

ABSTRACT

Urinary Tract Infections Among Patients of Bladder Outlet Obstruction

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Background: Bladder outlet obstruction (BOO) is defined as blockage at the neck of the urinary bladder. This is one of the most common conditions in elderly men. BOO results from several etiologies, which may be functional or anatomic. However, the main cause of BOO remains benign prostatic hyperplasia (BPH), secondary to BOO and carcinoma prostate. The complication of BOO can be devastating and long term. The resulting obstruction frequently produces lower urinary tract symptoms (LUTS) and becomes the main cause of lower urinary tract infections (LUTI).

Material and Methods: In this cross-sectional study, a total of 100 consecutive patients of BOO who presented to our tertiary care hospital were enrolled in this study. After recording the demographic profile their mid-stream urine samples were collected and cultured for bacterial pathogens. The bacterial isolates were identified using standard microbiological methods and tested against a wide spectrum of antimicrobial agents using Kirby Bauer's method following the Clinical & Laboratory Standards Institute (CLSI) guidelines.

Results: Out of the 100 patients studied, 78% had BPH, and urine culture was positive in 74%. Most of these patients were more than 50 years of age group (90.5%) (Mean age= 61.2 years). There were 97.3% males and 2.7% of females. BPH was the most common cause of UTI as compared to the other causes of BOO (p=0.00001). *Escherichia coli* 46(62.1%) was the most common uropathogen causing UTI followed by *Klebsiellapneumoniae* 12(16.2%), *Pseudomonas aeruginosa* 10(13.5%), and the gram-positive organisms (*Staphylococcus aureus*, CoNS, *Enterococcus faecalis* 2.7% each). The study of their antimicrobial susceptibility showed that antimicrobial resistance to two or more drugs was present in the gram-negative (68/74) and gram-positive (6/74) isolates.

Conclusion: The present study shows that BPH continues to be the most frequent cause of BOO. There is a high prevalence of UTI in these patients which is caused by multidrug-resistance organisms. This study has important implications in the treatment of urinary tract infections among BOO patients in our region.

Key Words: Bladder outlet obstruction (BOO), Benign prostatic hyperplasia (BPH), Multidrug-resistant (MDR), Urinary tract infection (UTI), Lower urinary tract syndrome (LUTS), Uropathogens

INTRODUCTION

Bladder outlet obstruction (BOO) is defined as blockage at the neck of the urinary bladder. This is one of the most common conditions in elderly men.¹As the age expectancy is increasing the number of men affected by BOO is expected to rise. The greatest increase is anticipated in developing countries like India.² BOO results from several etiologies, which may be functional or anatomic. The various reported causes of BOO are benign prostatic hyperplasia (BPH), carcinoma prostate, bladder stone, bladder carcinoma, posterior urethral valve, dysfunctional voiding, neurogenic-based detrusor-sphincter dyssynergia (DSD), bladder neck stenosis and obstruction from stress urinary incontinence surgery.³⁻⁴ However, the main cause of BOO remains benign prostatic enlargement, secondary to BPH and carcinoma prostate. BPH is a condition inevitably associated with ageing. Fifty per cent of men over the age of 40 develop BPH.⁵⁻⁶ In contrast, BOO is a poorly understood condition in females. It is much rare in them as compared to males and has the aetiology of bladder neck stenosis, urethral stricture, urethral diverticulum and retroverted uterus.⁷

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The Complication of BOO can be devastating and long term. BOO can permanently damage all parts of the urinary system.⁸The obstruction frequently produces lower urinary tract symptoms (LUTS) which can have a significant negative impact on the quality of life.9-11 There is urine stasis from incomplete voiding and the resultant residual urine serves as the medium for bacterial growth which leads to urinary tract infection (UTI). Lower UTI involves infections from the urinary bladder downward and includes urethritis, cystitis and prostatitis. Asfo-Adjeiet al. reported a 76.6 % incidence of urinary tract infections among their BOO patients and the main risk factor identified was catheterization.¹² Most of these infections are caused by a few genera of the family Enterobacteriaceae and the common uropathogens reported are Escherichia coli, Pseudomonas spp., Staphylococcus aureus, Enterococcus species, Klebsiella spp. and Proteus spp.¹³⁻¹⁵ The microbes causing infection differ in their susceptibility towards various antimicrobial drugs from place to place and time to time. The emergence of multiple drug resistance strains causing UTI is also escalating. It is a big challenge in our country because of the irrational use of antibiotics.

