

Original Article  
Urology



# Differences between Risk Factors for Sepsis and Septic Shock in Obstructive Urolithiasis

Sang Hyub Lee ,\* Taesoo Choi ,\* Jeonghyouk Choi , and Koo Han Yoo

Department of Urology, School of Medicine, Kyung Hee University, Kyung Hee University Hospital at Gangdong, Seoul, Korea



Received: Jun 12, 2020

Accepted: Aug 24, 2020

**Address for Correspondence:**

Koo Han Yoo, MD, PhD

Department of Urology, School of Medicine, Kyung Hee University, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea.

E-mail: yookoohan@khu.ac.kr

\*Sang Hyub Lee and Taesoo Choi contributed equally to this work.

© 2020 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://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.

**ORCID iDs**

Sang Hyub Lee

<https://orcid.org/0000-0002-4509-5846>

Taesoo Choi

<https://orcid.org/0000-0002-2800-5773>

Jeonghyouk Choi

<https://orcid.org/0000-0003-0650-7569>

Koo Han Yoo

<https://orcid.org/0000-0001-7952-7902>

**Disclosure**

The authors have no potential conflicts of interest to disclose.

**Author Contributions**

Conceptualization: Yoo KH. Data curation: Choi T, Choi J. Formal analysis: Choi T, Choi J. Investigation: Choi T, Lee SH, Yoo

## ABSTRACT

**Background:** Complicated acute pyelonephritis (APN) is a life-threatening condition that requires immediate intervention. This study examined the characteristics of APN occurring as a complication of ureteral stone.

**Methods:** We retrospectively reviewed 85 patients diagnosed with APN complicated by ureteral stone between December 2006 and July 2017 at our institution. Patients with concomitant renal stone, multiple ureteral stones, ureteral strictures, ureteral cancer, and urogenital anomalies, including vesicoureteral reflux were excluded. Clinical characteristics including age, sex, underlying disease, medical history, stone characteristics, initial laboratory data, and the procedure used to correct urinary obstruction were summarized, and the risk factors associated with sepsis and septic shock were analyzed.

**Results:** Sepsis was diagnosed at initial presentation in 62 patients, 17 of whom suffered from septic shock. Disease-related death did not occur in any patient. Previous history of stone ( $P = 0.015$ ), leukocytosis ( $P < 0.001$ ), elevated C-reactive protein levels ( $P = 0.006$ ), and low albumin ( $P = 0.038$ ) were significant risk factors for progression to sepsis. The absence of hypertension ( $P = 0.047$ ), thrombocytopenia ( $P = 0.006$ ), decreased erythrocyte sedimentation rate (ESR) ( $P = 0.003$ ), elevated blood urea nitrogen ( $P = 0.016$ ), and positive blood culture ( $P = 0.018$ ) were significant predictors for progression to septic shock. Multivariate analysis revealed that previous history of stone ( $P = 0.015$ ) was an independent risk factor for sepsis, while the absence of hypertension ( $P = 0.047$ ), thrombocytopenia ( $P = 0.013$ ), and decreased ESR ( $P = 0.009$ ) were risk factors for shock.

**Conclusion:** The risk factors associated with the progression from APN to sepsis differed from those associated with the progression from sepsis to septic shock. Various factors should be considered while selecting treatment options based on the severity of APN associated with ureteral stone. It should be managed with aggressive treatment and close observation, especially in the presence of risk factors.

**Keywords:** Urolithiasis; Sepsis; Septic Shock; Mortality

## INTRODUCTION

Acute pyelonephritis (APN) is a urologic disease that is commonly encountered in emergency departments and results in a significant number of hospital admissions.<sup>1</sup> The annual

KH. Methodology: Yoo KH, Lee SH, Choi T.  
Software: Lee SH, Yoo KH. Validation: Lee SH,  
Yoo KH. Writing - original draft: Lee SH, Choi T.  
Writing - review & editing: Lee SH, Yoo KH.

incidence rate of APN was reported as 15 to 17 cases per 10,000 individuals in the USA.<sup>2</sup> A Korean study reported that the annual incidence rate of APN per 10,000 individuals has been increasing every year.<sup>3</sup>

The clinical symptoms of APN range from costovertebral tenderness, voiding difficulties, and fever to a life-threatening condition or even death.<sup>4</sup> Uncomplicated APN is defined as APN that occurs in a normal genitourinary tract. On the other hand, complicated APN is defined as APN accompanied by infections in patients with genitourinary tract abnormalities.<sup>5</sup> The prognosis of complicated APN is considerably worse than that of uncomplicated APN, with mortality rates of 6% to 10%. Therefore, APN with obstructive uropathy usually requires emergency drainage of the upper urinary tract with percutaneous nephrostomy (PCN) or retrograde double J stenting.<sup>6</sup> Risk factors associated with high-mortality in patients with complicated APN include immunosuppression, advanced age, healthcare-associated infection, obstructive uropathy, thrombocytopenia, serum albumin level, high C-reactive protein (CRP) levels, and bacteremia.<sup>7-9</sup>

