ORIGINAL RESEARCH

Study of Uropathogens among Benign Prostatic Hyperplasia patients in a tertiary care hospital

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is one of the most common causes of Lower Urinary Tract Symptoms (LUTS). In this study we attempt to find out the bacterial and fungal aetiological agents of urinary tract infection among Benign Prostatic Hyperplasia patients and their antimicrobial susceptibility pattern. **Materials and Methods:** Present study was Hospitalbased Cross sectional study, conducted in adult patients diagnosed as having BPH admitted for Trans Urethral Resection of Prostate (TURP). Using a pretested questionnaire, brief history and investigation details were collected. Urine samples of BPH patients send to MCH Microbiology were processed, organism identified, antibiotic susceptibility testing done. **Results:** Out of the 203 BPH patients' urine samples, 113 (55.66%) were sterile and 90 (44.33%) yielded isolates. Monomicrobial organisms constitute 42.85% (n=87) and polymicrobial 1.5% (3). Among the 90 isolates, 87 (96.6%) were monomicrobial, of which 83 were bacteriae and 4 were fungi. In 3(3.33%) polymicrobial isolates , two isolates were *E.coli* and *Klebsiella pneumoniae* and one was *E.coli* and *Candida glabrata*. In catheterized urine samples also the commonest cause of UTI was E.coli 42.02 % (n=29), closely followed by *Klebsiella pneumoniae* 37.68% (n=26). Allthe *Candida* species isolated are 100% sensitive to the commonly used antifungals like Amphotericin B, Fluconazole and Itraconazole. In present study, majority of patients recoveredwell (90 %) while 9 patients had complications. **Conclusion:** UTI is a common finding in patients with symptomatic BPH in our setting (44.33%). There is a steady increase in the prevalence of UTI with increasing age group, among BPH patient in this study.

Keywords: Uropathogens, benign prostatic hyperplasia, *E coli, Candida species*.

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INTRODUCTION

Urinary tract infection (UTI) is the third most common infection experienced by humans after respiratory and gastro-intestinal infections. In fact, bacterial infections of the urinary tractare the most common cause of both community acquired and nosocomial infections for patients admitted to hospitals in United States¹. Estimated annual global prevalence of UTI is two hundred and fifty million^{2,3}.

UTI occur when normal protective mechanisms such as dislodging of bacteria during urination, high urea concentrate in the urine, antibacterial secretions from the prostate, high urine osmolality and white blood cells were fail⁴. The most common organism causing urinary tract infection in adult is *Escherichia coli* (*E.coli*), followed by *Klebsiella*, *Proteus and Pseudomonas species*.

Benign prostatic hyperplasia (BPH) is one of the most common causes of Lower Urinary Tract Symptoms (LUTS).⁵ Epidemiological studies have shown evidence of BPH in 20% of men aged 40 - 50 years and 80% of men aged 70 - 80 years. Additionally, 25% of men over the age of 40 have symptoms consistent with LUTS.⁶ In this study we attempt to find out the bacterial and fungal aetiological agents of urinary tract infection among Benign Prostatic Hyperplasia patients and their antimicrobial susceptibility pattern.

MATERIAL AND METHODS

Present study was a hospital based Cross sectional study, conducted in department of Microbiology, Govt. Medical College, Thiruvananthapuram and Dept. of Urology, Govt. Medical College, Thiruvananthapuram, India. Study duration was of 1 year (From 01/02/2017 to 31/01/2018). Study was approved by institutional ethical committee.

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Inclusion criteria

• Adult patients diagnosed as having BPH admitted for Trans Urethral Resection of Prostate (TURP) in the Dept. Of Urology Govt. Medical college, Thiruvananthapuram, willing to participate in present study

Exclusion criteria

- Adult males without BPH
- Immunocompromised patients
- Patients after TURP

Study was explained to participants in local language & written informed consent was taken. Using a pretested questionnaire, brief history and investigation details were collected. Urine samples of BPH patients send to MCH microbiology were processed, organism identified, antibiotic susceptibility testing done.

