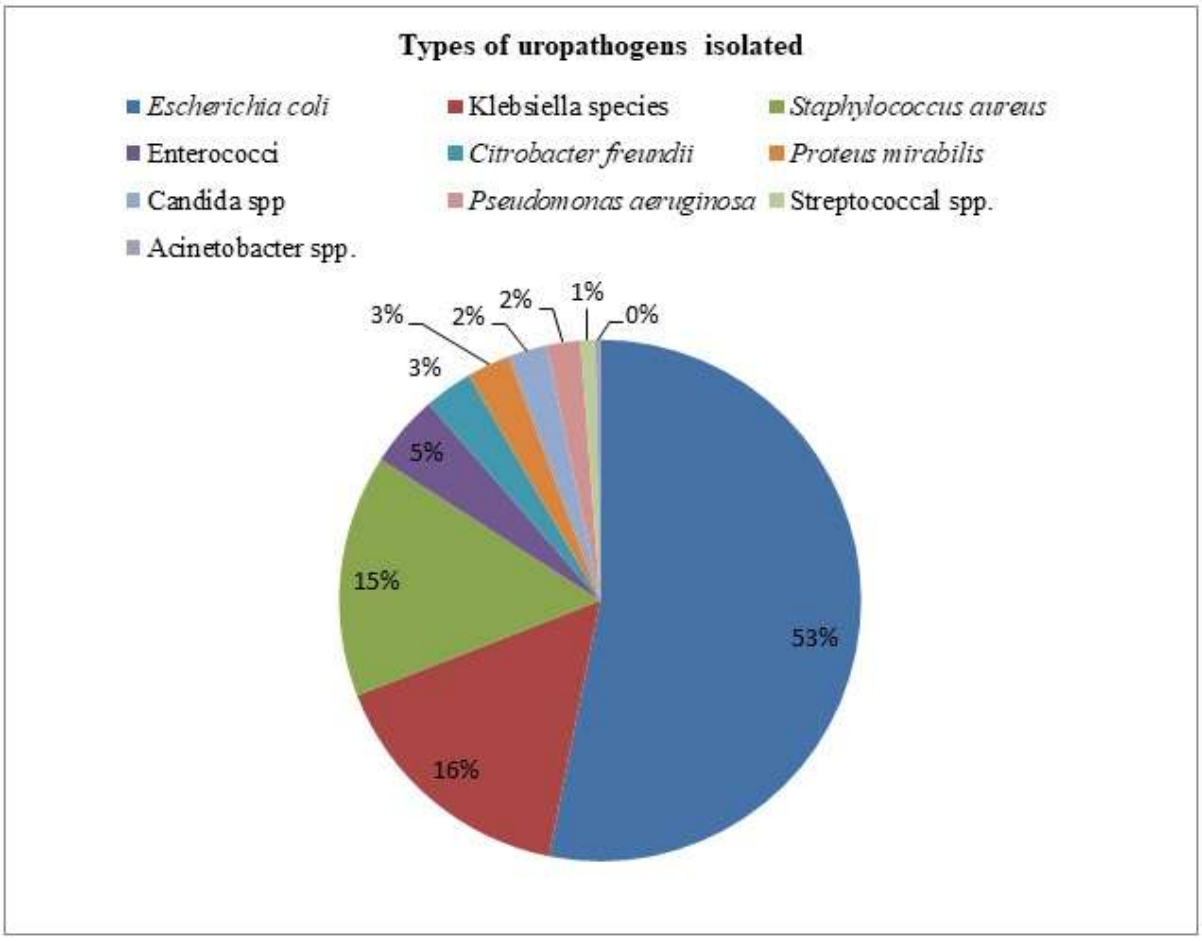

Fig 5: Types of uropathogens isolated

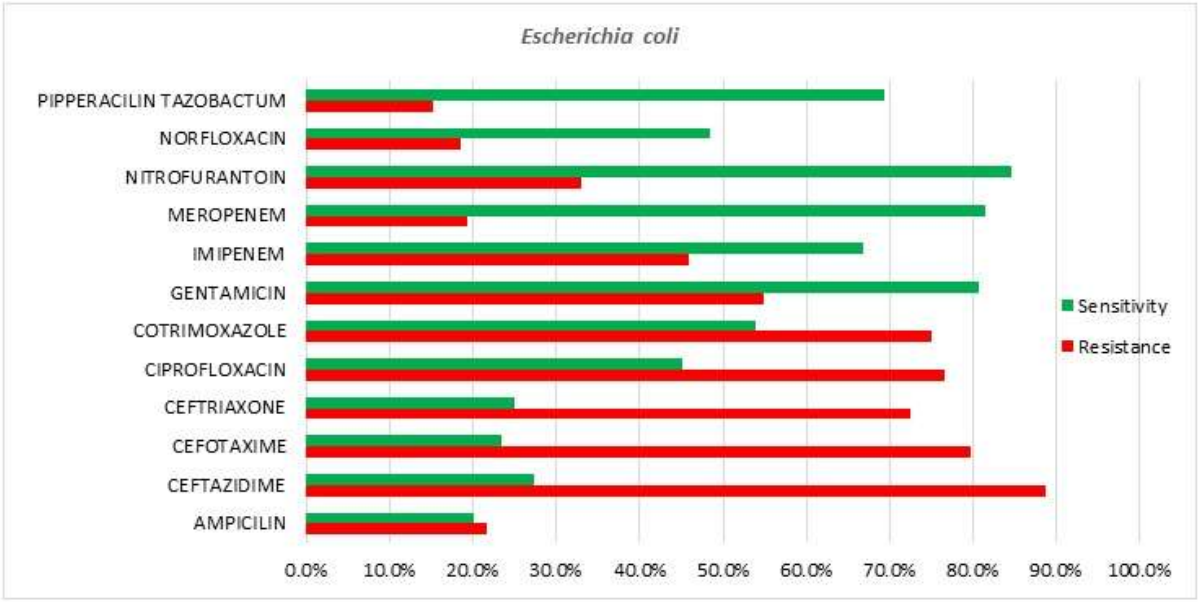

Figure 6: Antibiotic susceptibility pattern of *Escherichia coli.*

In Klebsiella spp. resistance was observed against, amoxicillin - clavulanic acid (93.55%), ampicillin (90.32%), cefotaxime (67.74%), ceftriaxone (67.74%) and ceftazidime (61.29%).It was susceptible to meropenem (70.97%), gentamicin (67.74%) and imipenem (61.29%) (Figure 7). Among the 53 Klebsiella spp. isolates, 10(18.86%) were ESBL producers.