Sepsis is defined as a systemic inflammatory response syndrome in the presence of suspected infection.<sup>10</sup> Moreover, sepsis is the strongest independent risk factor for septic shock and mortality in patients with APN.<sup>11</sup> Septic shock is defined as a subset of sepsis, which is characterized by profound circulatory, cellular, and metabolic abnormalities and is associated with a greater risk of mortality than that with sepsis alone.<sup>12</sup> Patients with septic shock commonly require vasopressor administration to maintain a mean arterial pressure of 65 mmHg or higher and a serum lactate level greater than 2 mmol/L in the absence of hypovolemia.<sup>12</sup>

Studies focusing on the risk factors associated with septic shock and complicated APN are rare. The aim of this study was to analyze the risk factors associated with sepsis and septic shock with cases of obstructive urolithiasis in our institution for 11 years.

## METHODS

The medical records of patients who visited the Department of Urology, Kyung Hee University School of Medicine, from December 2006 to July 2017 for APN with obstructive urolithiasis were reviewed. APN was defined as the presence of more than 5 white blood cells/high-power field, an isolated bacterial count of more than  $10^4$  colony-forming units in the urine specimen, high-grade fever of more than 38°C, and other related symptoms.<sup>9</sup> The patient's age, sex, underlying comorbidities (including diabetes mellitus, hypertension, ischemic heart disease, and stroke), history of urolithiasis and urinary tract infection (UTI), urinary stone size and location, and type of drainage were recorded. We also evaluated the results of blood and urine cultures before initiating antibiotic treatment. Laboratory examinations including blood leukocyte count, blood thrombocyte count at the nadir, CRP, serum creatinine, and total bilirubin level were performed prior to drainage.

Emergency drainage for the decompression of hydronephrosis was performed for severe cases (e.g., poor performance status, marked elevation in leukocyte count, and CRP level). Retrograde double J stenting or PCN was performed according to the urologist's preference. Retrograde double J stenting was performed under fluoroscopic guidance using a rigid cystoscope under local anesthesia. A 6-French polyurethane double J stent was used. PCN was

performed after ultrasound-guided renal puncture under local anesthesia. Guidewire insertion, fascial dilation, and 7-French pigtail catheter placement were performed using fluoroscopy.

The diagnosis of sepsis was made according to the criteria for systemic inflammatory response syndrome, which included two or more of the following conditions: body temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats per minute; tachypnea, presenting as a respiratory rate of greater than 20 breaths per minute or hyperventilation, as indicated by a partial CO<sub>2</sub> pressure of less than 32 mmHg; and a leukocyte cell count greater than 12,000/mm<sup>3</sup> or less than 4,000/mm<sup>3</sup>, or immature neutrophils greater than 10%.<sup>13,14</sup> Septic shock was defined as sepsis with a systolic blood pressure of less than 90 mmHg despite adequate fluid replacement or vasopressor administration for at least 1 hour.<sup>15,16</sup> We identified risk factors for septic shock by comparing patients whose condition did or did not progress to septic shock.

Data were analyzed using SPSS, version 18.0 (IBM Co., Armonk, NY, USA). Proportion comparisons for categorical variables were performed using  $\chi^2$  tests. The *P* value and relative ratio were calculated for risk factors. *P* values < 0.05 were considered statistically significant. Moreover, multivariate model analysis was performed to determine the progression of complicated APN to sepsis and septic shock.

#### Ethics statement

The study was approved by the Institutional Review Board (IRB) of Kyung Hee University Hospital at Gangdong (IRB No. KHNMC 2018-07-007-001). The need for informed consent was waived by the IRB.

## RESULTS

A total of 85 patients were treated for complicated APN associated with ureteral stone at our department during the 11-year period. The median age was 56.9 years and 65 (76.5%) events occurred in women. Thirty-two (37.6%) patients had a previous history of stone or UTI. All patients required hospitalization except for those who refused treatment. At initial diagnosis, 62 (72.9%) patients met the criteria for sepsis and 17 (27.4%) patients from among them had septic shock. Forty urine (47.1%) and twenty-five (29.4%) blood culture samples showed positive results on routine examination. Consistently, the most common pathogen was *Escherichia coli*, and *Proteus mirabilis* was the second most common cause. Furthermore, the incidence of *ESBL(-) E.coli* was dominant than that of *ESBL(+)* *E.coli* in each group. There was no significant difference among them.

