EXCELLENT PUBLISHERS

Asymptomatic Bacteriuria in Patients with Benign Prostate Hypertrophy before Transurethral Resection of Prostate (Turp)

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A B S T R A C T

Benign prostate hypertrophy (BPH) is a non- malignant condition characterized by proliferation of prostatic cells leading to an increase in prostate size, urethral obstruction, and lower urinary tract symptoms. For men, prostate hypertrophy with bladder outlet obstruction is reported to be the major predisposing factor for the development of asymptomatic bacteriuria. The Infectious Diseases Society of America (IDSA) established guidelines for the screening and treatment of asymptomatic bacteriuria (ASBU) in BPH, which recommends routine screening, and treatment of ASBU before transurethral resection of the prostate (TURP) and before other urological procedures, in which mucosal bleeding is anticipated. To study the distribution of asymptomatic bacteriuria in patients with Benign prostate hypertrophy (BPH) posted for transurethral resection of prostate (TURP), and to determine the bacterial profile of the pathogens causing ASBU and their antimicrobial susceptibility and resistance pattern. Urine samples were collected appropriately from 100 patients with BPH who were posted for TURP, and those who were not having symptoms of Urinary tract infection (UTI). The samples were cultured by standard semi-quantitative calibrated loop method. The isolated bacteria were identified by standard microbiological procedures. Antimicrobial susceptibility testing (AST) was performed according to the CLSI 2017 guidelines. Co morbid conditions were studied and the results were analyzed using SPSS software. ASBU was observed in 27% of the 100 patients in the study group with benign prostate hypertrophy. The bacterial profile as identified by urine culture in these patients, was E*scherichia coli* 13(48.7%), *Klebsiella pneumoniae* 4 (14.8%), *Klebsiella oxytoca* 4(14.8%), *Pseudomonas aeruginosa* 2(7.4%), *Acinetobacter baumannii 2* (7.4%), *Staphylococcus aureus* 1 (3.7%) and *Proteus mirabilis* 1 (3.7%). The AST by Kirby Bauer disc diffusion test revealed that all the 13 isolates of *Escherichia coli*(100%) were sensitive to Cotrimoxazole,92.3% to Imipenem,84.6% each to Amikacin and Ampicillin whereas, *Klebsiella species namely pneumoniae* and *oxytoca* demonstrated a higher percentage of susceptibility only to the second line of antibiotics like Imipenem and Piperacillin tazobactam at 75% and 100 % respectively. Antimicrobial resistance testing demonstrated that 5 of the 13 *E. coli* isolates (35%) and 2 of the 4 *K.pneumoniae* were ESBL producers, of which one isolate of *K. pneumoniae* was KPC producer too. MBL production was observed in one each of *A.boumanii* and *P.aeruginosa*. Statistical analysis using chi square test showed that Diabetes mellitus as a co morbid condition was significantly associated with ASBU (P value 0.017%). Routine screening for asymptomatic bacteriuria by culture and AST profile in patients with BPH undergoing TURP is appropriate especially in patients with co morbid conditions like Diabetes mellitus. so that prophylactic AST guided antibiotic therapy should be initiated in these patients to prevent complications.

Introduction

Benign prostate hypertrophy (BPH) is one of the leading conditions causing obstruction in urine flow in men of increasing age. BPH is a non- malignant condition characterized by proliferation of prostatic cells leading to a progressive increase in prostate size, and in chronic stage it causes urethral obstruction, resulting in incomplete bladder emptying and stasis which may predispose the patients to recurrent infections.[3]

For men, prostatic hypertrophy with bladder outlet obstruction is reported to be the major predisposing factor for the development of asymptomatic bacteriuria. Overt UTI in the male population remains uncommon until when enlargement of the prostate begins to interfere with emptying of the bladder, and if not identified and treated early.[3]