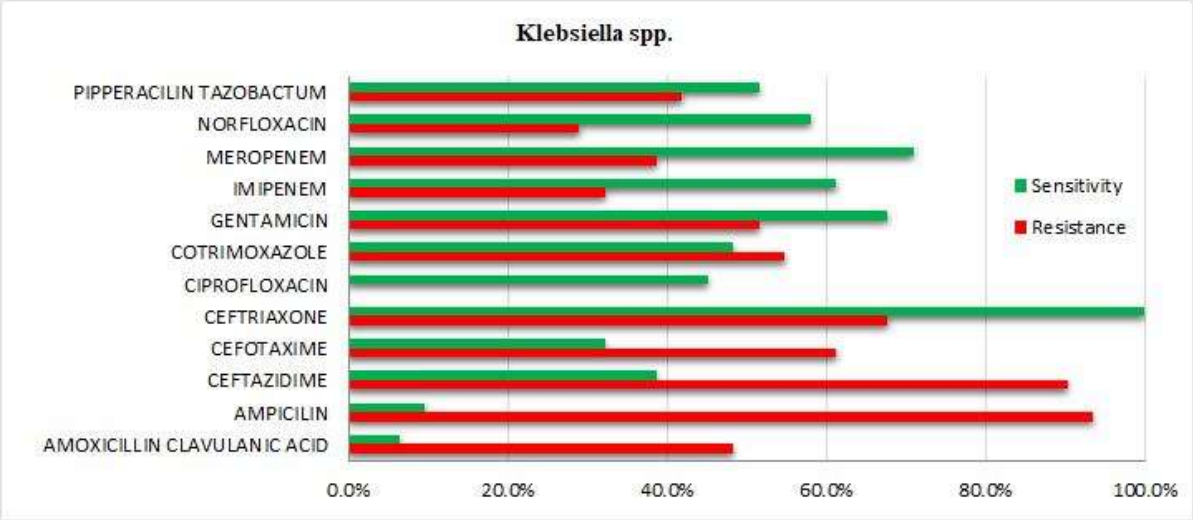

Figure 7: Antibiotic susceptibility pattern of *Klebsiella spp.*

Staphylococcus aureus showed 77.78% resistance to amoxicillin-clavulanic acid, 66.67% resistance to cefoxitin. 60% resistance was seen against novobiocin and oxacillin.60% (30/50) of the isolates were MRSA positive. 88.89% sensitivity was seen to vancomycin, 84.44% sensitivity to gentamicin and, 82.22% sensitivity was seen to linezolid, and 75.56% sensitivity to clindamycin (Figure 8).