**Tables 1 and 2** summarize the clinical characteristics of the patients who were divided based on the presence of sepsis and septic shock. Patients who experienced sepsis exhibited a greater tendency of having a history of genitourinary stones (35.5% vs. 8.7%; *P* = 0.015), higher leukocyte count ( $1.30 \times 10^3/\mu\text{L}$  vs.  $0.86 \times 10^3/\mu\text{L}$ ; *P* < 0.001), higher CRP levels (9.14 mg/dL vs. 4.53 mg/dL; *P* = 0.006) and lower albumin levels (3.99 g/dL vs. 4.12 g/dL; *P* = 0.038). Urologists preferred PCN (56.5% vs. 30.4%; *P* = 0.033) over ureteral stenting in septic conditions.

The incidence of positive blood culture (58.8% vs. 26.7%; *P* = 0.018), low platelet count (169 k/ $\mu\text{L}$  vs. 242 k/ $\mu\text{L}$ ; *P* = 0.006) and high blood urea nitrogen (BUN) (23.2 mg/dL vs. 17.6 mg/dL; *P* = 0.016) were significantly higher in the septic shock than that in the non-septic shock

**Table 1.** Baseline comparative data of patients with complicated acute pyelonephritis depending on the presence of sepsis

Variables	Sepsis (-) (n = 23)	Sepsis (+) (n = 62)	P value
Age, yr	55.9 (18-36)	57.3 (21-92)	0.734
Sex			0.568
Male	4 (17.4)	16 (25.8)	
Female	19 (82.6)	46 (74.2)	
Underlying disease			
DM	3 (13.0)	14 (22.6)	0.542
HTN	11 (47.8)	28 (45.2)	0.827
IHD	0 (0)	2 (3.2)	1.000
CVA	2 (8.7)	8 (12.9)	0.722
Medical history			
Stone Hx	2 (8.7)	22 (35.5)	0.015
UTI Hx	4 (17.4)	15 (24.2)	0.573
Stone			
Size, mm	7.26 (2-28)	8.33 (1.1-23)	0.428
Location			
Proximal	12 (52.2)	35 (56.5)	1.000
Mid	2 (8.7)	5 (8.1)	
Distal	9 (39.1)	22 (35.5)	
Drainage			
Ureteral stent	3 (13.0)	11 (17.7)	0.501
Percutaneous nephrostomy	7 (30.4)	35 (56.5)	0.033
None	13 (56.6)	16 (25.8)	
Culture			
Positive urine culture	7 (30.4)	33 (53.2)	0.061
Bacteremia	3 (13.0)	22 (35.5)	0.060
Mortality	0 (0)	0 (0)	
Initial Laboratory data			
Leukocyte count, $\times 10^3/\mu\text{L}$	0.86 (0.49-1.18)	1.30 (0.18-2.99)	< 0.001
Hemoglobin, g/dL	12.3 (9.4-15.2)	12.4 (8.5-16.0)	0.975
Hematocrit, %	36.7 (29.3-44.2)	36.7 (27.1-45.2)	0.956
Platelet count, $\times 10^3/\mu\text{L}$	226 (70-357)	222 (39-505)	0.852
Creatinine, mg/dL	0.96 (0.48-1.8)	1.22 (0.32-4.8)	0.074
ESR, mm/hr	34.5 (4-97)	42 (2-108)	0.343
CRP, mg/dL	4.53 (0.02-16.5)	9.14 (0.02-33.3)	0.006
Albumin, g/dL	4.12 (3.2-4.9)	3.99 (2.5-4.8)	0.038

Data are presented as median (interquartile range) or number (%).

DM = diabetes mellitus, HTN = hypertension, IHD = ischemic heart disease, CVA = cerebrovascular accident, Hx = history, UTI = urinary tract infection, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein.

group. In addition, a lower incidence of comorbid hypertension (23.5% vs. 53.3%;  $P = 0.047$ ) and lower erythrocyte sedimentation rate (ESR) (26 vs. 48;  $P = 0.003$ ) were observed in the septic shock group.

Previous history of genitourinary stone (relative risk [RR], 5.775; confidence interval [CI], 1.237-26.962;  $P = 0.015$ ) and abnormal leukocyte count ( $< 4,000/\text{mm}^3$  or  $< 10,000/\text{mm}^3$ ; RR, 5.391; CI, 1.925-15.092;  $P = 0.001$ ) were significant factors that indicated the presence of sepsis. On the other hand, thrombocytopenia ( $< 200 \text{ K}/\mu\text{L}$ ; RR, 4.350; CI, 1.299-14.569;  $P = 0.013$ ), abnormal BUN ( $< 8$  or  $> 20$ ; RR, 3.825; CI, 1.170-12.510;  $P = 0.022$ ) and positive blood culture (RR, 3.929; CI, 1.219-12.661;  $P = 0.018$ ) were associated with more catastrophic conditions, i.e., septic shock. Underlying hypertension (RR, 0.269; CI, 0.076-0.953;  $P = 0.047$ ) and high ESR ( $> 30$ ; RR, 0.144; CI, 0.033-0.622;  $P = 0.009$ ) had protective effects on the progression to septic shock (Table 3).