Epidemiological studies have shown evidence of BPH in 20% of men aged 40-50 years and 80% of men aged 70-80 years. About 50% of men over age 50 develops symptoms of BPH, but only a minority need medical or surgical intervention.[5] Though new methods for treating BPH have been developed, TURP remains the gold standard treatment and is the most commonly performed procedure for men suffering from BPH.[1]

Asymptomatic bacteriuria, or asymptomatic urinary infection, is isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection.[6] Screening of asymptomatic subjects for bacteriuria is appropriate if bacteriuria has adverse outcomes that can be prevented by antimicrobial therapy.[6] The Infectious Diseases Society of America (IDSA) established guidelines for the screening and treatment of asymptomatic bacteriuria, which recommends screening for, and treatment of

ASBU before transurethral resection of the prostate and before other urological procedures in which mucosal bleeding is anticipated.[6]

Patients with asymptomatic bacteriuria who undergo genitourinary procedures associated with mucosal bleeding have a high rate of post procedure bacteremia and sepsis. Bacteremia occurs in up to 60% of bacteriuric patients who undergo transurethral prostatic resection, and there is clinical evidence of sepsis in 6%−10% of these persons.[6] Hence this study was conducted to determine the rate of asymptomatic bacteriuria in patients with benign prostatic hypertrophy posted for transurethral resection of prostrate.

The main aim of this study includes, to study the distribution of asymptomatic bacteriuria in patients with Benign prostatic hypertrophy (BPH) undergoing transurethral resection of prostate, by performing culture isolation and identification of aerobic bacterial pathogens in the urine samples of patients with BPH and to study AST pattern of the pathogens & the distribution of the resistant pathogens among the isolates.

Materials and Methods

This Cross sectional study was conducted for a period of 6 months at Rajiv Gandhi Government General Hospital, Chennai. 100 patients aged >30 years attending the Urology OP and ward with clinical and radiological diagnosis of BPH and who did not have symptoms of UTI were included in the study.

Patients on antibiotic therapy and those who were symptomatic for UTI like frequency, urgency, hesitancy, straining, or difficulty initiating the urinary stream, and incomplete bladder emptying were excluded from the study. Institutional Ethics Committee approval was obtained

Urine from patients posted for TURP who did not have symptoms of UTI were collected as per standard procedures. Mid stream clean catch urine from non catheterized patients and samples from the sample port in catheterized patients were collected in sterile containers and were processed as per standard microbiological protocol. The urine specimens were inoculated using a standard wire loop into Cysteine Lactose Electrolyte Deficient [CLED] agar and incubated aerobically at 37^0 C for 24 hours, and examined for significant bacterial growth.

In non catheterized men, a single voided specimen with a quantitative count of a potential uropathogen $\geq 10^5$ CFU/ml was considered diagnostic of bacteriuria and for patients with short term in dwelling urinary catheters $\geq 10^2$ CFU/ml was diagnostic of ASBU.[6]

Isolates were phenotypically characterized and identified up to species level. Antibiotic susceptibility tests were carried out using Kirby-Bauer disc diffusion method and interpreted as per CLSI guidelines.[7] The resistant isolates were further screened by phenotypic methods for characterization of resistance mechanisms.

Detection of antimicrobial resistance

Phenotypic screening methods

All the Enterobacteriaeceae isolates were subjected to

1) Extended Spectrum Beta-lactamase (ESBL) screening test using Ceftazidime (30μg) and Cefotaxime (30μg),
2) AmpC beta-lactamase screening test using Cefoxitin (30μg) and
3) Carbapenemase screening test using Imipenem (10μg) and Meropenem (10μg) discs.

Those isolates which were positive in the screening test were subjected to confirmatory Phenotypic tests.

Phenotypic confirmatory test for ESBL production- combined disc method[8]

In this method, a lawn culture of the test isolates was made as for disc diffusion method. Ceftazidime (30μg) and ceftazidime-clavulanic acid (30μg/10μg) discs- Himedia, were placed at a distance of 20mm centre to centre on the Mueller-Hinton agar plate, incubated at 37ºC for 20-24 hours. The test isolate was considered to produce ESBL if the zone of inhibition around the ceftazidime-clavulanic acid disc was ≥5mm that the zone around ceftazidime disc alone with appropriate controls (Positive control - *K. pneumoniae* ATCC 700603 Negative control- *E. coli* ATCC 25922).

