Original Research Article

A clinical and microbiological profile of urinary tract infection in patients with chronic kidney diseases

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ABSTRACT

Background: Urinary tract infections (UTIs) are a major public health problem in terms of morbidity and financial cost in CKD patients in India. The resistance pattern of community acquired uropathogens in CKD patients has not been extensively studied. Thus, knowledge of local antimicrobial susceptibility patterns of common uropathogens is essential for prudent empiric therapy of community acquired UTIs.

Methods: It is a cross sectional study conducted in a tertiary care hospital involving 65 chronic kidney disease patients with UTI who attended general medicine OPD and those admitted in wards after fulfilling the inclusion and exclusion criteria, after obtaining written informed consent. Blood sample and urine samples were collected from these patients and sent for blood analysis, urine analysis and urine culture and sensitivity.

Results: Among 65 CKD participants with UTI who were studied, *E. coli* (47.7%) and *K. pneumoniae* (15.4%) were the most common isolates which were sensitive in order of colistin, polymyxin B, meropenem (carbapenem) and less sensitive to other commonly used antibiotics.

Conclusions: The main purpose of this study was to find the various common local uropathogens in CKD patients and their antibiotic profile which will help in formulating antibiotic therapies. As previously stated, there are very few studies regarding profile and management of UTI in CKD patients. Hence this study can throw some light into this area.

Keywords: Antibiotic sensitivity, Chronic kidney disease, Urinary tract infection

INTRODUCTION

Urinary tract infections (UTIs) stand a major public health problem in terms of morbidity as well as financial cost among urological diseases. It exceeds that of chronic renal failure even when renal dialysis and renal transplantation are included.[1] UTI estimates to 150 million per annum worldwide.[2] The main problem with current antibiotic therapies is the rapid emergence of resistance in hospitals and community.[3]

The incidence of infections is three times is larger in chronic kidney disease (CKD) patients who are not on dialysis, than the general population.[4] The higher UTI susceptibility in CKD group may be explained, in part, by a greater incidence of urinary obstruction, which in turn leads to infections, commonly due to benign prostatic hypertrophy, renal stones and urinary tract cancers. The resistance pattern of uropathogens in CKD patients is not widely studied in subcontinent like India.[5-7] It is vital to realize that there might be significant differences between several geographic areas within an enormous country like India. Since most of the UTIs are empirically treated in country like India the choice of selecting antimicrobial agent should be limited not only by the most likely

organism but also by its anticipated drug susceptibility pattern.

Thus, knowledge of local antimicrobial susceptibility patterns of common uropathogens occurring in CKD patients is essential for prudent empiric therapy of community acquired UTIs, so authors wanted to study the clinical profile and microbiological profile of UTI in CKD patients attending our hospital.

METHODS

This was a cross-sectional study, which was conducted in Pondicherry, India, a rural tertiary care hospital. Those CKD patients having signs and symptoms of UTI were the study participants. The purpose of this study was explained to each patient and a written consent was obtained from the patient prior to the commencement of the study. Also, they were also assured that, their identity would be kept strictly confidential and they have the option to refuse participation in the study. Written informed consent was obtained from the study participant prior to the interview.

Patients were advised to collect clean catch midstream urine sample in a wide mouth sterile container provided from the lab. Urine samples were sent for culture and sensitivity testing within 2 hours of voiding and was plated on the blood agar medium and cysteine lactose electrolyte deficient (CLED) using calibrated one micro litre loop and cultured semi quantitatively. Antibiotic susceptibility test was performed using Kirby-Bauer disc diffusion method according to CLSI guidelines.

A part of the fresh urine sample was also sent for microscopic analysis for deposits including pus cells, red cells, bacteria and casts. For determining the amount of pus cells, urine sample will be centrifuged at 2000 rpm for 5 minutes. Blood samples from each patient were taken for urea, creatinine, total leukocyte and platelet count which were analyzed. Creatinine clearance was found using Cockcroft-Gault formula and CKD staging was done using national kidney foundation KDOQI guidelines.

Inclusion criteria

- Patients aged above 16 years including both male and female patients,
- Patients with chronic kidney disease stage 3 to stage 5 according to national kidney foundation KDOQI clinical practice guidelines,
- Patients having symptoms of UTI like burning urination, frequency or urgency of urination, abdomen or loin pain, fever and urine culture having significant bacteriuria.

Exclusion criteria

- Patients who are on dialysis therapy,

- Patients who have underwent renal transplantation,
- Patients on immunosuppressive therapy for other medical illness,
- Patients who have taken antibiotics within 48 hours preceding the urine sample collection.

Statistical method

Statistical analysis was carried out using SPSS version 16.0 (IBM SPSS, US) software with regression modules installed and Microsoft Word and Excel have been used to generate graphs, tables etc. Descriptive statistics with mean, standard deviation, proportion (%) was calculated for quantitative variables. Using chi square test association between variables was assessed and p value <0.05 was considered as significant.