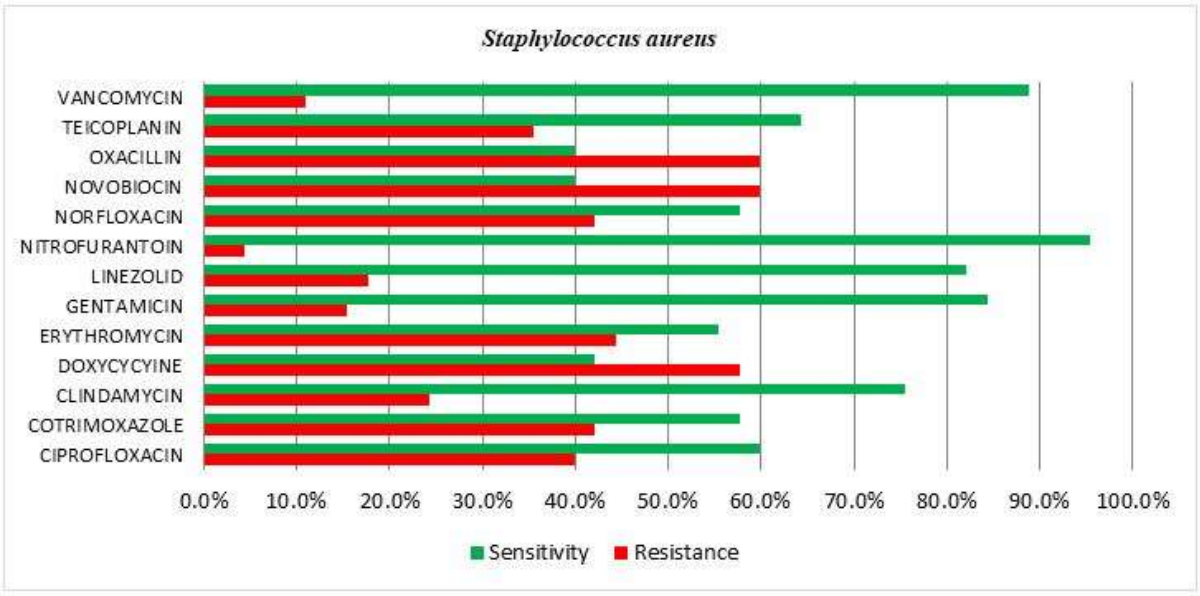

Figure 8: Antibiotic susceptibility pattern of *Staphylococcus aureus.*

In Enterococcus spp. resistance was seen to amoxicillin clavulanic acid (90.91%), ampicillin (81.82%) and ciprofloxacin (90.91%). It showed 81.82% sensitivity to vancomycin, tetracycline and nitrofurantoin. It showed 72.73% sensitivity to linezolid and gentamicin (Figure 9)