Phenotypic test for AmpC detection[13]

The isolates which were resistant to cefoxitin (30μg) with zone diameter of < 18mm were considered as AmpC screening test positive. AmpC production was confirmed by placing cefoxitin (30μg) and cefoxitin- cloxacillin at a distance of 20mm on the Muller-Hinton agar plate. The test isolate that demonstrated a zone of inhibition of ≥ 5mm around cefoxitin-inhibitor than that around the cefoxitin alone was considered as AmpC producer. The test was performed with appropriate positive and negative controls.

Metallo beta-lactamase (MBL) detection[13]

Metallo-β-Lactamase production for the carbapenem resistant isolates was screened by Imepenem (10μg) and Imepenem ((10μg) - EDTA (930μg). An increase in zone size of ≥ 7 mm around combination disc compared to disc without inhibitor was considered as MBL positive. The test was performed with appropriate positive and negative controls.

Klebsiella pneumoniae carbapenamase detection by phenotypic method[13]

In this method a lawn culture of the test isolates was made as for disc diffusion procedure. Two Ertapenem discs (10µg), (Himedia) were placed 20-24mm distance on the surface of the plate. 10 µl of phenyl boronic acid solution (200µg) was added to one of the Ertapenem discs.

The plate was incubated at 37˚C for 24 hrs. The test isolates were considered to produce KPC if the zone size around the inhibitor combination disc was increased by ≥5mm than the disc without boronic acid.

Results and Discussion

This study is a cross sectional study conducted in the Microbiology department, recruiting patients attending Urology department in the Rajiv Gandhi Government General Hospital, a South Indian tertiary care super specialty hospital. A total number of 100 patients with BPH without symptoms of UTI undergoing TURP were included in the study (Fig. 1 and 2; Table 1–7).

Statistical analysis

Data analysis was done using Statistical package for Social Sciences version 22; Level of significance was set at $p < 0.05$.

Table.1 Urine Culture positivity in patients with BPH (n=100)

Number of samples	Culture positive	No growth
100	27(27%)	73(73%)

Table.2 Distribution of bacterial Uropathogens among patients with BPH (n=27)

Isolated Pathogens	Number	Percentage
Escherichia coli (n=13)	13	48.1%
Klebsiella pneumoniae(n=4)	4	14.8%
Klebsiella oxytoca (n=4)	4	14.8%
Pseudomonas aeruginosa(n=2)	2	7.4%
Acinetobacter baumannii (n=2)	2	7.4%
Proteus mirabilis(n=1)	1	3.7%
Staphylococcus aureus(n=1)	1	3.7%
Total	27	27%

Table.3 Antibiotic susceptibility pattern among Enterobacteriaeceae

Organisms	Amikacin (30µg)	Gentamicin (10µg)	Norfloxacin (300µg)	Nitrofurantoin (30µg)	Cefotaxime (30µg)	Imipenem (10µg)	Cotrimoxazole (1.25/23.75µg)	Ampicillin (30µg)	Piperacillin Tazobactam (100/10µg)
Escherichia coli (n=13)	11(84.6%)	8 (61.5%)	5(38.4%)	9 (69.2%)	8 (61.5%)	8 (61.5%)	13 (100%)	11(84.6%)	10(76.9%)
Klebsiella pneumoniae (n=4)	1(25%)	1(25%)	1(25%)	3(75%)	2(50%)	3(75%)	2(50%)	-	3(75%)
Klebsiella oxytoca (n=4)	2(50%)	1(25%)	0%	2(50%)	3(75%)	4(100%)	2(50%)	-	4(100%)
Proteus mirabilis(n=1)	1(100%)	1(100%)	0%	0%	1(100%)	1(100%)	-	-	1(100%)