Hence, the present study was undertaken with aim of determining the proportion of UTI and various uropathogens causing it in the clinically suspected patients of BOO attending the urology department of our tertiary care centre. There is a paucity of such studies from this area of Punjab (North India).

MATERIAL AND METHODS

This prospective cross-sectional study was conducted on a total of 100 consecutive patients of BOO who were attending the urology department of our tertiary care centre. Ethical approval of this study was obtained from the institutional review committee (BFUHS/2K19p-TH/8906). After recording the demographic profile of the patients in the prescribed Performa, their urine samples were collected, using all the sterile precautions.

The patients were asked to collect midstream urine samples in sterile containers, which were transported to the microbiology department within 2 hours of collection. The urine specimen was processed within 30 minutes of arrival in the laboratory. Specimens were initially inoculated on a standard culture media, Cystine–Lactose–Electrolyte-Deficient (CLED) agar, using a standard calibrated loop. Following incubation in an ambient air incubator at 35-37° C for 18 hours colonies were counted and counts of $\geq 10^5$ CFU/ mL were assessed as significant bacteriuria. The bacterial growth was identified based on their colonial morphology, Gram's staining, and biochemical reactions which included the Catalase test, slide and tube Coagulase test, Oxidase test, Indole test, MR test, Citrate utilization test, Triple sugar iron

test (TSI). Oxidation/fermentation test, Urease test, Nitrate reduction test, VP (Voges-Proskauer) test.16-17The isolated and identified colonies were then tested for antimicrobial susceptibility on Mueller Hinton agar using the Kirby-Bauer disc diffusion method according to Clinical Laboratory Standard Institute (CLSI) guidelines.¹⁸ The antibiotic discs and their concentration used in the study were Ampicillin (2µg), Cefoxitin (30µg), Cefotaxime (30µg), Ceftriaxone (30µg), Ceftazidime (30µg), Cefepime (30µg), Gentamicin (10µg), Amikacin (30µg), Imipenem (10µg), Norfloxacin (10µg), Ciprofloxacin (10µg), Levofloxacin (10µg), Piperacillin-Tazobactam (100/10µg), Amoxicillin-Clavulanic acid (30µg/10µg), Nitrofurantoin (300µg), Vancomycin (30µg), Linezolid (30µg), High-level Gentamicin (120µg), Colistin/ Polymyxin B (100 unit) for Staphylococci, MIC (minimum inhibitory concentration) of Vancomycin was determined and value of $\leq 2 \mu g/ml$ was considered as sensitive.

Data so obtained was analyzed using Microsoft Excel software and Statistical Package for the Social Sciences (SPSS). The Chi-square test was employed to study the association of current LUTI status with other factors. The variables were compared using cross-tabulation statistical methods and the p-value <0.05 was considered statistically significant.

RESULTS

Table-1 summarizes the demographic profile of 100 patients who were suspected to have clinical evidence of BOO by the treating urologist. The mean age of the study population was 61.2 years (9-83 years). The maximum patients 83(83%) were more than 50 years of age followed by 5-15 years (9%). Most (93%) of them were males and the females constituted only 7% of the study population. A total of 73% were literate and had education up to 5th standard or more. In terms of occupation, pensioners were predominant (54%) followed by those in jobs (employed) (34%). In the present study, the most common cause of BOO was found to be benign prostatic hyperplasia (78%) followed by prostate cancer (14%), bladder neck stenosis (4%), and posterior urethral valve (2%) (Table-1). There was a history of acute and chronic retention and chronic urinary catheterization in 69%. The most common comorbidity among the patients of BOO observed was hypertension (43%) followed by diabetes (9%).

