Useful predictive factors for bacteremia among outpatients with pyelonephritis

Title:

Useful Predictive Factors for Bacteremia among Outpatients with Pyelonephritis

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None

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Abstract

Objectives: The aim of this study was to identify predictive factors for bacteremia conveniently and quickly among outpatients diagnosed with pyelonephritis.

Patients: All patients who were diagnosed with pyelonephritis at the outpatient clinic in the Department of General Medicine of Juntendo University Hospital from April 1, 2008, to June 30, 2015, were enrolled. Patients from whom blood cultures had not been taken were excluded.

Methods: Clinical information was extracted from medical charts. Factors potentially predictive of bacteremia were analyzed using a t-test and Fisher's exact test, followed by a multivariable logistic regression model analysis.

Results: Blood cultures were drawn from 116 patients, and 25 (22%) presented with bacteremia. A multivariate analysis with the age, chills, platelet count and urine nitrite test results revealed that older age, positive urinary nitrite test results and chills tended to be associated with bacteremia, respectively. (older age: unit odds ratio [OR] 1.02, p=0.052, 95% confidence interval [CI] 1.00-1.05, positive urinary nitrite test findings: OR 2.5, p=0.092, 95% CI 0.86-7.7, chills: OR 2.5, p=0.096, 95% CI 0.84-7.65). The area under the receiver operating characteristic (ROC) curve of this model was 0.77. Regardless of age, positive urinary nitrite test findings were significantly associated with bacteremia (OR 3.1, p=0.033, 95% CI 1.1-9.2), and chills tended to be associated with bacteremia (OR 2.7, p=0.07 95% CI 0.93-7.9) The area under the ROC curve of this model was 0.75.

Conclusions: Bacteremia should be considered in pyelonephritis patients with rapidly assessable factors in outpatient clinic. In particular, a model including a urinary nitrite test has the potential to aid in the prediction of bacteremia.

Key words: Pyelonephritis, Bacteremia, Urinary nitrite test

Introduction

Pyelonephritis is a common infectious disease. Approximately 250,000 cases of pyelonephritis occur each year in the US.[1] The management guidelines for urinary tract infections in the US and Japan recommend that patients with mild, uncomplicated pyelonephritis be treated in an outpatient clinic.[2][3] However, previous studies have reported that 15%-32% of pyelonephritis cases were complicated with bacteremia.[4][5] In addition, severe pyelonephritis accompanied by bacteremia has a mortality rate of 10% to 20%.[6][7]

Bacteremia is one of the most severe complications of pyelonephritis, so physicians must have a high index of suspicion in patients with pyelonephritis. To enhance the likelihood of good outcomes, it is important to initiate adequate antimicrobial treatment before blood culture results return as positive.[8] Some previous studies have revealed predictive factors for pyelonephritis with bacteremia.[4][5][9] However, these studies did not include outpatients.

The aim of this study was to identify predictive factors for bacteremia conveniently and quickly among patients diagnosed with pyelonephritis in an outpatient clinic.

Materials and methods

In this study, we retrospectively investigated the medical records of all patients who were diagnosed with pyelonephritis at the outpatient clinic in the Department of General Medicine in Juntendo University Hospital from April 1, 2008, to June 30, 2015. We excluded patients from whom blood cultures had not been taken. Bacteremic pyelonephritis was defined as the detection of identical causative bacteria from blood and urine cultures.

We collected demographic data, vital signs, subjective symptoms, objective physical findings, laboratory findings, results of blood culture and urine culture, antimicrobial course, surgical interventions, and outcomes of the treatment as shown in Table 1. All male participants and participants with any underlying conditions listed in Table 1 were categorized as complicated pyelonephritis patients. Other participants were recognized as uncomplicated patients.

Because of the retrospective study design, the requirement for informed consent was waived. Study approval was obtained from the ethical committee of Juntendo University Hospital, with the approval number 15-123. Data analyses were performed using the JMP software program (version 11.0.0; SAS Institute Inc., Cary, NC, USA).

We used Fisher's exact test to compare the proportions of categorical variables between the groups. A t-test was used to compare continuous variables between the groups. A multivariate logistic regression analysis was then conducted based on the results of the univariate analysis ($p<0.05$) and previous studies to investigate the model for predicting bacteremia in the study population. We chose "chills" as the variable for the multivariate analysis, regardless of the univariate analysis results, because "chills" has been reported as a predictive factor by previous studies and is quickly assessable in outpatients. [5][9][10]