Table 4 Antibiotic susceptibility pattern among nonfermentors

Organisms	Amikacin (30µg)	Gentamicin (10µg)	Norfloxacin (300µg)	Nitrofurantoin (30µg)	Ceftazidime (30µg)	Meropenem (10µg)	Piperacillin Tazobactam (100/10µg)
Pseudomonas aeruginosa(n=2)	1	1	1	0%	1	1	1
Acinetobacter baumannii (n=2)	1	1	1	1	1	2	2

The single isolate of methicillin susceptible *Staphylococcus aureus* (MSSA) was sensitive to Norfloxacin, Nitrofurantoin, Cotrimoxazole, Penicillin & Vancomycin

Table.5 Antimicrobial resistance pattern of the isolates

Organism	ESBL	KPC	AmpC	MBL
Escherichia coli (n=13)	5 (38.5%)	NP	1(7.6%)	NP
Klebsiella pneumoniae(n=4)	2 (50%)	1(25%)	NP	NP
Acinetobacter baumannii (n=2)	NT	NT	NP	1(50%)
Pseudomonas aeruginosa (n=2)	NT	NT	NP	1(50%)

(NP- non producer, NT- not tested)

Table.6 Diabetes Mellitus as a comorbid condition in BPH with ASBU patients

	Diabetic (n =27)	Non diabetic (n = 73)	Total
ASBU	13(48.1%)	14(19.1%)	27
No ASBU	14(51.8%)	59(80.8%)	73
Total	27	73	100

Statsitical Analysis was done, and the finding was significant with P value of 0.017 (p <0.05) by Pearson Chi-Square method

Table.7 Presence of indwelling urinary catheter as a co-morbid condition in ASBU patients

|	Catheterized patients (n = 36)	Non catheterized patients (n =64)	Total
ASBU	21(58.3%)	6(9.3%)	27
No ASBU	15(41.6%)	58(90.6%)	73
Total	36	64	100

Indwelling urinary catheter was found to be a significant condition associated with ASBU, with P value of 0.001 (p<0.05)

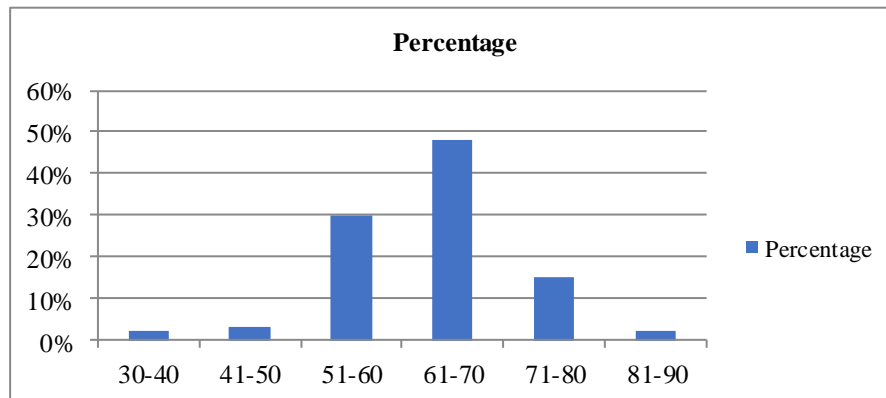**Fig.1** *Klebsiella pneumoniae* producing extended spectrum beta lactamases (ESBL)

CAZ – Ceftazidime; CAC- Ceftazidime with clavulanic acid.
Zone enhancement of > 5mm with CAC

Fig.2 *Pseudomonas aeruginosa* producing Metallo beta lactamases (MBL)
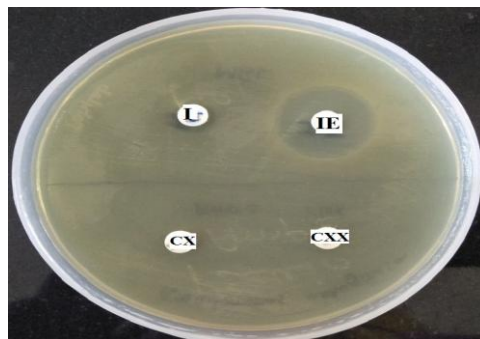
I - Imipenem IE – Imipenem with EDTA
Zone enhancement of > 7mm with IE