On culture, significant bacterial growth was obtained in 74(74%). Of these 67(90.5%) were more than 50 years of age. The culture positivity in this age group showed a statistically significant difference from in the 5-15 years of age group (p-value: a and b= 0.02). Out of 74 culture-positive patients, 72(97%) were males and 2(2.7%) were females and the difference was statistically significant (p-value: c and d= 0.01). BPH 67(90.5%) was the main cause of LUTI followed by various other causes which also showed a statistically significant years.

nificant difference (p-value: e and f= 0.000001) (Table 1).

Of the 74 positive bacterial cultures, 68(91.9%) showed the growth of gram-negative bacteria while only 6(8.1%)were gram-positives. E. coli found to be the most frequent 46(62.1%) isolate followed by K. pneumonia 12(16.2%)and P. aeruginosa 10(13.5%). The gram-positive bacteria isolated were S. aureus, coagulase-negative staphylococci (CoNS) and *Enterococcus faecalis* 2(2.7%) each (Figure-1). The result of antimicrobial susceptibility testing of the 74 isolated organisms is shown in (Table-2). E. coliwhich was the most prevalent organism causing UTI in the present study was found to be 100% resistant to Amikacin, all the three 3rd generation and 4th generation cephalosporins (Cefotaxime, Ceftriaxone, Ceftazidime, cefepime) and Ciprofloxacin. This was followed by resistance to Imipenem (73.9%), Norfloxacin and Levofloxacin (60.8% and 54.3% respectively). Resistance to aminoglycosides (Gentamicin and Amikacin) was less than 50%. While Nitrofurantoin was effective in more than 80%, no strain was found to be resistant to colistin. The 12 isolates of K. pneumoniae showed an almost similar pattern of resistance as that of E. coli. The exception was that K. pneumoniae strains were more resistant to Imipenem (83.3%) and even Nitrofurantoin (50%) than those of E. coli. All the 10 strains of P. aeruginosa showed 100% resistance to Ampicillin, cephalosporins, Norfloxacin and Ciprofloxacin, and more than 80% resistance to Gentamicin, Amikacin, and Imipenem. Amongst the gram-positive cocci, the resistance to Ampicillin, Aminoglycosides (Amikacin and Gentamicin), and fluoroquinolones (Levofloxacin, Ciprofloxacin, and Norfloxacin) was 100%. But all the strains were sensitive to Vancomycin, and Linezolid. Resistant to two or more drugs was observed in all the gram-negative and gram-positive isolates. Thus, the overall prevalence of multidrug resistance was 100% in our study (Table-2).

DISCUSSION

The focus of the present study was to determine the important causes of BOO and the common uropathogen causing LUTI among patients of BOO in our region (North India). We observed that the mean age of our study participants was 61.2 years and 83% were more than 50 years of age. This is similar to the findings of two studies of Gyasi-Sarpong*et al.*^{9,19}In both studies, the mean age was 62 years.Shetty*et al.* observed it to be 57 years and the range was between 18-80 years.⁸There was a predominance of males (93%) and the male, the female ratio was 13.2 in our study. Other authors have also reported that BOO, more commonly affects men especially those of the old age group.^{9,12,19} male and female ratio in the study of Katakwar and Thakur was 15.6 which is similar to that of the present study.²⁰ The most frequent cause of BOO in the present study was BPH (78%) which corroborates the findings of Asafo-Adjei*et al.* and other authors.^{12,20}Shetty*et al.* had reported that the most common cause of BOO was BPH in males and bladder neck stenosis in females.⁸ Four of the 7 females of our study were suffering from bladder neck stenosis (Table-1).