Instructions were given to patients to collect the midstream urine sample by clean catch technique. The mid-stream of urine sample was collected in a sterile plastic universal container provided from the laboratory. In catheterized patients, the catheter tubing was clamped to allow collection of freshly voided urine. Then the wall of the catheter was cleaned with 70% ethanol, and urine aspirated with a sterile needle and syringe. Suprapubic aspirate was collected in certain patients in whom it was indicated.

All the samples were first examined with naked eye to assess whether they were clear or turbid or blood stained. Direct microscopy by wet film examination and gram staining of smears made from urine samples were done. All samples were processed uncentrifuged and undiluted. Urine sample was mixed carefully and a drop of it is transferred on to the middle of glass slide. Then a cover slip is applied avoiding bubbles and is examined underhigh power field for leucocytes (pus cells). A drop of urine sample is transferred on to a clean glass slide. It was allowed to dry. Grams staining was done and examined under oil immersion field for organisms and pus cells. Urine sample was mixed thoroughly before plating. Then a standard sterile loop was inserted into the urine vertically. Urine was inoculated by semi quantitative method using standard loop into the following culture media as Blood agar/ Mac Conkey agar/ CLED agar/ SDA agar. Data was collected and compiled using Microsoft Excel, analyzed using SPSS 23.0 version.

RESULTS

As per the inclusion and exclusion criteria urine samples were taken from 203 consecutive cases. 44.33% (n=90) had UTI and 55.67% (n=113) had no bacteriuria. Presence of UTI in BPH patients was maximum in the 80 – 89 year age group (66.66%), and minimum in the 40– 49 year age group (20%). UTI in other age group of BPH patients was 29.78% in 50 – 59 years, 33.78% in 60 – 69 years and 64.7% in 70 – 79 years. Presence of UTI increases as age advances with maximum prevalence was seen in 80 – 89 year age group (66.66%) and the leastprevalence in 40 – 49 year age group (20%).

Age in years	Number of BPH	Number of UTI	Percentage of UTI (%)
40 - 49	5	1	20
50 - 59	47	14	29.78
60 - 69	74	25	33.78
70 - 79	68	44	64.7
80 - 89	9	6	66.66

 Table 1: Distribution of cases of BPH and presence of UTI according to age group

Among 106 BPH patients who were catheterized and the prevalence of UTI in them was 62.26% (n=66) whereas in non-catheterized patients (n=97) the prevalence was 24.7% (n=24).

Fable 2: Distribution of UTI in BPH patients in relation to bladder catheterization
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	No. of cases	No. of UTI	Percentage of UTI
Catheterized	106	66	62.26
Not catheterized	97	24	24.7
Total	203	90	

Out of the 203 BPH patients' urine samples, 113 (55.66%) were sterile and 90 (44.33%) yield isolates. Monomicrobial organisms constitute 42.85% (n=87) and polymicrobial 1.5%(3). Among the 90 isolates, 87 (96.6%) were monomicrobial, of which 83 were bacteria and 4 were fungi. In 3 (3.33%) polymicrobial isolates, two isolates were *E.coli* and *Klebsiella pneumoniae* and one was *E.coli* and *Candida glabrata*. So total bacterial isolates including monomicrobial and poly microbial accounts to 88

(94.62%) and the fungal isolates 5 (5.38%).

In our study *E.coli* 42.22% (n=38) was the most common bacterial uropathogen isolated, followed by *Klebsiella pneumoniae* 35.55% (n=32), *Pseudomonas aeruginosa* 6.66% (n=6), *Acinetobacter baumanii* 3.33% (n=3), *Proteus vulgaris* 2.22% (n=2), *Serratia marcescens* 1.11% (n=1) and *Enterococcus* 1.11% (n=1).The distribution of bacterial uropathogens are given in table-6.Among fungal aetiological agents *Candida glabrata* was more common 2.30% (n=2),

Candida albicans 1.15 %(n=1) and *Candida parapsilosis* 1.15% (n=1) form the rest. Out of the 3 polymicrobial aetiological agents two of them were

caused by *E.coli* and *Kebsiella pneumoniae* and one was a combination of bacteria and fungus(*E.coli* and *Candida glabrata*).