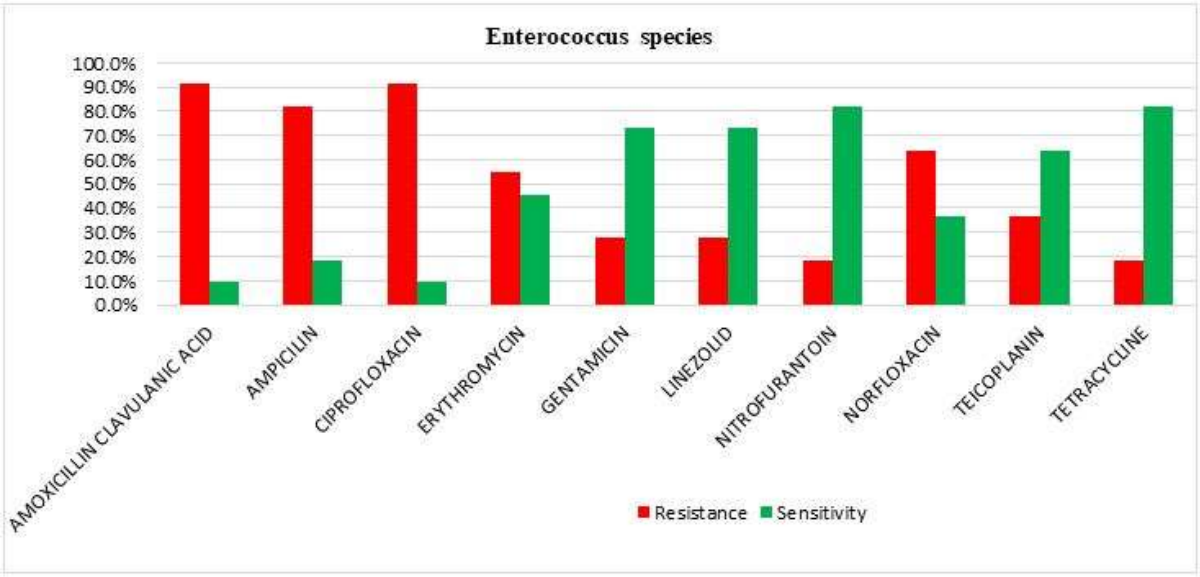

Figure 9: Antibiotic susceptibility pattern of Enterococcus spp.

Of the 10 isolates of *Citrobacter freundii* that were isolated during the study, 100% resistance was observed against amoxicillin-clavulanic acid. It showed 83.33% resistance to ampicillin and cotrimoxazole. 66.67% resistance was seen to ceftazidime, ceftriaxone and ciprofloxacin.66.67% sensitivity was seen towards piperacillin - tazobactum and gentamicin (Figure 10).

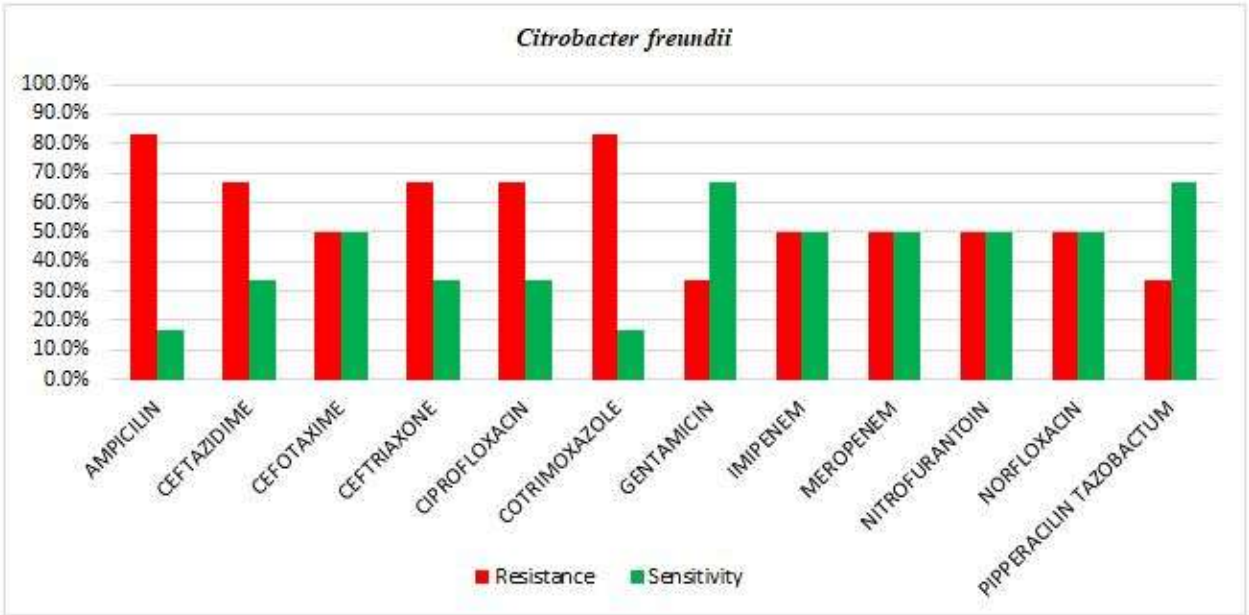

Figure 10: Antibiotic susceptibility pattern of *Citrobacter freundii*.

Among the *Proteus mirabilis* isolates , 71.43%resistance was observed against amoxycillin- clavulanic acid ,ampicillin and nitrofurantoin .It showed 85.71% sensitivity to imipenem, meropenem and, amikacin. It showed 71.43% sensitivity to ceftazidime, cefotaxime and piperacillin- tazobactum (Figure 11).

