

A study of risk factors for bacteremia caused by urinary tract infections



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ABSTRACT

Background: Urinary tract infections are not only one of the most common infections, but also one of the most common sources of bacteremia in both the general population and hospitalized patients. **Aims and Objectives:** The objective of this study was to identify risk factors for bacteremia caused by urinary tract infections. **Materials and Methods:** This was a prospective case control study conducted from October 2012 to July 2014 in a tertiary care teaching hospital in southern India. Urinary tract infections were diagnosed based on the CDC criteria. Patients with a set of blood cultures and urine culture isolating same organism were grouped as cases while patients with urine culture alone isolating organism with sterile blood cultures were identified as controls. **Results:** Out of the 198 patients in the study, 66 were cases while 132 were controls. E coli was the most organism isolated (81% of cases and 66% of controls). Risk factors for bacteremia based on univariate and multivariate analysis were diabetes mellitus with uncontrolled sugars (univariate: $p = 0.001$; OR = 5.250 [2.044-13.582]; and multivariate: $p = 0.01$; OR = 6.023 [1.52-23.51]) and pyelonephritis (univariate: $p = 0.001$; OR = 6.56 [2.87-14.8]; and multivariate: $p = 0.047$; OR = 4.95 [1.02-24.12]). **Conclusion:** Upper UTI and complicated UTI patients should be evaluated for bacteremia since prompt and targeted treatment may be required.

Key words: Risk factors; Bacteremia; UTI

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INTRODUCTION

Urinary tract infection is one of the most common infections seen in day to day life.¹ It has various clinical presentations ranging from simple self-limiting fever and lower urinary tract symptoms to very severe form of sepsis and septic shock causing prolonged morbidity and mortality depending on underlying host and pathogen factors.² Escherichia coli is the most common organism causing urinary tract infection.¹ Some of the other common organisms that leads to this infection are klebsiella species, enterococcus species, proteus mirabilis, staphylococcus aureus and pseudomonas aeruginosa.

Urinary tract is the most common source of bacteremia both in general population and hospital acquired infections.

Mortality and morbidity is very high in UTI complicated with bacteremia.^{3,4} Certain groups of urinary tract infected patients were at high risk for developing bacteremia and the factors associated with bacteremia were poorly understood.² An early and effective treatment should be initiated so that complications of bacteremia can be minimized.

Present study is aimed at identifying the risk factors for urinary source bacteremia.

MATERIALS AND METHODS

The present study was a prospective case control study conducted in Kasturba hospital, Manipal. Kasturba Hospital. This was a time bound study conducted from

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October 2012 to July 2014. The study has been approved by the Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee, an institutional ethics committee.

Case - A set of blood cultures and urine culture isolating same organism.

Control- Urine culture alone isolating organism with sterile blood cultures.

Blood cultures were performed using BacT/ALERT® FA Plus BIOMERIEUX, INC. Durham, NC bottles and were inoculated with 8-10 mL of blood per culture bottle.

Inclusion criteria

All adult (> 18 years) inpatients who met the criteria of UTI and blood cultures taken within 24-hour time period of urine cultures were included.

Exclusion criteria

- 1) Isolation of Polymicrobial growth in cultures.
- 2) Blood culture and urine culture isolating different organisms.
- 3) Partially treated cases and antibiotics started before sending cultures were excluded.

Detailed history including age, sex, occupation and symptomatology were recorded along with detailed general and systemic clinical examination. A fasting sugar, postprandial sugar and glycosylated hemoglobin was done for all diabetics. Diabetes mellitus was diagnosed as per American diabetic association (ADA) criteria.⁵

Urinary tract infection was diagnosed by CDC criteria.⁶

Patients with positive urine cultures underwent appropriate investigations in the form of ultrasound and/or CT abdomen to aid in the clinical management.

Defining the risk factors

Indwelling catheter

Foleys catheter, suprapubic catheter or intermittent catheterization associated urinary tract infection (CAUTI) as diagnosed by IDSA criteria.

Instrumentation

Urinary tract infection post procedures like transurethral resection of prostate, cystoscopy, percutaneous nephrolithotomy.

Renal stone disease

Patients presenting with any of the signs and symptoms of renal calculi like acute onset of flank pain radiating to pelvis and genitalia, hematuria, increased urinary frequency, nausea,

vomiting and supporting imaging (USG KUB, CT KUB etc.) evidence of calculi.