Significant figures

- + Suggestive significance (P value: 0.05<P<0.10)
- Moderately significant (P value: 0.01<P ≤ 0.05)
- **Strongly significant (P value: P≤0.01).

RESULTS

Among 65 participants from this study, 21 (32.3%) patients were in the age group of 61 to 70 years and 20 (30.8%) patients were in the age group of 51-60 years, above 70 years 11 (16.9%) patients were recorded. Very few of 7.7% participants and 1.5% participants were in 31-40 years and less than 30 years respectively. The sex distribution was found to be more or less equal with male comprising 50.8% and females 49.2% in this study (Figure 1).
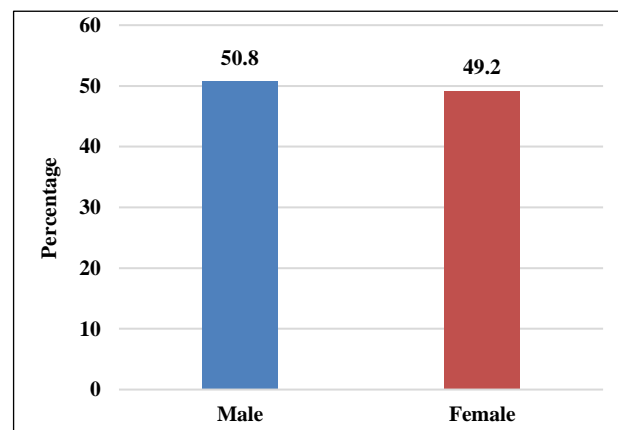

Figure 1: Gender of the participants.

Urine specimen showed bacterial growth in 46 (70.8%) patients, no bacterial growth in 18 (27.7%) patients and 1 patient had (1.5%) occasional growth in the urine sample. Among 65 participants in the study profile done on pus cells, 24 (36.9%) participants had 6-10 pus cells in the urine sample, followed by 18 (27.7%) had plenty pus cells, 12 (18.5%) patients had 11-20 pus cells and 11 (16.9%) showed less than 5 pus cells in the urine sample.

Among the 65 study patients with CKD, 44.6% were found in stage IV disease, 32.3% in stage III and 23.1% in stage V kidney disease. Fever (63.1%) and abdominal pain (41.5%) were the predominant presenting symptoms in the study.

Total leucocyte count was found to be elevated in 44 (67.7%) patients and 21(32.3%) patients had normal count.

From the urine culture it was found 47.7% had *E. coli* growth, the next common organism found was *K. pneumoniae* at 15.4%. In 12.3% the inference was sterile with no bacterial growth. Citrobacter diversus was seen in 6.2% patients and 4.6% showed growth of enterococcus and non-albicans candida each. *Acinetobacter baumannii* was seen in 3.1% patients and other species (candida species, *E. coli* with *K. pneumoniae, Proteus mirabilis, Proteus vulgaris*) were

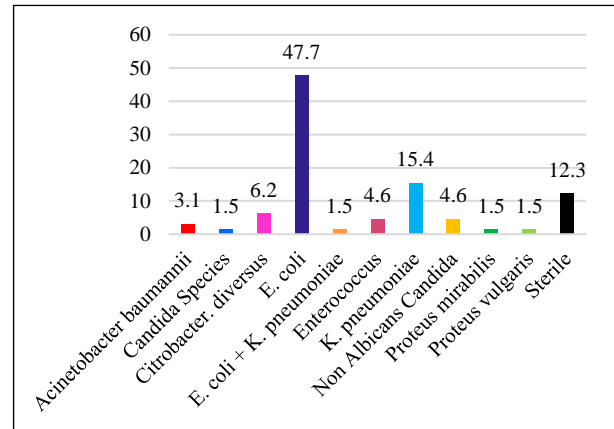also observed in 1.5% participants of the study (Figure 2).

Figure 2: Proportion of cases with different organisms.

Table 1: Proportion of cases with respect to sensitivity pattern in percentage.