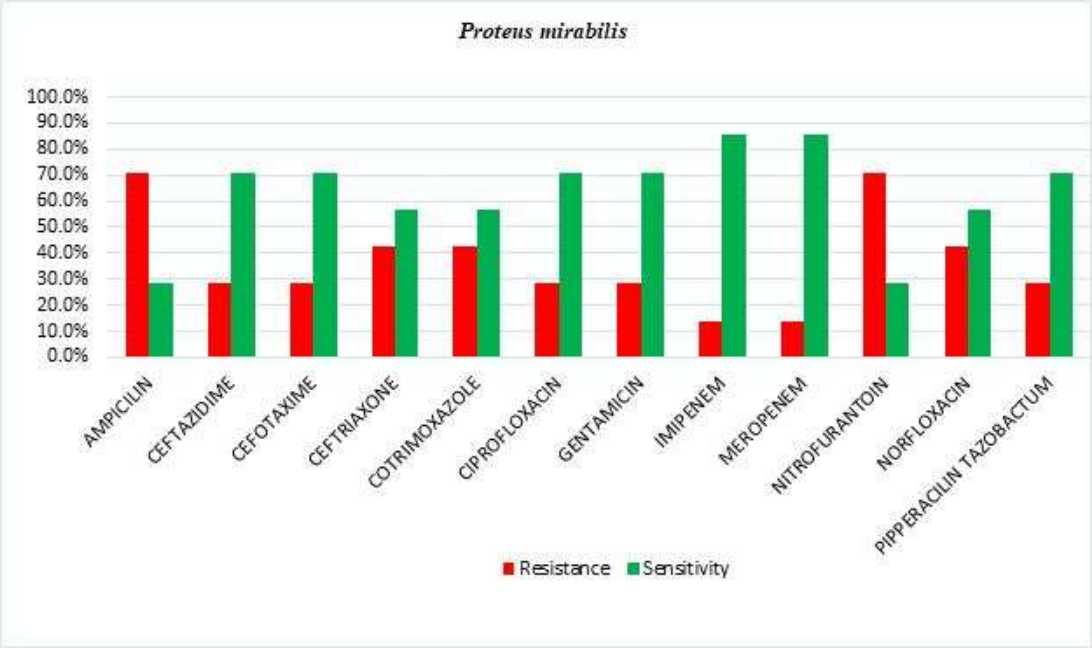

Figure 11: Antibiotic susceptibility pattern of *Proteus mirabilis*.

Pseudomonas aeruginosa strains showed 100% sensitivity to aztreonam, amikacin and norfloxacin. It showed 83.33% sensitivity to gentamicin imipenem meropenem and ciprofloxacin. It showed 66.67% sensitivity to ceftazidime, cefipime, colistin, levofloxacin, netilmycin and tobramycin.However, resistance was seen to tegicycline (66.67%) (Figure 12).