Pyelonephritis

Kidney infection characterized by costovertebral angle pain and tenderness, with fever and/or imaging showing features of pyelonephritis.

Benign prostatic hyperplasia

Patients presenting with lower urinary tract symptoms including obstructive symptoms (e.g., urinary hesitancy and weak stream) and bladder storage symptoms (e.g., urinary frequency and nocturia) supported by urodynamic and imaging studies (ultrasound prostate).

Statistical analysis

A conditional logistic regression was carried out to estimate the exposure odds ratios and the 95% confidence intervals. First, univariate analysis was performed separately for each of the variables. The exposure odds ratios were calculated using the lowest exposure level stratum as the baseline. After identifying potential risk factors from the univariate analysis with a p value of less than or equal to 0.20, a multivariate analysis was carried out using a stepwise procedure to select the independent risk factors that together best predict the bacteremia. In instances in which the univariate analysis suggested an increasing odds ratio with a higher level of exposure, the variable was treated as a continuous variable in the multivariate analysis. Otherwise, the variable was categorized as either the presence or absence of the risk factor.

Each case was compared with two controls.

P-value of <0.05 was taken as statistically significant.

All the data were analyzed using SPSS v.15.

Since it was a time bound study no attempt was made to calculate the sample size.

RESULTS

198 patients were included in the study based on inclusion criteria out of which 66 cases of urinary source bacteremia (cases) were compared with 132 urinary tract infected patients without bacteremia (controls).

Factors which were studied as risk factors for urinary source bacteremia

- Age
- Sex
- Diabetes mellitus
- Renal stone disease
- Instrumentation

- Indwelling catheter
- Urethral stricture
- Benign prostatic hyperplasia

Age distribution

Mean age of the study population was 55.1 +/- 14 in cases and 54.9 +/- 13 in controls. Subjects with age less than 60 years were more in cases but this was not statistically significant (P value 0.179 and Odds ratio - 1.662 (0.790-3.496)).

Gender

Males were more in number compared to females in cases but statistically did not have increased risk of bacteremia (OR - 1.582(0.870-2.876), p -0.131). Gram negative organisms were most common organisms both in cases and controls. E.coli was the most common organism (141 patients; 71%) followed by klebsiella (28 patients; 14%). Details of the organisms isolated from the study population are detailed in Table 1.

E coli are the most common organism causing urinary source bacteremia. Amongst all the risk factors (diabetes, history of instrumentation, BPH, renal calculi and catheter associated UTI) E. coli was the most common organism.

Clinical features

Fever

Fever was the predominant feature both in cases and controls (Cases=81.8%; Controls=82.6%; p=0.895).

Lower urinary tract symptoms (LUTS)

Lower urinary tract symptoms were more common in controls but this was not statistically significant

(Cases=34%; Controls=58%; p=0.840). Patients presenting with high WBC count (> 12,000) had a higher chance of having bacteremia (p=0.001).

Pyelonephritis

Patients presenting with pyelonephritis had 6 times higher chance of having bacteremia (p=0.001; OR=6.56 [CI=2.87-14.8]).

RISK FACTOR ANALYSIS

Diabetes mellitus

Diabetic patients were 2.5 times at higher risk for developing urinary source bacteremia when compared to non-diabetic patients (p=0.002; OR=2.537 [CI=1.38-4.65]).

Urinary tract infected patients who had uncontrolled diabetes had 5 times higher risk for bacteremia (p=0.001; OR=5.250 [CI=2.044-13.582]).

There was no statistically significant difference between cases and controls with respect to indwelling urinary catheterization for urinary source bacteremia (p=0.280; CI=0.667 [0.318-1.396]), undergoing instrumentation (p=0.356; OR=1.505 [CI=0.630-3.598]), presence of renal stone disease (p=0.471; OR=1.353 [0.584-3.085]) and presence of benign prostatic hyperplasia (p=0.784; OR=1.129 [CI=0.474-2.692]). Important risk factors for urinary source bacteremia are shown in Table 2.

Urethral stricture

A statistically insignificant difference was seen in urethral stricture between bacteremia group {4(6%)} and the non- bacteremia group {2(1.5%)}.

Risk factors significant in univariate analysis

Diabetes mellitus with uncontrolled blood sugars and pyelonephritis were identified as statistically significant risk factors for bacteremia.

Multivariate analysis

Table 3 shows that on multivariate logistic analysis, diabetes mellitus with uncontrolled blood sugars and pyelonephritis emerged as the most important factors associated with urinary source bacteremia.

