



Risk Factors of Sepsis in Obstructive Acute Pyelonephritis Associated with Urinary Tract Calculi

Chae Hong Lim, Jae Seung Hwang, Dae Ji Kim, Seok Heun Jang, Jeong Hwan Son, Dae Sung Cho, Jae Won Lee

Department of Urology, Bundang Jesaeng General Hospital, Seongnam, Korea

Purpose: The aim of this study is to identify the risk factors for development of sepsis in patients with obstructive acute pyelonephritis (APN) associated with urinary tract calculi.

Materials and Methods: Between January 2004 and December 2013, 73 patients with obstructive APN associated with upper urinary tract calculi were admitted to our institution. Medical records of 73 patients (14 men and 59 women, mean age of 57 years) were reviewed retrospectively. The risk factors for sepsis were analyzed using multivariate logistic regression analysis.

Results: Of 73 patients, 37 (50.7%) developed sepsis. Old age and history of hypertension were more common in the sepsis group than in the non-sepsis group ($p < 0.001$ and $p = 0.018$). The white blood cell count, neutrophil count, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein level were significantly higher in the sepsis group ($p = 0.011$, $p = 0.001$, $p = 0.042$, $p < 0.001$ and $p = 0.006$, respectively). Lymphocyte count, platelet count, and albumin level were significantly lower in the sepsis group ($p < 0.001$, $p = 0.008$ and $p < 0.001$, respectively). Multivariate logistic regression analysis indicated that old age (odds ratio [OR], 2.13; $p = 0.023$), decrease in serum albumin level (OR, 4.27; $p = 0.041$), and high NLR (OR, 3.83; $p = 0.037$) were independent risk factors for development of sepsis.

Conclusions: Elderly patients with obstructive APN associated with urinary tract calculi who have low serum albumin levels and high NLR should be treated carefully against development of sepsis.

Keywords: Pyelonephritis; Sepsis; Calculi

Received: 22 August, 2015

Revised: 23 September, 2015

Accepted: 2 October, 2015

Copyright © 2015, Korean Association of Urogenital Tract Infection and Inflammation. All rights reserved.



This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Jae Won Lee

<http://orcid.org/0000-0002-1844-3673>

Department of Urology, Bundang Jesaeng General Hospital, 20 Seohyeon-ro 180 beon-gil, Bundang-gu, Seongnam 13590, Korea

Tel: +82-31-779-0165, Fax: +82-31-779-0169

E-mail: urojwlee@dmc.or.kr

INTRODUCTION

Acute pyelonephritis (APN) is defined as inflammation of the kidney and renal pelvis. The diagnosis is clinical and the clinical spectrum ranges from sepsis to cystitis with mild flank pain. The classical presentation is abrupt-onset chills, fever, unilateral or bilateral flank pain, and costovertebral angle tenderness. These upper urinary tract signs

are often accompanied by signs of bladder irritation, including dysuria, increased urinary frequency, and urgency. APN may be accompanied by gastrointestinal tract symptoms such as nausea, vomiting, abdominal pain, and diarrhea.

The infections in patients with APN can be subdivided into uncomplicated infections that do not warrant hospitalization, uncomplicated infections in patients with normal urinary tracts who are ill enough to warrant hospi-

talization for parenteral therapy, and complicated or obstructive infections associated with hospitalization, catheterization, or urologic surgery. Obstructive APN is defined as an infection of the renal parenchyma and perirenal tissue associated with organic or functional urinary tract abnormalities.

APN with obstructive uropathy is a common cause of urological morbidity and can progress to urosepsis and septic shock. Sepsis is a clinical syndrome characterized by extremes of body temperature, heart rate, respiratory rate, and white blood cell (WBC) count occurring in response to an infection. Sepsis is defined as a systemic inflammatory response to infection, and systemic inflammatory response syndrome (SIRS) includes two or more of the following: 1) fever greater than 38°C or less than 36°C; 2) a heart rate of greater than 90 beats per minute; 3) tachypnea, as manifested by a respiratory rate exceeding 20 breaths per minute or hyperventilation, as indicated by a partial CO₂ pressure of less than 32 mmHg; and 4) an altered WBC count, including a count greater than 12,000/mm³ or less than 4,000/mm³, or more than 10% immature neutrophils [1-3]. SIRS should be managed rapidly and appropriately; urosepsis and septic shock associated with obstructive uropathy frequently require drainage.

APN with obstructive uropathy is not uncommon and often progresses to serious conditions, including sepsis and septic shock. Therefore, it is important to find the prognostic factor for developing sepsis or septic shock and helpful to establish therapeutic plans. We assessed the risk factors for progression to sepsis in patients with obstructive APN associated with urinary tract calculi.