Results

During the study period, 141 patients were diagnosed with pyelonephritis at outpatient clinic. Blood cultures were drawn from 116 pyelonephritis patients, 25 of whom (22%) presented with bacteremia. Eighty-eight cases (75.9%) were categorized as uncomplicated pyelonephritis. Demographic factors are shown in Table 1. Bacteremia was significantly associated with an older age (bacteremia: 62.0±21 years old; non-bacteremia: 48.1±22 years old; p=0.006). No association was found between bacteremia and complications. Table 2 shows the results of urine cultures and blood cultures. *Escherichia coli* was the most frequent causative microorganism. Table 3 shows the clinical symptoms and laboratory results. A low platelet count (bacteremia: $19.8\pm6.7\times10^3/\mu L$; non-bacteremia: $23.0\pm7.5\times10^4/\mu L$; p=0.037) and positive urinary nitrite test findings (bacteremia: 48%; non-bacteremia: 31%; p=0.043) were associated with bacteremia. In contrast, general inflammatory parameters, such as body temperature, white blood cell count, neutrophil count and C-reactive protein, were not associated with bacteremia.

Table 4 shows the clinical course of all included patients. Patients with bacteremia were prone to require hospitalization for treatment (bacteremia: 22 patients [88%]; non-bacteremia: 31 patients [34%]; p<0.001), longer hospitalization (bacteremia: 12.5±9.2 days; non-bacteremia: 4.2±8.7 days; p<0.001) and a longer total duration of antimicrobial treatment than non-bacteremia patients (bacteremia:15.0±2.3 days; non-bacteremia:12.4±6.2 days). No patients died during the treatment course.

The results of the multivariate analysis are shown in Tables 5 and 6. For the multivariate analysis, we chose the variables that showed p<0.05 in the univariate analysis and "chills", based on the findings of previous studies of bacteremia [5] [9] [10]. Table 5 shows the results of a multivariate analysis including four factors: older age, positive urinary nitrite test, chills and a low platelet count. Older age, positive urinary nitrite test and chills all

tended to be associated with bacteremia (age: unit odds ratio [OR] 1.02, p=0.052, 95% confidence interval [CI] 1.00-1.05, positive urinary nitrite test: OR 2.5, p=0.092, 95% CI 0.86-7.7, chills: OR 2.5, p=0.096, 95% CI 0.84-7.65). The area under the receiver operating characteristic (ROC) curve of this model was 0.77. Regardless of age, a positive urinary nitrite test was significantly associated with bacteremia (OR 3.1, p=0.033, 95% CI 1.1-9.2), and chills tended to be associated with bacteremia (OR 2.7, p=0.07 95% CI 0.93-7.9). The area under the ROC curve of this model was 0.75.

Discussion

In this study, we investigated the predictive factors for bacteremia among pyelonephritis cases. In the study population, three factors were significantly associated with bacteremia in a univariate analysis: a positive urinary nitrite test, an older age and a lower platelet count. The results of the multivariate analysis showed that older age, positive urinary nitrite test and chills tended to be associated with bacteremia. Regardless of age, a positive urinary nitrite test was associated with bacteremia, and chills tended to be associated with bacteremia.

Our study found that positive urinary test results were associated with bacteremia. Positive urinary nitrite test findings have not been mentioned as a predictive factor of bacteremia in pyelonephritis patients. Many previous studies have reported that urinary tract occlusion [5][9][12], diabetes mellitus [4][9] or the presence of an indwelling urinary catheter [4] , chills[5][9][10] and neutrophilia [5][9][11] were significantly associated with bacteremia in pyelonephritis. However, these factors are all related to complicated pyelonephritis, except for neutrophilia and chills. Because the present study mainly involved uncomplicated pyelonephritis patients, no factors related to complicated pyelonephritis showed any significant association with bacteremia.

The urinary nitrite test is a rapid and convenient point-of-care test for clinics and emergency rooms. It is useful for predicting bacteriuria, and its sensitivity and specificity are 27%-35% and 97.5%-99%, respectively. [13][14][15] The urinary nitrite test is often used in combination with the urinary leukocyte esterase test in practice. While previous studies have suggested that pyelonephritis may be present when either urinary leukocyte esterase or nitrite is positive, with a sensitivity of 75% and a specificity of 82%, [14][16][17] no studies have shown that a nitrate test is useful for predicting bacteremia in these patients. The microbial spectrum of uncomplicated cystitis and pyelonephritis consists mainly of nitrite-producing *Escherichia coli* and other species of *Enterobacteriaceae*. [18][19][20] The prevalent causative

bacteria of pyelonephritis in this study was family *Enterobacteriaceae*, so the positive urinary nitrite test may reflect a long incubation time of nitrite-producing bacteria in urinary tracts, resulting in bacteremia. [21] The sensitivity and specificity of the urinary nitrate test of bacteremia in this study were not sufficiently high (48% and 75%, respectively), but to our knowledge, there have been no studies suggesting a positive urinary nitrite test as an associated factor of bacteremia in uncomplicated pyelonephritis. In this retrospective study, physicians might have tended to hospitalize patients when the blood culture results turned positive. As such, the urinary nitrite test may be useful for assisting physicians in deciding on a treatment plan for pyelonephritis patients.