Organism	Case	control
E coli	54 (81%)	87 (66%)
Klebsiella	8 (12%)	20 (15%)
Enterococcus	1 (1.5%)	17 (12.9%)
Acinetobacter	1 (1.5%)	2 (1.5%)
MSSA	0	1 (0.8%)
MRSA	0	2 (1.5%)
Pseudomonas	1 (1.5%)	2 (1.5%)
Proteus	0	1 (0.8%)
Salmonella	1 (1.5%)	0

Risk factor	Cases (n=66)	Controls (n=132)	P value	Odds ratio with CI
Diabetes mellitus	38 (57%)	46 (38.4%)	0.002	2.537 (1.38-4.65)
Glycohb >8	28 (73%)	16 (35%)	0.001	5.250 (2.044-13.582)
Indwelling urinary catheter	12 (18%)	33 (25%)	0.280	0.667 (0.318-1.396)
History of instrumentation	10 (15%)	14 (10.6%)	0.356	1.505 (0.630-3.598)
Renal stones	11 (16.7%)	17 (12.9%)	0.471	1.353 (0.584-3.085)
Benign prostatic hyperplasia	12 (28%)	17 (27%)	0.784	1.129 (0.474-2.692)

Table 3: Multivariate analysis of risk factors

Factor	P value	Odds ratio with CI
Uncontrolled diabetes mellitus	0.010	6.023 (1.52-23.51)
Pyelonephritis	0.047	4.95 (1.02-24.12)

DISCUSSION

Urinary tract infection is one of the most common sources of bacteremia both in community and hospital acquired infections with increased mortality (ranging from 10-25 percent) and prolonged hospital stay.^{3,9} Fifteen percent of symptomatic UTI patients would be having bacteremia in the general population.⁷ Many studies tried to identify the risk factors for urinary source bacteremia which were poorly understood.^{2,7} In this study we tried to study various risk factors for urinary source bacteremia.

Mean age of the study population was 55 years which was similar (55-70 years) to other studies.^{3,13} However, we did not get any association between bacteremia and advanced age (more than 60 years). In fact unlike other studies, the present study reports a marginally higher proportion of bacteremia among the younger individuals although was not statistically significant. Literature reported advanced age (>60 years) as a risk factor for urinary source bacteremia which they attributed to increased incidence of benign prostatic hyperplasia in elderly men and multiple comorbidities seen in elderly population.¹³

A slight male (59%) preponderance was observed in the present study though not statistically significant (p value = 0.179) which confirms with most other studies not identifying gender as a risk factor for urinary source bacteremia.^{2,12} Male predominance in bacteremia group in this study may be attributed to benign prostatic hyperplasia.

Seventy one percent of urinary source bacteremia patients presented with Leucocytosis (WBC > 12,000) when compared to 40% in UTI without bacteremia patients (p = 0.001). Hence leukocytosis is an important factor in predicting bacteremia. In a community based study done by Ybahagon et al (2007), patients presenting with fever with shaking chills and neutrophilia had a higher chance of bacteremia.⁷

E coli and Klebsiella continue to be the most common organisms for both UTI and urosepsis.¹³ Even though E coli is the most common cause of UTI, which alone could not explain increased risk of bacteremia. Virulent strains of E coli with pap adhesin, type 1 fimbriae and few serotypes like O1, O2, O4, O16 have more invasive properties and also cause dysfunction of ureter motility causing easy upper urinary tract infection and bacteremia.^{10,11}

Pyelonephritis has higher risk for bacteremia (odds ratio - 4.95 and p value - 0.047). Many other studies also proved the same.^{8,14} In a study done by Hsu et al (2006), 42% of patients with pyelonephritis developed bacteremia.⁸ In another study done by Gisela Otto et al (1993), patients with pyelonephritis had a higher chance for bacteremia if E coli with p fimbriae strain was the etiological agent. In another study done by Smith et al (1993), 35% of the patients presenting with pyelonephritis had bacteremia.¹⁴ The kidney, being an organ with a rich blood supply, results in a breach in the blood barrier due to pyelonephritis causing infection and inflammation paving easy access for organisms into the blood leading to bacteremia.