MATERIALS AND METHODS

We conducted a retrospective medical chart review of all admissions for the treatment of APN with urinary tract calculi to the Department of Urology, Bundang Jesaeng General Hospital, Seongnam, Korea, from January 2004 to December 2013. The criteria for study enrollment were as follows: 1) met the definition of SIRS; 2) positive urine culture with greater than 10⁵ colony-forming units (CFU)/ml and no antibiotic therapy just before consultation in our urological department or greater than 10² CFU/ml or pyuria, defined as 10 or more leukocytes per high power field in the centrifuged specimen with flank pain, and some antibiotic therapy just before consultation in our department;

and 3) no clinical focus of infection outside the urinary tract [4]. In males, a digital rectal examination and palpation of the epididymides and prostate were performed to rule out acute prostatitis and acute epididymitis. Blood and midstream urine cultures were performed in all patients with antimicrobial susceptibility testing. When susceptibility testing indicated resistance to the initial empirical treatment, the antibiotics were replaced with another susceptible one.

The following data were recorded: patient demographics; laterality; presence of hypertension and diabetes mellitus; performance status; WBC, lymphocyte, and neutrophil counts; platelet-to-lymphocyte ratio (PLR); neutrophil-to-lymphocyte ratio (NLR); and C-reactive protein (CRP) and serum albumin levels.

The variables in the different groups were compared using the independent sample t-test or chi-square test. Independent predictors of septic shock were determined using a multivariate logistic regression analysis. Results with a probability of less than 0.05 were considered statistically significant. The statistical analyses were performed using PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

Of 73 patients, 37 (50.7%) developed sepsis. The mean patient age was 57 years and the male/female ratio was 0.23. There was a significant difference in age between the sepsis and non-sepsis groups ($p < 0.001$). Performance status ($p = 0.698$) and diabetes mellitus ($p = 0.258$) did not differ significantly between the groups. Hypertension was significantly ($p = 0.018$) more common in the sepsis group than in the non-sepsis group. There was no significant difference in stone laterality between the groups. The WBC, lymphocyte, and neutrophil counts, serum albumin level, PLR, NLR, and CRP level differed significantly between the sepsis and non-sepsis groups. The WBC count, neutrophil count, PLR, NLR, and CRP level were significantly higher in the sepsis group ($p = 0.011$, $p = 0.001$, $p = 0.042$, $p < 0.001$, and $p = 0.006$, respectively), while the lymphocyte count, platelet count, and serum albumin level were significantly lower in the sepsis group ($p < 0.001$, $p = 0.008$, and $p < 0.001$, respectively) (Table 1).

A multivariate logistic regression analysis showed that old age (odds ratio [OR], 2.13; $p = 0.023$), decreased serum albumin level (OR, 4.27; $p = 0.041$), and high NLR (OR, 3.83;

p=0.037) predicted septic shock in patients with obstructive APN associated with urinary tract calculi (Table 2).

DISCUSSION

Urosepsis accounts for 20-30% of all septic patients; frequent causes of urosepsis are obstructive diseases of the urinary tract, including urinary stones, stenosis, and tumors [5]. The severity of urosepsis depends on the host response and local factors. The host response is affected by age, hypertension, diabetic mellitus, and performance status or immunosuppression, such as with acquired immunodeficiency syndrome, transplant recipients, and long-term steroid use. Local factors include urinary calculi, congenital abnormalities of the ureter, neurogenic bladder, and iatrogenic factors such as endoscopic surgery.

Table 1. A comparison of the clinical characteristics of patients with and without sepsis

Characteristic	Sepsis		p-value
	Yes	No	
Patients	37 (50.7)	36 (49.3)	
Age (y)	64±13	49±13	<0.001
Gender			0.515
Male	8 (22.2)	6 (16.2)	
Female	28 (77.8)	31 (83.8)	
Laterality			0.549
Right	15 (41.7)	18 (48.6)	
Left	21 (58.3)	19 (51.4)	
Hypertension			0.018
Negative	26 (72.2)	16 (43.2)	
Positive	10 (27.8)	21 (56.8)	
Diabetes mellitus			0.258
Negative	31 (86.1)	28 (75.7)	
Positive	5 (13.9)	9 (24.3)	
Performance status			0.698
0-1	30 (83.3)	17 (45.9)	
2-4	6 (16.7)	20 (54.1)	
White blood cell count ($\times 10^3/\mu\text{l}$)	11.8±3.9	14.5±5.0	0.011
Lymphocyte count ($\times 10^3/\mu\text{l}$)	1.6±0.8	0.9±0.5	<0.001
Neutrophil count ($\times 10^3/\mu\text{l}$)	9.3±4.3	12.9±4.7	0.001
Platelet count ($\times 10^3/\mu\text{l}$)	2.3±0.6	1.8±0.9	0.008
Platelet to lymphocyte ratio	173.8±71.3	244.2±191.3	0.042
Neutrophil to lymphocyte ratio	8.0±6.5	18.5±13.3	<0.001
C-reactive protein (mg/dl)	7.2±6.3	11.5±6.5	0.006
Serum albumin (g/dl)	3.9±0.4	3.4±0.6	<0.001

Values are presented as number (%) or mean±standard deviation.