Organisms	Gentamicin	Amikacin	Imipenem	Meropenem	Colistin	Polymyxin B	Cefoperazone Sulbactam	Cotrimoxazole	Cefotaxime	Nalidixic acid	Nitrofurantoin	Norfloxacin	Vancomycin	Teicoplanin	Linezolid	Amphotericin B
Acinetobacter	100	100	100	100	100	100	100	100	100	100	0	100	0	0	0	0
Candida spp.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100
C. diversus	50	25	66.7	66.7	100	100	66.7	50	50	50	33.3	50	0	0	0	0
E. coli	51.7	58.3	44.8	77.4	93.8	87	63.3	20	19.4	3.5	50	17.9	0	0	0	0
E. coli and K. pneumoniae	0	100	0	100	100	100	100	0	0	0	0	0	0	0	0	0
Enterococcus	50	0	0	0	0	0	0	0	0	0	0	0	100	33.3	100	0
K.pneumoniae	33.3	44.4	11.1	37.5	100	87.5	22.2	33.3	12.5	12.5	12.5	25	0	0	0	0
Non albicans Candida	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P. mirabilis	100	100	0	100	0	0	100	0	100	0	0	100	0	0	0	0
P. vulgaris	100	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Culture and drug sensitivity showed overall *Acinetobacter baumannii* was 100 % sensitive to gentamicin, amikacin, imipenem, meropenem, colistin, polymyxin B, cefoperazone sulbactam, cotrimoxazole, cefotaxime, nalidixic acid and norfloxacin. *Candida* species was 100% sensitive to amphotericin B. Citrobacter diversus was found to be sensitive in order of colistin (100%), polymyxin B (100%), imipenem, meropenem and cefoperazone sulbactam (66.7%) each. Gentamicin, cotrimoxazole, cefotaxime, nalidixic acid and norfloxacin at 50%, nitrofurantoin at 33.3% and amikacin at 25% (Table 1).

E. coli was found to be sensitive in order of colistin (93.8%), polymyxin B (87%), meropenem (77.4%),

cefoperazone sulbactam (63.3%), amikacin (58.3%), gentamicin (51.7%), nitrofurantoin (50%), imipenem (44.8%) and very less sensitivity was found in cotrimoxazole (20%), cefotaxime (19.4%), norfloxacin at 17.9% and nalidixic acid at 3.5% (Table 1).

K. pneumoniae was found to be sensitive in order of colistin (100%), polymyxin B (87.5%), amikacin (44.4%), meropenem (37.5%), gentamicin and cotrimoxazole (33.3%), norfloxacin (25%). Very less sensitivity was found in cefoperazone sulbactam at 22.2%, with cefotaxime, nalidixic acid and nitrofurantoin at 12.5% (Table 1).

P. mirabilis was found to be sensitive for gentamicin, amikacin, meropenem, cefoperazone sulbactam, Cefotaxime and Norfloxacin while P. vulgaris was found to be sensitive for gentamicin and amikacin. For 12.3% patients who had CKD with UTI the inference was sterile with no growth of bacteria. The above-mentioned Sensitivity pattern gives overall sensitivity to a particular organism which differs for individual specimen taken from CKD patients (Table 1).

DISCUSSION

The clinical profile of UTI in CKD is less commonly studied area in our country. It is very essential to know the common organisms involved and their antibiotic profile in providing empirical antibiotic therapy. This study was done mainly in that purpose.

Age distribution

In this study conducted among 65 CKD participants who had UTI, mostly belonged to the age group of 61-70 years followed by 51-60 years and above 70 years. Very few participants were less than 40 years of age which was similar to other studies.

Eshwarappa M et al, studied the age group of patients with UTI and found it around 52.84±22.25 years.[8] Most of the cases were recorded in the elderly age group (50-79 years) which was also observed in another study by Manjunath GN et al.[9]

Gender distribution

The sex distribution among the study patients with CKD who had UTI were found to be more or less equal, this can be due to small study population whereas many studies like Orret FA et al, and Shurland HS et al, Gales AC et al, Tambekar DH et al, Adedeji BA et al, and Kebira AN et al, reported female predominance.[10-14] Close proximity to female urethral meatus to anus, shorter urethra and sexual intercourse have been reported as factors that influences this higher prevalence in women.

Presenting symptoms

In this study, it was observed that commonest presenting symptoms were fever and abdominal pain, while vomiting and burning micturition were less common. In a study done by Eshwarappa M et al, it was reported that dysuria and fever to be the common symptoms which was almost similar to this study except for dysuria.[8] Mahesh E et al, reported in their study showed fever (29.4%) to be the most common presenting symptom of UTI followed by dysuria (26.8%).[15] But the predictability of UTI by these symptoms is to be questioned. Two or more symptoms taken together can have good predictive value of UTI. Though dysuria was less prevalent in

patients, urine culture was very essential in diagnosing UTI.

Urine analysis

It was found that 54 patients (83.1%) were having pus cells >5/hpf. The most accurate microscopic method for quantifying pyuria is to measure the urinary leukocyte excretion rate.[16] This test is impractical for clinical use, however, making it necessary for laboratories to use other methods. An alternative method is to count urine leukocytes with a hemocytometer. Comparison of hemocytometer counts with urinary leukocyte excretion rates has shown that a hemocytometer counts of ≥ 10 leukocytes/ cubic mm correlates with a urinary leukocyte excretion rate of ≥ 400000 leukocytes/hour. There is no difference in cut off for urine pus cells in literature.