The prevalence of UTI among the patients of BOO in our study was 74% and the maximum positive cultures were obtained in patients of more than 50 years of age followed by 5-15 years (age group). Statistically, the difference between the two age groups was significant (p-value: a and b= 0.0003) Table 1. In a study, Gyasi-Sarpong *et al.* reported a 76% prevalence of UTI among BOO patients of more than 70 years of age.¹⁹ Jarvis *et al.* also observed that the prevalence of UTI was often indicative of BOO secondary to BPH, especially in elderly men.²¹

A wide range of bacterial organisms was observed to cause UTI in the present study. There was a predominance of members of the family Enterobacteriaceae and *E. coli* was the most frequent (62.1%). The other isolates identified were *Klebsiella spp.* (16.2%), *Pseudomonas spp.* (13.5%) and *Staphylococcus spp.* (5.4%) and Enterococci (5.4%). This is similar to the studies of Asafo-Adjei*et al.* and Ahmed *et al.*^{12,22} However, *Enterococcus faecalis* which was found to be an important gram-positive uropathogen in our study was not isolated in the study of Asafo-Adjei*et al.*¹² In another study *Klebsiella spp.* (36.6%) and *P. aeruginosa* (27%) were the most prevalent organisms.²³ This variation in the aetiology of UTI could be because of differences in the periods of the studies, in the places/regions/countries of the study, and the study population.

All the gram-positive and gram-negative organisms causing UTI in the present study were found to be resistant to two or more drugs. The alarming finding was that all (100%) strains of E. coli resistant to Ampicillin, Cefotaxime, Ceftriaxone, Cefepime and Ciprofloxacin. They also showed very high resistance to Imipenem (73.9%). Only Colistin and Nitrofurantoin were found to be effective with the sensitivity of 100% and 80.5% respectively. Hussain et al. also reported the maximum resistance of E.coli to Ampicillin, 3rd generation cephalosporins, Norfloxacin and Gentamycin.24 Asfo-Adjeiet al observed high resistance of E. coli to fluoroquinolones.¹² The strains of K. pneumoniae of the present study had shown an even higher level of resistance as compared to those of E. coli which also corroborates the findings of Hussain et al.24 However, a reverse trend was observed by Ranbeeret al. They found 89% sensitivity to Gentamycin, 93% to Imipenem and 98% to Nitrofurantoin.25 The isolated strains of P. aeruginosa also showed a very high level of resistance to all antimicrobials agents including Imipenem (80%). A similar pattern was observed in the study of Asfo-Adjeiet $al.^{12}$ This could be because UTI is often treated empirically which results in inappropriate and non-judicious use of these high-end antimicrobial agents leading to MDR (multiple drug resistance) infections in patients with UTI.

In our study, there were only four strains of Staphylococcus species and two of them were resistant to Cefoxitin. These two methicillin-resistant *Staphylococcus aureus*(MRSA) strains were showed resistance to Ampicillin and aminogly-cosides. However, these were found to be sensitive to Vancomycin and Linezolid. Thus, we were left with the option of treatment of these infections by Linezolid or Vancomycin. Enterococcus *faecalis* was found to be causing significant bacteriuria in two patients. Both these strains were highly resistant. They showed sensitivity only to only Vancomycin and Linezolid. It is an alarming situation as Vancomycin-Resistant Enterococcus (VRE) causing UTI are difficult to manage. Linezolid, the oral drug could be used but only 30% of each dose of it is excreted in the urine.²⁶

CONCLUSION

The present study confirms that BPH continues to be the most common cause of BOO and UTI caused by multi drugresistant organisms is highly prevalent in these patients for the adequate treatment of these patients, appropriate antibiotics selected after urine culture and antimicrobial susceptibility testing should be used. This could also help to contain the problem of drug resistance. The drug monitoring system that augments drug administration and associates a more personalized methodology to recommended treatment may also help.

Conflict of interest

The authors declare no conflicts of interest.

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Author's contribution

Study conception and design: Jindal N. Data collection: Shakya BK and Sahota SK. Laboratory work: Shakya BK. Analysis and interpretation of data: Jindal RP, Shakya BK and Sahota SK. Final drafting of manuscript: Jindal RP, Shakya BK, Jindal N and Sahota SK. All authors commented and approved the final manuscript.