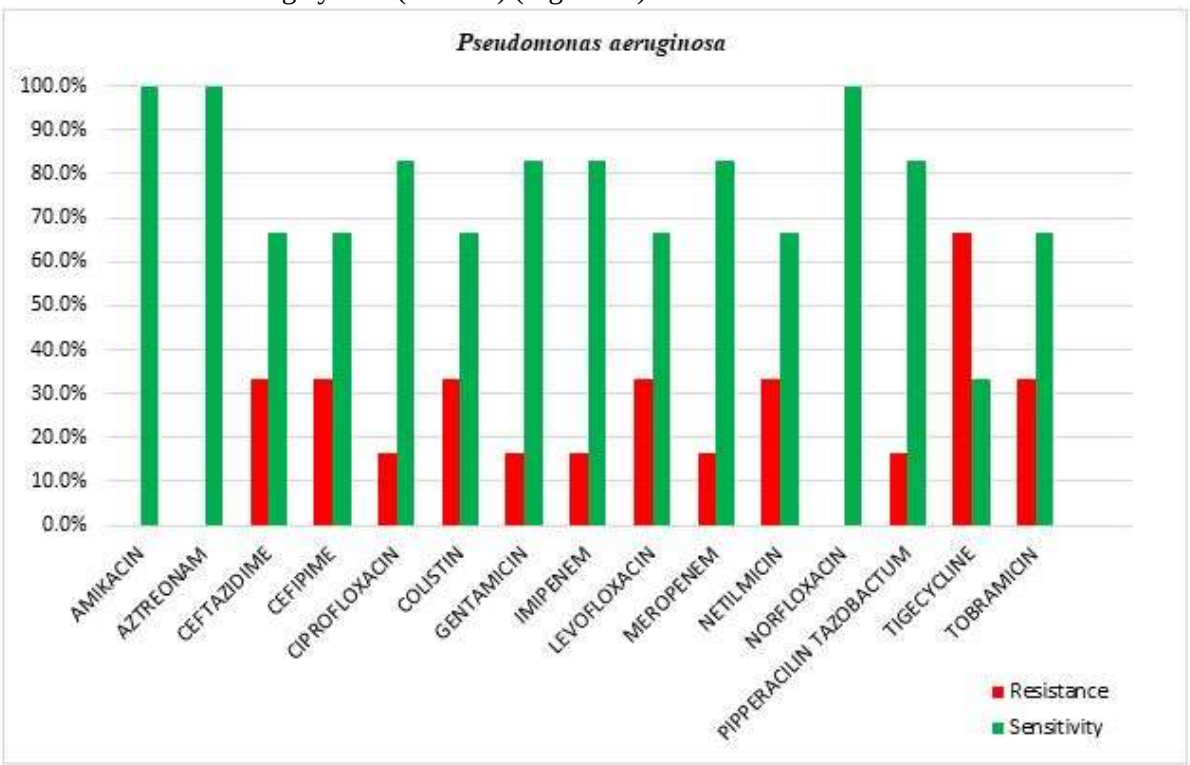

Figure 12: Antibiotic susceptibility pattern of *Pseudomonas aeruginosa*.

Streptococci species showed 100% resistance to cefoxitin and amoxiclav. It showed 100% sensitivity to nitrofurantoin and vancomycin. (Refer figure 13)

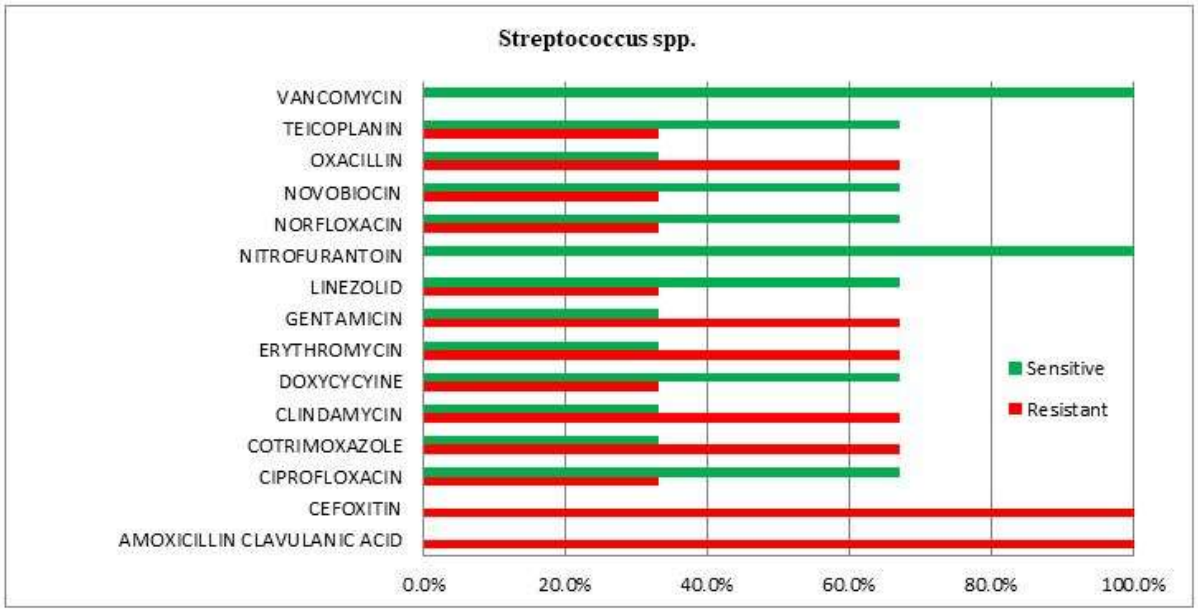

Figure 13: Antibiotic susceptibility pattern of Streptococcus spp.