Microbial flora	Number	Percentage
Monomicrobial	87	42.85
• E. coli	38	42.22
Klebsiella pneumoniae	32	35.55
Pseudomonas aeruginosa	6	6.66
Acinetobacter baumannii	3	3.33
Proteus vulgaris	2	2.22
Serratia marcescens	1	1.11
Enterococcus	1	1.11
Polymicrobial	3	1.5
E.coli+K.pneumoniae	2	2.22
E.coli+C.glabrata	1	1.11
Fungal	5	5.38
Candida albicans	1	1.15
Candida parapsilosis	1	1.15
Candida glabrata	2	2.30

Out of the 93 pathogens isolated 44.08% (n=41) were *E.coli* ,36.55% (n=34) were *K.pneumoniae* and 6.45% (n=6) *Pseudomonas aeruginosa*. The remaining 13% were constituted by *Acinetobacter baumanni*, *Proteus vulgaris*, *Serratia marcescens*, *Enterococcus faecalis*, *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*.

 Table 4: Total number of organisms isolated (monomicrobial+polymicrobial)

Organism	Ν	umber	Percentage	
	Monomicrobial	Polymicrobial	Total	
E.coli	38	3	41	44.08
Klebsiella pneumoniae	32	2	34	36.55
Pseudomonas aeruginosa	6		6	6.45
Acinetobacter baumannii	3		3	3.22
Proteus vulgaris	2		2	2.15
Serratia marcescens	1		1	1.07
Enterococcus faecalis	1		1	1.07
Candida albicans	1		1	1.07
Candida parapsilosis	1		1	1.07
Candida glabrata	2	1	3	3.22
Total	87	6	93	

In catheterized urine samples also the commonest cause of UTI was *E.coli* 42.02% (n=29), closely followed by *Klebsiella pneumoniae* 37.68% (n=26).Other microorganisms isolated were *Pseudomonas aeruginosa* 7.24% (n=5), *Acinetobacter baumannii* 4.34% (n=3), *Proteus vulgaris* 2.89% (n=2),*C.albicans* 1.44% (n=1)*C.parapsilosis1*.44% (n=1) and *C.glabrata* 2.89% (n=2). All the 3 polymicrobial isolates obtained were from catheterized patients. Out of the 5 fungal isolates, 4 of themwere from catheterized patients.

Table	5: Dist	ribution	of aetic	ological	agents in	n catheterized	urine samples
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Isolates	Number	Percentage
E.coli	29	42.02
Klebsiella pneumoniae	26	37.68
Pseudomonas aeruginosa	5	7.24
Acinetobacter baumannii	3	4.34
Proteus vulgaris	2	2.89
C.albicans	1	1.44
C.parapsilosis	1	1.44
C.glabrata	2	2.89

Total	69	

All the Candida species isolated are 100% sensitive to the commonly used antifungals like Amphotericin B, Fluconazole and Itraconazole.

Antifungal tested	C.albica	ins	C.paraps	ilosis	C.glabrata		
	Number	%	Number	%	Number	%	
Amphoterecin B	1	100	1	100	3	100	
Fluconazole	1	100	1	100	3	100	
Itraconazole	1	100	1	100	3	100	

 Table 6: Antifungal susceptibility pattern of Candida species isolated

First generation Cephalosporin tested was Cefazolin. Third generation Cephalosporin tested was Ceftriaxone except in Pseudomonas aeruginosa where Ceftazidime was used. Among the E.coli isolates, 58.5 % were sensitive to Gentamicin, 95.1% to Amikacin, 97.6% to Cefoperazone + Sulbactam, Piperacillin + Tazobactam, Imipenem and Meropenem and 100% sensitive to Colistin. Antibiotic sensitivity of E.coli to first and third generation Cephalosporin, Ciprofloxacin, Nalidixic acid, Norfloxacin and Cotrimoxazole are poor whereas sensitivity to Nitrofurantoin was good (73.2%).None of the E.coli was sensitive to Ampicillin.