Diabetes mellitus with uncontrolled sugars is an important risk factor for bacteremia as observed in the present study using multivariate logistic regression analysis (OR= 6, p=0.010). Postulated mechanisms are immune dysfunction in the form of decreased complement function, leucocyte adherence and bactericidal activity. It also causes innate immunity dysfunction and neutrophil dysfunction due to increased intracellular calcium thus interfering with phagocytosis. High blood sugar levels itself act as a thriving ground for pathogens.¹⁵

Even though we did not find any statistically significant association between urinary catheter and bacteremia, it is an important risk factor for bacteremia.^{3,7} Approximately 15% of hospital acquired bacteremia is due to urinary tract infections and bacteriuria is the most common source of bacteremia. However bacteremia complicates catheter associated bacteriuria in only 1% to 5% of CAUTI.^{16,17} Various risk factors for catheter associated bacteriuria are colonization of the drainage bag, catheter insertion without aseptic precautions, rapidly fatal underlying illness, older age, diabetes mellitus, elevated serum creatinine and long term catheterization.^{12,18} Rudman D et al (1988) reported urinary catheterization was associated with 39 fold increase in incidence of bacteremia.¹⁹

Patients with prior history of instrumentation did not have increased risk for bacteremia (p value = 0.356). In a study done by Magnus Arpi et al (1986), of 33 patients included in the study 14 underwent transurethral resection of prostate, 14 underwent cystoscopy and 5 underwent urethrotomy. None of the above patients received prophylactic antibiotic prior to procedure and 21% of the patients developed urinary source bacteremia post procedure.²⁰ Jonas marshal et al (2012) reported a history of urogenital surgery as an important risk factor for bacteremia.² Iatrogenic modification of the urogenital tract might lead to the disruption of urothelium and increased infection risk due to easy access for organisms.² In the present study, a majority of patients received prophylactic antibiotics prior to the

procedure and this might be the reason for no association of instrumentation with bacteremia.

Benign prostatic hyperplasia was not associated with bacteremia (28% in cases versus 27% in controls, p value – 0.784). In the literature as well there are very few studies which associate benign prostatic hyperplasia as a risk factor for bacteremia.² In a study done by Jonas Marshall *et al* (2012), benign prostatic hyperplasia with symptoms of urinary hesitancy and retention was an important risk factor for bacteremia.² Benign prostatic hyperplasia patients will have symptoms of urinary retention and hesitancy due to which there is a prolonged stasis of urine and colonization of bacteria which invades the urothelium causing recurrent and chronic urinary tract infection, leading to bacteremia in susceptible individuals.²¹ Certain *E. coli* traits (hemolysin and cytotoxic necrotizing factor) that promote prostatic invasion may be relevant for the pathogenesis of urinary tract infection in BPH patients.²² In literature, BPH was not a risk factor for bacteremia.⁷

Renal stone disease was not associated with bacteremia (17% in cases vs 13% in controls, p value – 0.471). In literature, renal stone disease was a risk factor for urinary tract infection and bacteremia.²³ A renal calculus causes a structural abnormality in the urinary tract and it also gets infected due to obstruction and stasis of urine proximal to obstruction, thus predisposing the patient to pyelonephritis. As it causes structural abnormalities, urinary tract infection is considered as complicated and hence there is a higher risk of bacteremia.²⁴ Sheffield *et al* (2005) had observed renal calculi along with frequent sexual activity and diabetes mellitus as risk factors for pyelonephritis.²⁵

Mortality in the present study was very low (1.5%). Mortality in urinary source bacteremia ranges very widely between 5% and 25% depending on the underlying host and pathogen factors.²⁹ In a study done by Ackerman *et al* (1996) in older individuals, out of 183 urinary source bacteremic episodes, the mortality rate was 16% and was attributed to many comorbid conditions seen in elderly patients.⁹

This study was done in a single tertiary care center in a particular area so results could not be extrapolated. Since this was a time bound study adequate sample size to study all the risk factors could not be obtained. Less number of sample size in the study might be the cause for advanced age not emerging as a risk factor for urinary source bacteremia.

Urinary tract infections are common source of bacteremia. Blood culture should be drawn in patients presenting with uncontrolled diabetes and pyelonephritis as there is high possibility of bacteremia these patients. Empirical antibiotic therapy should target bacteremia.

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Author s contribution:

MV- Concept and design of the study, critical revision of the manuscript; **SKP**-Reviewed the literature, collected data manuscript preparation, preparing first draft of manuscript; **VKE**-Concept, literature search; **AK**- Statistically analyzed and interpreted; **RS**- Reviewed the literature, collected data, manuscript preparation

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