In Acinetobacter spp. 100% resistance was seen to amoxicillin - clavulanic acid, ampicillin, cefuroxime, nitrofurantoin, piperacillin- tazobactum. It showed 100% sensitivity to amikacin, ceftazidime, cefotaxime, ceftriaxone, cotrimoxazole, ciprofloxacin, gentamicin, imipenem, meropenem and norfloxacin (Figure 14)

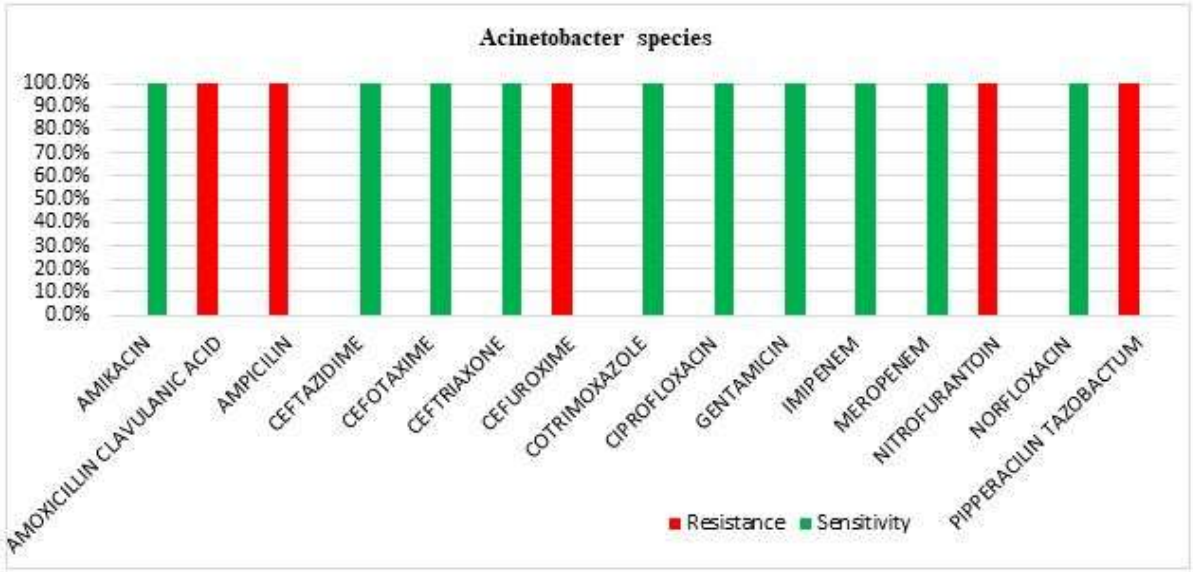

Figure 14: Antibiotic susceptibility pattern of Acinetobacter spp.

DISCUSSION

In the current study, gram negative organisms were the most common causative agents of UTI and constituted almost 80% of the isolates. The spectrum of isolates of uropathogens isolated in the current study is very similar to studies done in other regions of India, Bangladesh, Nepal and Ethiopia (Akram M, 2007; Somashekhara *et al*., 2014; Haque *et al*., 2015; Ahmed, 1996; Rabindra, 2013; Mamuye, 2016;). In

this study, the majority of pathogens were isolated from the middle aged (40-60) years adult patients (53.47%). UTI was more common in women (56%), as reported in studies conducted by Akram *et al*., 2007; Haque *et al*., 2015; Mamuye, 2016 and Somashekhara *et al*., 2014 . The uropathogens isolated in this study are *Escherichia coli* (53.15%) *Klebsiella* (15.92%) and *Staphylococcus aureus* (15.02%).Enterococci spp. (4.5%) *Citrobacter freundii* (3%). *Proteus mirabilis* (2.7%) and *Pseudomonas aeruginosa* (2.10%).Streptococcal spp. and Acinetobacter spp. were identified in less than 1% of the samples. This is similar to the studies conducted by Akram *et al*., 2007; Haque *et al*., 2015; Mamuye Y, 2016 and Somashekhara *et al*., 2014.

There is a growing threat of antibiotic resistance worldwide and it is increasing over the years. However this antibiotic resistance varies from country to country and region to region (Akram *et al*., 2007).In our study *Escherichia coli* was the predominant uropathogen. It showed (79.84%) resistance to ampicillin. This finding is similar to the studies conducted by Somashekhara *et al*., 2014, Mandal *et al*., 2019, Gupta, 2007, Manjunath, 2011 and Gupta *et al*., 2007. Ampicillin resistance as high as 96.2% has been reported in a study conducted by Murugan, 2012 (Figure 6). In a study conducted in Southern India by Somashekhara *et al*., 2014 reported 75% resistance to amoxycillin-clavulanic acid in *Escherichia coli*. In studies conducted by Krishna *et al*., 2013 and Shalini *et al*., 2011, report 72% and 64.3% resistance to amoxycillin-clavulanic acid respectively. However in our study, resistance to amoxycillin-clavulanic acid is 88.71%, which his high when compared to the above mentioned studies (Figure 6).