Fasolo LR et al, studied the diagnostic relevance of pyuria in dialysis patients and found that the cut off of 5 cells/ hpf gave a negative predictive value of 96%.[17] In Schreier's textbook of diseases of the kidney the cut off of 5 pus cells/hpf was taken as a standard value.[18] The reasons for limited reliability of pyuria relate to variables such as time of centrifugation, number of rotations of the centrifuge, initial urine volume, the amount of volume of resuspension after centrifugation, observer bias (tendency to count in areas of higher number of cells),limited counting accuracy when gridlines are not used, and the observation that centrifugation causes a variable and unpredictable loss of leukocytes.[19] Majority of the patients involved in this study were in the stage 4 of CKD (44.6%) followed by CKD stage 3 (32.3%), and CKD stage 5(23.1%).

Organism profile

In microbiological culture of urine samples, the most common isolate grown was *E. coli* (47.7%), the next common organism found in the culture was *K. pneumoniae* (15.4%). For 12.3% patients with UTI the inference was sterile with no growth of bacteria. citrobacter diversus, enterococcus and non-albicans candida were less common, while *acinetobacter baumannii, E. coli with K. pneumoniae, Proteus mirabilis, Proteus vulgaris*, candida species were also observed in a small quantity in this study. However, there were no staphylococcus spp. isolate.

This result in similar to many other studies done worldwide like Linhares I et al, while Stapleton A et al, found that the organisms casing UTI in diabetic patients are significantly different than those in nondiabetics.[20,21] Bonadio M et al, reported that diabetes made no difference to the uropathogen profile or antibiotic sensitivity profile. Oluremi BB et al, in their study reported that *E. coli* (46.7%) was the commonest organism causing UTI in elderly people.[22,23]

As *E. coli* was observed to be the commonest organism, it was compared with other organisms in diabetics and non-diabetics. The p value was done using Fischer's exact test and it was 0.759 which is statistically insignificant. During another comparison of *E. coli* with other organisms in female and male patients the p value was found to be 0.903 which is statistically insignificant.

Kattel HP et al, studied the distribution of uropathogens in male and female patients and found that E. coli was significantly predominant (p<0.05) in both female and male patients.[24]

Antibiotic sensitivity profile

In culture and drug sensitivity overall, it was found *E. coli, K. pneumoniae and Acinetobacter baumannii* which were the common isolates of the study were sensitive in order of colistin, polymyxin B and meropenem (carbapenem) however it was found imipenem had less sensitivity. Commonly used empirical antibiotics such as 3rd generation cephalosporin and fluoroquinolones had high resistance. *P. mirabilis* and *P. vulgaris* were highly sensitive to aminoglycosides and carbapenems.

The above-mentioned sensitivity pattern gives overall sensitivity to commonly isolated organism which differs for individual specimen taken from CKD patients.

In a study done by Eshwarappa M et al, it was noted that ciprofloxacin was resistant to nearly three- fourth of all the isolated samples (74.1%).[8] Their study also revealed that carbapenems were almost sensitive to all the isolated organisms with resistance rate around 3.9%. Although quinolones were considered as one of the drugs of choice for the treatment of UTI, the increasing resistance rate necessitates a change in the empirical treatment.

The overall resistance to carbapenems reported by the ECDC in 2009 was 3.7% with wide variations between countries.[25] Susceptibility reports for Romania evaluating 378 pseudomonas spp. isolates showed increased resistance to imipenem of 43%.[26] Carbapenem resistance has increased dramatically in Greece from below 1% in 2001 to 30%, 39%, and 74% in medical, surgical and intensive care wards, respectively.[27]

Until recently, carbapenems were almost uniformly active against resistant gram-negative organisms but some strains have now developed very effective ways to deal with the carbapenems. There are various mechanisms by which these organisms develop resistance, by producing beta lactamases which destroy the antibiotics by blocking the entry of these antibiotics, or by efflux pumps which actively pump out these antibiotics.[28] Limitations of this study were based on larger sample size and study duration could have yield better results. ESBL pattern in the isolated organisms could have been studied. MIC values of susceptible antibiotics is not studied.[7]

CONCLUSION

The main purpose of this study was to find the various common uropathogens in CKD patients and their antibiotic profile which will help in formulating antibiotictherapies. As previously stated, there are very few numbers of studies regarding profile and management of UTI in CKD patients. Hence this study can throw some light into this area. UTI is a common complication of CKD with the potential to produce morbidity. CKD patients presenting with fever may have nonspecific symptoms of UTI, and a high index of suspicion is appropriate in this setting, as bacteriuria would indicate a high probability of upper tract infection. Present study has shown an overview of the common uropathogens found in south India. Escherichia coli and Klebsiella pneumoniae were the most predominant strains in CKD patients with urine tract infection (UTI). Drug susceptibility differs in every geographical area for each and every organism. Drug susceptibility of this local region was discussed in detail in this study.

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