Several limitations associated with this study warrant mention. First, the overall study population was small, and the study was conducted at a single center. Second, a common diagnostic criterion of pyelonephritis was not used because of the retrospective study design. These factors might have created bias in the results and should be resolved in a future prospective study.

In conclusion, pyelonephritis is common and often complicated with bacteremia. It is therefore important for physicians working in outpatient clinics not to miss a diagnosis of bacteremia due to limited information and tests. A model including the urinary nitrite test may be useful for predicting bacteremia in the outpatient setting and facilitating the direct early management of pyelonephritis, thereby potentially reducing any delay in hospitalization.

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References

(1) Ramakrishanan K, Scheid DC. Diagnosis and management of acute pyelonephritis in adults. Am Fam Physician 2005;71:933-42.

(2) Gupta K, Hooton TM, Naber KG, *et al*. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e20.

(3) Yamamoto S, Ishikawa K, Hayami H, et al. JAID/JSC Guidelines for the treatment of urinary tract infections and male genital infection. Nihon Kagakuryohou Gakkai Zasshi 2016;64:1-30 (in Japanese).

(4) Leibovici L, Greenshtain S, Cohen O, *et al.* Toward improved empiric management of moderate to severe urinary tract infections. Arch Intern Med 1992;152:2481–6.

(5) Bahagon Y, Raveh D, Schlesinger Y, *et al.* Prevalence and predictive features of bacteremic urinary tract infection in emergency department patients. Eur J Clin Microbiol Infect Dis 2007;26:349-52.

(6) Ispahani P, Pearson NJ, Greenwood D: An analysis of community and hospital-acquired bacteremia in a large teaching hospital in the United Kingdom. Q J Med 1987;63:427-40.

(7) Roberts FJ, Geere IW, Goldman A. A three-year study of positive blood cultures, with emphasis on prognosis. Rev Infect Dis.1991;13:34-46.

(8) Weinstein MP, Towns ML, Quartey SM, *et al.* The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis. 1997;4:584-602.

(9) Oshida Y, Hirashima O, Tanaka T, *et al.* The characteristics of urinary tract infection with urosepsis. Kansenshogaku Zasshi. 2014;5:678-84. (in Japanese)

(10) Tokuda Y, Miyasato H, Stein GH:A simple prediction algorithm for bacteremia in patients with acute febrile illness. QJM 2005;98:813— 20.

(11) Fukui S, Uehara Y, Fujibayashi K, *et al.* Bacteraemia predictive factors among general medical inpatients: a retrospective cross-sectional survey in a Japanese university hospital. BMJ Open. 2016;7:e010527.

(12) Marschall J, Zhang L, Foxman B, *et al.* CDC Prevention Epicenters Program: Both host and pathogen factors predispose to *Escherichia coli* urinary-source bacteremia in hospitalized patients. Clin Infect Dis. 2012;12:1692-8.

(13) Hooton TM. Uncomplicated Urinary Tract Infection N Engl J Med 2012;366:1028-37.

(14) Chernow B, Zaloga GP, Soldano S, *et al.* Measurement of urinary leukocyte esterase activity: A screening test for urinary tract infections. Ann Emerg Med 1984;13:150-4.

(15) Loo SY, Scottolini AG, Luangphinith S, *et al.* Urine screening strategy employing dipstick analysis and selective culture: an evaluation. Am J Clin Pathol 1984;81:634-42

(16) Bent S, Nallamothu BK, Simel DL, *et al.* Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002;287:2701-10.

(17) Hurlbut TA III, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. Am J Clin Pathol 1991;96:582-8.

(18) Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO. SENSProject. J Antimicrob Chemother 2003;51:69–76.

(19) Naber KG, Schito G, Botto H, *et al.* Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. Eur Urol 2008;54:1164–75.

(20) Zhanel GG, Hisanaga TL, Laing NM, *et al.* Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents 2006;27:468–75.

(21) Lie JT. Evaluation of a nitrite test kit (stat-test) for the detection of significant bacteriuria. J Clin Pathol 1968;21:443-4.