Escherichia coli, Klebsiella spp. and *Citrobacter freundii* showed resistance to third generation cephalosporins. This finding is similar to the studies conducted by Mamuye, 2016; Mandal *et al*., 2019.In our study, 29.94% of *Escherichia coli and 18.86% of* Klebsiella spp. are ESBL producers. In a study conducted by Akram *et al*., 2007, 34.42% of *Escherichia coli and 27.3% of* Klebsiella spp. were ESBL producers, which is slightly higher than our stud. (Figures 6, 7, and 10) In our study, 60% (30/50) of the *Staphylococcus aureus* were MRSA. There is 11.11% resistance observed to vancomycin (Figure 8). This is of grave concern, as the clinicians may have to use third generation cephalosporins and other beta–lactum drugs with a lot of caution.

In our study, both *Escherichia coli* and Klebsiella spp. showed good susceptibility to imipenem, meropenem, gentamicin, nitrofurantoin and norfloxacin. When compared to Klebsiella spp. (51.61%), *Escherichia coli* (69.35%) showed good susceptibility to piperacillin-tazobactum. Klebsiella spp. was more resistant to imipenem (38.71%) and meropenem (29.03%) when compared to *Escherichia coli* (33.06% and 18.55% respectively) (Figures 6, 7).

With regards to nitrofurantoin, only *Escherichia coli* (84.68%) *and Staphylococcus aureus* (95.56%) showed good susceptibility. Low resistance to nitrofurantoin was observed in a study conducted by Haque R *et al*., 2015; Mandal J *et al*., 2019.With regards to norfloxacin, both *Pseudomonas aeruginosa* and Acinetobacter spp. showed 100% sensitivity (Figures 12 and 14). *Pseudomonas aeruginosa* also showed 100% sensitivity to amikacin and aztreonam.

In our study, both Klebsiella spp. (54.84%) and *Escherichia coli* (54.84%) showed similar resistance to ciprofloxacin.With ciprofloxacin, the following uropathogens showed good susceptibility: Acinetobacter spp. (100%), *Pseudomonas aeruginosa* (83.3%), *Proteus mirabilis* (71.43%) and *Staphylococcus aureus* (60%). A similar finding where ciprofloxacin resistance was less in *Pseudomonas aeruginosa* and Proteus spp. was observed in a study conducted by Mandal *et al*., 2019.

In this study, the gram negative isolates showed less resistance imipenem, meropenem, amikacin and gentamicin. This is probably because there is less use of these antibiotics as they are injectable antibiotics. This is similar to the finding in a study conducted by Somashekhara *et al*., 2014. The gram positive isolates showed good susceptibility to vancomycin and linezolid. However, it is recommended that the clinician pays heed to the antibiotic sensitivity report of the uropathogen, to prescribe antibiotics. The uropathogens isolated in our study show resistance to more than four antibiotics. This means that all the isolates are multi-drug resistant. This is of grave concern, as there are limited therapeutic options for

multi-drug resistant uropathogens. This will add to the problem of increasing antibiotic resistance in uropathogens, which is already a global issue.

LIMITATIONS

One of the limitations of this study was that this being a retrospective study, we were unable to look into the risk factors in the patient. Secondly, the resistance that was noted in the uropathogens was not confirmed by MIC (Minimum Inhibitory Concentration) method, E-test or by other genotypic methods.

CONCLUSION

Hence, from this study we conclude that routine monitoring of antibiotic susceptibility patterns of uropathogens is vital and it should reflect in good antibiotic prescription practices. Antibiotic susceptibility reports of uropathogens, should guide the clinicians in drawing up an appropriate antibiotic policy for our teaching hospital. An empirical therapy with careful selection of antibiotic agents is an extremely important step in preserving the long term efficacy of the antibiotics used to treat UTI. This will prevent indiscriminate use of antibiotics and prevent the further development of antimicrobial resistance.

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Conflict of interest: None

Source of support: None

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