Antibiotic sensitivity of *Klebsiella pneumoniae* to Gentamicin was 61.8%, Amikacin was 88.2%, Cefoperazone + Sulbactam and Piperacillin + Tazobactam was 88.2%, Imipenem and Meropenem was 91.2% and Colistin was 100%. Antibiotic sensitivity of *Klebsiella pneumoniae* to first and third generation Cephalosporin, Ciprofloxacin, Nalidixic acid, Norfloxacin and Co-trimoxazole are less than 50% whereas sensitivity to Nitrofurantoin was good (64.7%).

All the 6 *Pseudomonas aeruginosa* isolated was 100% sensitive to Piperacillin + Tazobactam, Imipenem, Meropenem and Colistin. 50% of them are sensitive to Gentamicin and Ciprofloxacin, 83.3% are to third generation Cephalosporin and 66.7% were to Amikacin. Antibiotic susceptibility of *Pseudomonas aeruginosa* to Ampicillin, 1st generation

Cephalosporin, Cefoperazone+ Sulbactam, Nalidixic acid, Norfloxacin, Nitrofurantoin and Co-trimoxazole were not tested Antibiotic sensitivity pattern of *Acinetobacter baumannii* were very favourable.

They were 100% susceptible to antibiotics like Gentamicin, Amikacin, 3rd generation Cephalosporin, Piperacillin + Tazobactam, Cefoperazone + Sulbactam, Imipenem, Meropenem and Colistin. Sensitivity to other antibiotics were as follows, 1st generation Cephalosporin 66.7%, Ciprofloxacin (33.3%), Nalidixic acid (33.3%), Norfloxacin (33.3%), Nitrofurantoin (66.7%), Co-trimoxazole (33.3%), Ampicillin (0%).

All the two Proteus vulgaris isolated, were 100% sensitive to 3rd generation cephalosporin, Cefoperazone + Sulbactam, Piperacillin + Tazobactam, Imipenem, Meropenem, Colistin and 50% sensitive to Gentamicin, Amikacin, generation Ciprofloxacin,1st Cephalosporin, Norfloxacin, Co-trimoxazole none of them were sensitive to Ampicillin, 1st generation Cephalosporin and Nitrofurantoin.

Serratia marcescens 100% was sensitive to Ciprofloxacin,3rd generation Cephalosporin, Cefoperazone +Sulbactam, Piperacillin +Tazobactam, Imipenem, Meropenem, Colistin, Nalidixic acid, Norfloxacin, Co-trimoxazole whereas not sensitive to Ampicillin, Gentamicin, Amikacin 1st generation Cephalosporin and Nitrofurantoin.

AntibioticsTested	icsTested E.coli (41)		K.pneum P.aeruginosa(6) oniae(34)			A.bauma nnii(3)		P.vulgari s (2)		Serratia (1)		
	Ν	%	No	%	No	%	Ν	%	Ν	%	Ν	%
	0						0		0		0	
Ampicillin	0	0	0	0	NT	NT	0	0	0	0	0	0
(25µg)												
Gentamicin	2	58.	21	61.8	3	50	3	100	1	50	0	0
(10µg)	4	5										
1 st generation	1	24.	8	23.5	NT	NT	2	66.	0	0	0	0
Cephalosporin	0	4						7				
(30 µg)												
Ciprofloxacin	8	19.	11	32.4	3	50	1	33.	1	50	1	10
(5 µg)		5						3				0
3 rd generation	1	41.	13	38.2	5	83.	3	100	2	10	1	10
cephalosporin(30 µg)	7	5				3				0		0

Table 7: Antibiotic sensitivity pattern of gram negative isolates

Amikacin(30 µg)	3	95.	30	88.2	4	66.	3	100	1	50	0	0
	9	1				7						
Cefoperazone+	4	97.	30	88.2	NT	NT	3	100	2	10	1	10
Sulbacta m (75/30	0	6								0		0
μg)												
Piperacillin+	4	97.	30	88.2	6	100	3	100	2	10	1	10
	0	6								0		0
Tazobactam												
(100/10 µg)												
Imipenem	4	97.	31	91.	6	100	3	100	2	10	1	10
(10 µg)	0	6		2						0		0
Meropenem	4	97.	31	91.	6	100	3	100	2	10	1	10
(10 µg)	0	6		2						0		0
Nalidixic acid	5	12.	9	26.	NT	NT	1	33.	1	50	1	10
		2		5				3				0
Norfloxacin	7	17.	10	29.	NT	NT	1	33.	1	50	1	10
		1		4				3				0
Nitrofurantoin	3	73.	22	64.	NT	NT	2	66.	0	0	0	0
	0	2		7				7				
Co-trimoxazole	1	41.	15	44.	NT	NT	1	33.	1	50	1	10
	7	5		1				3				0
Colistin	4	100	34	100	6	100	3	100	2	10	1	10
(MIC)	1									0		0