234 **Table 1. Patient characteristics and clinical classification**

	Bacteremia n=25	Non-bacteremia n=91	*p* value
Age, years; mean (SD)	62.0 (21)	48.1 (22)	0.006*
Female, n (%)	22 (88)	81 (89)	1.00
Underlying disorders, n (%)			
Diabetes mellitus	2 (8.0)	3 (3.3)	0.29
Anatomic abnormality of urinary tract	0 (0)	6 (6.6)	-
Indwelling urinary catheter	0 (0)	0 (0)	-
Neurogenic bladder	1 (4.0)	0 (0)	-
Immunosuppressive agents	2 (8.0)	3 (3.3)	0.29
Uncomplicated pyelonephritis, n (%)	17 (68)	71 (88)	0.30
History of pyelonephritis, n (%)	6 (24)	16 (18)	0.56

235 SD: standard deviation. Uncomplicated pyelonephritis patients were those without any
236 factors of complications, male gender or any underlying disorders listed above.

Table 2. Results of urine and blood cultures

	Urine culture results (n=116)	Blood culture results (n=116)
Escherichia coli, n (%)	65 (56)	23 (20)
Proteus mirabilis, n (%)	3 (2.6)	1 (0.9)
Citrobacter koseri, n (%)	3 (2.6)	
Group B *Streptococcus*, n (%)	2 (1.7)	
Klebsiella pneumoniae, n (%)	1 (0.9)	
Enterococcus faecalis, n (%)	1 (0.9)	1 (0.9)
Lactobacillus, n (%)	1 (0.9)	
Polymicrobial*, n (%)	7 (6.0)	
Negative, n (%)	33 (28)	92 (79)

* *Escherichia coli+Enterococcus faecalis, Escherichia coli+Klebsiella pneumoniae, Escherichia coli+Klebsiella pneumoniae+Pseudomonas aeruginosa, Escherichia coli+Proteus mirabilis, Escherichia coli+Klebsiella pneumoniae, Proteus vulgaris+Myroides odoratus+Staphylococcus aureus+Enterococcus faecalis*

242 **Table 3. Vital signs, clinical symptoms and laboratory results**

	Bacteremia n=25	Non-bacteremia n=91	*p* value
Vital signs			
Body temperature, °C (SD)	38.2 (1.17)	38.1 (1.06)	0.84
Symptoms			
Macrohematuria, n (%)	1 (4.0)	4 (4.4)	1.00
Pain in urination, n (%)	3 (12)	10 (11)	1.00
Back pain, n (%)	8 (32)	34 (37)	0.81
Chills, n (%)	11 (44)	24 (26)	0.14
Vomiting, n (%)	4 (16)	9 (9.9)	0.47
Nausea, n (%)	0 (0)	7 (7.7)	-
Diarrhea, n (%)	5 (20)	7 (7.7)	0.13
Clinical signs			
CVA tenderness (+), n (%)	17 (68)	60 (66)	1.00
Laboratory results			
White blood cells $\times 10^9$/L (SD)	11.6 (5.6)	12.3 (4.4)	0.56
Neutrophils $\times 10^9$/L (SD)	10.5 (4.1)	9.7 (5.7)	0.54
Platelet $\times 10^4$/μL (SD)	19.8 (6.7)	23.0 (7.5)	0.037*
BUN mg/dL (SD)	17.1 (12.9)	12.7 (6.2)	0.11
Creatinine mg/dL (SD)	0.81 (0.44)	0.70 (0.30)	0.26
CRP mg/dL (SD)	10.8 (8.9)	9.9 (7.3)	0.65
Urinary nitrite test (+), n (%)	12 (48)	28 (31)	0.043*

243 SD: standard deviation; CVA: costophrenic angle; BUN: blood urea nitrogen; CRP:
244 C-reactive protein; *: $p<0.05$

Table 4. Clinical courses of the patients

	Bacteremic n=25	Non-bacteremic n=91	*P* value
Hospitalization required, n (%)	22 (88)	31 (34)	<0.001*
Length of total antimicrobials, day (SD)	15.0 (2.3)	12.4 (6.2)	0.002*
Hospital stay, days (SD)	12.5 (9.2)	4.2 (8.7)	<0.001*
Death, n (%)	0 (0)	0 (0)	-

SD: standard deviation; *: $p<0.05$

247 **Table 5. Multivariate analysis 1**

	OR	95% CI	*p* value
Urinary nitrite test (+)	2.5	0.86-7.8	0.094
Age	1.02*	1.0-1.1	0.052
Platelet	1.0	0.99-1.0	0.20
Chills	2.5	0.86-7.7	0.095

248 R^2 was 0.15 (p<0.01).

249 *Unit odds ratio, OR: odds ratio; CI: confidence intervals

Table 6. Multivariate analysis 2

	OR	95% CI	*p* value
Urinary nitrite test (+)	3.1	1.1-9.2	0.033**
Chills	2.7*	0.93-7.9	0.068
Platelet	0.99	0.99-1.01	0.11

R^2 was 0.11 (p=0.01).

*: Unit odds ratio, **: $p< 0.05$; OR: odds ratio; CI: confidence interval