Although urinary calculi are among the most common urological diseases, they can be lethal if associated with a urinary tract infection and obstructive uropathy resulting in bacteremia and urosepsis [6].

This study suggests that in patients with obstructive APN, old age predicts the development of urosepsis. Yamamoto et al. [7] reported that old age and paralysis were risk factors for urosepsis in patients receiving emergency drainage for APN with upper urinary calculi. In another study, age, sex, and performance predicted the development of urosepsis in patients with obstructive APN.

In this study, we found that a decreased serum albumin level predicted the development of urosepsis in patients with obstructive APN. A systemic inflammatory response can be assessed by the concentration of acute phase proteins (e.g., CRP, ferritin, fibrinogen, albumin, and transferrin) or blood leukocyte components, including neutrophils and lymphocytes [8]. In patients with an infection, Bossink et al. [9] found that a decreased serum albumin level predicted urosepsis in a univariate analysis. The low albumin in patients developing shock can be explained by consumption of fibrinogen in the course of low-grade intravascular coagulation or by impaired hepatic synthesis of circulating proteins in the course of serious infections. Tambo et al. [10] reported that a decreased platelet count and serum albumin level were risk factors for urosepsis in patients with obstructive APN. It is thought that, although this is partly associated with the consumption of platelets by concurrent disseminated intravascular coagulation, other factors also contribute.

Recent studies combining traditional infection markers and lymphocyte counts showed the additional value of the latter in predicting bacterial sepsis. As the physiological immune response of circulating leukocytes to various stressful events is often characterized by an increase in the neutrophil count and a decline in the lymphocyte count, Zahorec [11] proposed using the ratio of the two as an additional infection marker in clinical intensive care unit

Table 2. Multivariate logistic regression analysis of risk factors for sepsis

Variable	Occurrence of sepsis		
	Odds ratio	95% confidence interval	p-value
Old age (≤ 60 vs. >60 y)	2.13	1.88-4.79	0.023
Serum albumin (>3.5 vs. ≤ 3.5 g/dl)	4.27	0.62-7.16	0.041
Neutrophil to lymphocyte ratio ($\leq 10:1$ vs. $>10:1$)	3.83	0.75-5.14	0.037

practice. The NLR is an easily quantifiable parameter of systemic inflammation and stress in clinically ill patients. There is an association between the pretreatment NLR and various cancers, including colorectal cancer, hepatocellular carcinoma, ovarian cancer, non-small cell lung cancer, and gastric cancer [12-15]. In this study, a high NLR was also associated with urosepsis in patients with obstructive APN.

One limitation of our study is that it did not investigate the impact of emergency drainage during sepsis. In addition, the results of mid-stream urine and blood cultures were not considered. Moreover, this study was limited by the small number of enrolled patients. Future studies should examine a larger prospective cohort and include a greater number of risk factors.

CONCLUSIONS

This study found that in patients with obstructive APN, a decreased serum albumin level, high NLR, and old age predicted the development of urosepsis. Patients with obstructive APN associated with urinary tract calculi who have these risk factors should be treated carefully.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644-55.
2. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864-74.
3. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* 2003;29:530-8.
4. Yoshimura K, Utsunomiya N, Ichioka K, Ueda N, Matsui Y, Terai A. Emergency drainage for urosepsis associated with upper urinary tract calculi. *J Urol* 2005;173:458-62.
5. Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Intensive Care Med* 2000;26 Suppl 1:S64-74.
6. Amano T, Matsui F, Takashima H, Takemae K. Analysis of patients with septic shock due to urosepsis brought on by ureteral calculi. *Hinyokika Kyo* 2003;49:1-4.
7. Yamamoto Y, Fujita K, Nakazawa S, Hayashi T, Tanigawa G, Imamura R, et al. Clinical characteristics and risk factors for septic shock in patients receiving emergency drainage for acute pyelonephritis with upper urinary tract calculi. *BMC Urol* 2012;12:4.
8. Ohno Y, Nakashima J, Ohori M, Hatano T, Tachibana M. Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. *J Urol* 2010;184:873-8.
9. Bossink AW, Groeneveld AB, Koffeman GI, Becker A. Prediction of shock in febrile medical patients with a clinical infection. *Crit Care Med* 2001;29:25-31.
10. Tambo M, Okegawa T, Shishido T, Higashihara E, Nutahara K. Predictors of septic shock in obstructive acute pyelonephritis. *World J Urol* 2014;32:803-11.
11. Zahorec R. Ratio of neutrophil to lymphocyte counts: rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* 2001;102:5-14.
12. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. *Oncology* 2007;73:215-20.
13. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. *Cancer Immunol Immunother* 2009;58:15-23.
14. Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP, et al. Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. *World J Surg* 2008;32:1757-62.
15. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2009;137:425-8.