NT-Not Tested

One gram positive bacteria isolated was *Enterococcus faecalis* and was 100% sensitive toall the antibiotics tested in this study (Ampicillin, Gentamicin, Ciprofloxacin, Levofloxacin, Linezolid, Vancomycin, Nitrofurantoin)

Table 8: Antibiotic sensitivity pattern of Enterococcus faecalis

Antibiotics tested	Enterococcus faecalis (1)		
	Number (sensitive)	Percentage	
Ampicillin (25µg)	1	100	
Gentamicin (120µg)	1	100	
Ciprofloxacin (5 µg)	1	100	
Levofloxacin (5 µg)	1	100	
Linezolid (30 µg)	1	100	
Vancomycin (30 µg)	1	100	
Nitrofurantoin (300 µg)	1	100	

Among the *E.coli* (n=41) isolates, 56.1 %(n=23) were ESBL producers and 2.44%(n=1) were MBL producers. Out of the 34 *Klebsiella pneumoniae* 50% (n=17) were ESBL producers and 8.82% (n-3) were MBL producers. Among the *Pseudomonas aeruginosa* isolated 33.3% were ESBL producers and none of them were MBL producer. ESBL and MBL producers among those patients with recent history of antibiotic intake was 61.22%.

Table 9: Distribution of mechanism of drug resistance

Resistance mechanism	E.co	di (41)	K.pne	umoniae 34)	P.aer	uginosa (6)	A.bau	mannii 3)	P.vulg	garis)
	No	%	No	%	No	%	No	%	No	%
ESBL	23	56.1	17	50	2	33.33	0	0	0	0
MBL	1	2.44	3	8.82	0	0	0	0	0	0

In present study, majority patients recovered well (90 %) while 9 patients had complications. Table 10:

Outcome of patients with UTI after TURP

Outcome	Number	Percentage
Resolved	81	90
Complications	9	10

DISCUSSION

Benign prostatic hyperplasia is a common urological problem affecting elderly males³¹. Most men will develop histological BPH as the age advances. Approximately, half of the men will develop benign prostatic enlargement (BPE) and about half of them will get bladder outflow obstruction, which in turn leads to detrusor wall hypertrophy. Most of them will have only lower urinary tract symptoms (LUTS) but a significant number will also suffer the other complications of BPH.⁷

Urinary infections associated with benign prostatic hyperplasia (BPH) occur as patients are unable to completely empty their bladder and the stagnant urine acts as a growth medium for bacteria. Many organisms are responsible for complicated urinary infection and they tend to be more resistant to antimicrobials.⁸ A major cause of bacteriuria in aging males is bladder outlet obstruction due to BPH. Moreover, UTI is one of the most common infections encountered as a complication of BPH in elderly males.⁹

In the present study a population of 203 cases of BPH were studied. The mean age for patients who underwent TURP was 65.6 years \pm 9.24), that correlate well with similar studies reported from India. George C *et al.*,¹⁰ reported that the mean age of the patient undergoing TURP was 69.36 years \pm 8.18. Rajeev R *et al.*,¹¹ studied 327 patients who underwent TURP over a period of 5 years and the mean age was 66.4 years.