Chart.1 Age wise distribution of the patients (n=100)

Population studies throughout the world have shown a rise in the prevalence of asymptomatic bacteriuria. Asymptomatic bacteriuria is uncommon in young men, but for men over the age of 65 years, the prevalence ranges from 5-21% and is highest in those men over the age 90.[10] The prevalence in men increases substantially after the age of 60 years, presumably because of obstructive uropathy and voiding dysfunction associated with prostatic hypertrophy.[6]

Screening for and treatment of asymptomatic bacteriuria before transurethral resection of the prostate is recommended according to IDSA guidelines. Hence the study was done to determine the prevalence of asymptomatic bacteriuria in BPH patients undergoing TURP.

The study included 100 BPH patients without symptoms of UTI and those who were planned for transurethral resection of prostate. Majority of the patients 48 (48%) belonged to 61-70 years of age. Among the 100 patients 27% were culture positive for aerobic bacteria. In the study conducted by Nicolle E et al[11] on effectiveness of IDSA guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults, the prevalence of ASBU among elderly male was reported as 15%.

Of the 27 patients with ASBU, the uropathogens causing ASBU were Escherichia coli (48.7%) followed by *Klebsiella pneumoniae* (14.8%), *Klebsiella oxytoca* (14.8%), *Pseudomonas aeruginosa* (7.4%), *Acinetobacter baumannii* (7.4%), and one isolate each of *Staphylococcus aureus* and *Proteus mirabilis*. The study conducted by Richard Colgan *et al.,* [14] on Asymptomatic Bacteriuria in Adults*, Escherichia coli* was the most common organism isolated. Similarly, in the study conducted in by Deepak S. Ipe[12] on Asymptomatic bacteriuria, Escherichia coli was reported to be the commonest bacterium, followed by *Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus spp., Staphylococcus aureus, and coagulase-negative staphylococci.*

The AST by Kirby Bauer disc diffusion test revealed that all the 13 isolates of *Escherichia coli* (100%) were sensitive to Cotrimoxazole, 92.3% to Imipenem, 84.6% each to Amikacin and Ampicillin whereas, *Klebsiella species namely pneumonia and oxytoca* demonstrated a higher percentage of susceptibility only to the second line of antibiotics like Imipenem and Piperacillin tazobactam at 75% and 100 % respectively.

On analysis of antibiotic resistance pattern among 13 *Escherichia coli,* 5 exhibited extended spectrum beta lactamases (ESBL) production and one isolate produced AmpC beta lactamase. Among 4 *Klebsiella oxytoca* one was ESBL producer. Similarly one *Klebsiella pneumoniae* was ESBL producer and another was both ESBL & KPC producer. Among the 4 Non fermenter gram negative bacilli one *Acinetobacter baumannii* and one *Pseudomonas aeruginosa* were MBL producer. The rate of drug resistance (6.75%) recorded in the present study needs to be evaluated further with a higher sample size.

For most of the patient populations with asymptomatic bacteriuria, the management strategies are based on various evidence based guidelines and standard protocol. According to IDSA guidelines screening of asymptomatic subjects for bacteriuria is appropriate if bacteriuria has adverse outcomes like risk of recurrent urinary tract infection, bacteremia with sepsis, worsening functional status, and progression to chronic kidney disease, which can be prevented by antimicrobial therapy.

Routine screening for asymptomatic bacteriuria by culture and AST profile in patients with BPH undergoing surgical interventionsis suggested especially in patients with co morbid conditions like diabetes mellitus, so that prophylactic AST guided antibiotic therapy should be initiated as per the guidelines, in these patients to prevent complications.

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