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Table 1: Demographic and clinical features of the study participants.

Age (years)	N=100	Z=74	P-value
5-15 ^a	9(9%)	4(5.4%)	
16-40	3(3%)	1(1.4%)	a and b = 0.0003
41-50	5(5%)	2(2.7%)	
>50 ^b	83(83%)	67(90.5%)	
Gender			
Male ^c	93(93%)	72(97.3%)	c and $d = 0.01$
Female ^d	7(7%)	2(2.7%)	
Education status			
Literate	73(73%)	59(79.7%)	
Illiterate	27(27%)	15(20.2%)	
Occupation			
Unemployed	12(12%)	10(13.5%)	
Employed	34(34%)	15(20.3%)	
Pensioner	54(54%)	49(66.2%)	
Cause of BOO			
BPH ^e	78(78%)	67(90.5%)	
Prostate cancer	14(14%)	5(6.8%)	e and f**= 0.00001
Bladder neck stenosis	4(4%)	1(1.4%)	
Posterior urethral valve	2(2%)	0	
Bladder carcinoma	1(1%)	1(1.4%)	
Bladder stone	1(1%)	0	
Comorbidities			
Hypertension	42(42%)	7(9.4%)	
Diabetes	29(29%)	3(4%)	
Stroke	5(5%)	1(1.4%)	
Other	2(2%)	0	

BPH = benign prostatic hyperplasia, BOO= bladder outlet obstruction. "N" = number of study subjects, "Z" = number of cultures positive, "f" = Causes of BOO other than BPH.

ANTIBIOTICS	EC(n=46)	KP(n=12)	PA(n=10)	SA(n=2)	CoNS(n=2)	EF(n=2)
Ampicillin	46(100)%	12(100)%	10(100%)	2(100)%	2(100)%	2(100)%
Cefoxitin	NT	NT	NT	2(100)%	o(o%)	NT
Cefotaxime	46(100)%	12(100)%	10(100%)	NT	NT	NT
Ceftriaxone	46(100)%	12(100)%	10(100%)	NT	NT	NT
Ceftazidime	46(100%)	12(100%)	8(80%)	NT	NT	NT
Cefepime	46(100)%	12(100)%	10(100%)	NT	NT	NT
Gentamicin	20(43.4%)	6(50%)	8(80%)	2(100)%	2(100)%	1(50%)
Amikacin	19(41.3%)	6(50%)	8(80%)	2(100%)	2(100%)	2(100%)
Nitrofurantoin	9(19.5%)	6(50%)	6(60%)	NT	NT	2(100)%
Norfloxacin	28(60.8%)	8(66.6%)	8(80%)	o(o%)	o(o%)	2(100)%
Ciprofloxacin	46(100)%	12(100)%	10(100%)	2(100)%	2(100%)	2(100%)
Levofloxacin	25(54.3%)	7(58.3%)	NT	2(100%)	2(100%)	2(100%)
Imipenem	34(73.9%)	10(83.3%)	8(80%)	NT	NT	NT
Pipracillin +Tazobactum	18(39.1%)	4(33.3%)	4(40%)	NT	NT	NT
Amoxicillin+cavulanic acid	25(54.3%)	10(83.3%)	NT	NT	NT	NT
Vancomycin	NT	NT	NT	o(o%)	o(o%)	o(o%)
Linezolid	NT	NT	NT	o(o%)	o(o%)	o(o%)
High level Gentamicin	NT	NT	NT	NT	NT	o(o%)
Colistin/polymyxin B	o(o%)	o(o%)	o(o%)	NT	NT	NT

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EC= *E. coli*, KP= *K. pneumoniae*, PA=*P. aeruginosa*, SA= *S.aureus*, CoNS= coagulase negative staphylococcus, EF=*Enterococcus faecalis*, NT= Not tested.



Figure 1: Uropathogens isolated.