Among the 203 cases of BPH urine samples, culture yields organism in 90 cases where as 113 cases had no bacteriuria. Overall prevalence of urinary tract infection (UTI) in BPH patient in this study was 44.33 %(p =0.087), which vary among different studies in the literature. A prevalence rate of 63% was reported by Mishra PP etal.,12 44.7% by Agbugui JO et al.,¹³ 33% by A.J.Oshodi et al.,¹⁴. A high prevalence rate of 63% in the first study could be due to inclusion of patients with prostatitis along with BPH, but other two studies considered only symptomatic BPH patients. There is a steady increase in the prevalence of UTI with increasing age group, among BPH patient in this study. In 40-49 year, age group the prevalence of UTI was 20% that rose to 66.66% when the age group is 80-89year. The mean age of the patient with UTI in this study was 68.27

 ± 8.57 . This is attributed to the decreasing concentration of prostatic zinc-associated antimicrobial factor and increased alkalinity of urine in elderly males.

Majority of uropathogens isolated in BPH patients in this study was bacterial 94.62% (n=88), but it yielded fungus in 5.38% (n=5) cases. Similar studies conducted showed isolation of only bacterial pathogens such as studies by Agbugui JO *et al.*,¹³ & A.J.Oshodi *et al.*,¹⁴. This finding is probably because we included BPH patients on prolonged or repeated urinary catheter and history of antibiotic treatment, whereas the above mentioned studies excluded those patients on bladder catheter. Indwelling bladder catheter are at risk of acquiring candiduria especially in elderly.

The susceptibility pattern of uropathogens in the study shows a higher rate of susceptibility to Cefoperazone-Sulbactam (90%-97%), Amikacin (90%-95%) and Nitrofurantoin (90%-95%) compared to other antibiotics. The reduced susceptibility to Quinolones and third-generation Cephalosporins is probably due to their irrational over the counter prescription in our region. Nitrofurantoin seems to be the only promising oral antibiotic effective in this scenario.

Antibiotic susceptibility testing in the present study revealed a high degree of resistance to the Cephalosporins, Fluoroquinolones and Cotrimoxazole, that go well with similar studies (Agbugui JO et al.,¹³ Mishra PP et al.,¹²). The organisms recorded no resistance against Colistin and least resistance against carbapenems (4.6%). In short, a high rate of ESBL-positive organisms and their resistance to commonly used antibiotics brings a concern for future options in treating these conditions. This may be due to the fact that these antibiotics have been abused in the past as a result of self-medication and inappropriate use by general practitioner in our region. The incidence of resistance recorded for Ciprofloxacin а fluoroquinolone, commonly prescribed for the empiric treatment of UTI, was 71.27% in the present study. Similarly, Ciprofloxacin resistance among E. coli strains has been on the upward trend over the years in different regions of the world¹⁶, especially among the aging population^{17,18}. This creates a challenge in the empirical management of patients presenting with UTI.

Major limitation of this study was that it didn't address the effect of preoperative antibiotics on the outcome following TURP in terms of reduction in bacteriuria and urinary sepsis. Previous studies by Viitanen J *et al.*,¹⁹ and Berry A *et al.*,²⁰ have shown a reduction in the incidence of bacteriuria after prostatectomy with antibiotic prophylaxis.

Therefore, it is important to have periodic region wise analysis of changing trends of drug resistance among urinary isolates to formulate local guidelines for treating UTI. We hope that this study would help the clinicians in deciding the antibiotic therapy for UTIs and also would help in formulating an antibiotic policy in the hospitals. The most probable interpretation of these trends can lead to therapeutic improvements including more widespread and timely surgery, introduction of less invasive techniques, such as transurethral prostatectomy, and possibly the development of medical treatments has hada favorable and substantial impact on BPH mortality.

CONCLUSION

UTI is a common finding in patients with symptomatic BPH in our setting (44.33%). There is a steady increase

in the prevalence of UTI with increasing age group, among BPH patient in this study. Most cases of UTI were caused by organisms in the enteric flora and majority of isolates were E coli followed by Klebsiella pneumoniae, Pseudomonas aeruginosa. Other organisms isolated were Proteus vulgaris, Acinetobacter baumannii,, Serratia marcescens, Enterococcus faecalis and Candida species.

Due to its relatively low cost and acceptable susceptibility profile, there may be a greater role for Nitrofurantoin in the prophylaxis and treatment of complicated UTI in patients with BPH. Most of the fungal isolates were from catheterized patients and they belong to *Candida* species. All the *Candida* species isolated were susceptible to commonly used antifungal drugs.

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