**Table 2.** Subgroup analysis of sepsis in patients with complicated acute pyelonephritis according to the presence of septic shock

Variables	Septic shock (-) (n = 45)	Septic shock (+) (n = 17)	P value
Age, yr	56.5 (21-91)	59.4 (32-92)	0.484
Sex			0.194
Male	14 (31.1)	2 (11.8)	
Female	31 (68.9)	15 (88.2)	
Underlying disease			
DM	11 (24.4)	3 (17.6)	0.739
HTN	24 (53.3)	4 (23.5)	0.047
IHD	1 (2.2)	1 (5.9)	0.476
CVA	7 (15.6)	1 (5.9)	0.427
Medical history			
Stone Hx	16 (35.6)	6 (35.3)	0.985
UTI Hx	10 (22.2)	5 (35.3)	0.555
Stone			
Size, mm	8.62 (1.1-23)	7.61 (1.4-22)	0.484
Location			
Proximal	27 (60.0)	8 (47.1)	0.687
Mid	4 (8.9)	1 (5.8)	
Distal	14 (31.1)	8 (47.1)	
Drainage			
Ureteral stent	11 (24.5)	2 (11.8)	0.756
PCN	24 (53.3)	11 (64.7)	0.420
None	10 (22.2)	4 (23.5)	
Culture			
Positive urine culture	23 (51.1)	10 (58.8)	0.587
Bacteremia	12 (26.7)	10 (58.8)	0.018
Mortality	0 (0)	0 (0)	
Initial Laboratory data			
Leukocyte count, $\times 10^3/\mu\text{L}$	1.38 (0.31-2.99)	1.10 (0.18-2.16)	0.103
Hemoglobin, g/dL	12.6 (8.5-16.0)	11.7 (9.4-14.1)	0.058
Hematocrit, %	37.4 (27.1-45.2)	35.0 (27.5-41.5)	0.087
Platelet count, $\times 10^3/\mu\text{L}$	242 (57-505)	169 (39-281)	0.006
Creatinine, mg/dL	1.14 (0.32-4.8)	1.42 (0.66-3.7)	0.207
ESR, mm/hr	48 (2-108)	26 (6-21)	0.003
CRP, mg/dL	8.07 (0.02-29.08)	11.8 (0.06-33.3)	0.161
Albumin, g/dL	4.07 (2.5-4.8)	3.77 (2.7-4.5)	0.062

Data are presented as median (interquartile range) or number (%).

DM = diabetes mellitus, HTN = hypertension, IHD = ischemic heart disease, CVA = cerebrovascular accident, Hx = history, UTI = urinary tract infection, PCN = percutaneous nephrostomy, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein.

**Table 3.** The distinct indicators suggesting the progression of complicated APN to sepsis and septic shock

Risk factors	Relative risk (95% CI)	P value
Complicated APN to sepsis		
Previous stone history	4.131 (1.048-16.280)	0.015
Sepsis to septic shock		
HTN	0.721 (0.531-0.977)	0.047
Thrombocytopenia, $< 200 \text{ K}/\mu\text{L}$	1.493 (1.052-2.118)	0.013
ESR, $> 30$	0.611 (0.408-0.914)	0.009

APN = acute pyelonephritis, CI = confidence interval, HTN = hypertension, ESR = erythrocyte sedimentation rate.

## DISCUSSION

Urosepsis, which is defined as sepsis caused by urogenital tract infection, accounts for 20%–30% of all septic conditions.<sup>17,18</sup> Obstructive diseases of the upper urinary tract, such as urinary stones, stenosis or tumors, are the main cause of urosepsis.<sup>17</sup> Older individuals, patients with diabetes, immunocompromised patients, transplant recipients, and patients

with acquired immunodeficiency syndrome exhibit reduced host defense immunity. Moreover, local factors, such as urolithiasis, obstructive uropathy, congenital uropathy, neurogenic bladder disorders, and endoscopic procedure, can affect the severity of urosepsis. Lee et al.<sup>7</sup> analyzed the risk factors associated with septic shock in patients with bacteremic APN who were admitted to the department of urology. The overall mortality rate was 6.7%, but the mortality rate of 54 patients who initially presented with shock was 25.9%. Multiple logistic regression analyses revealed that the presence of urinary tract obstruction (odds ratio [OR], 4.391), healthcare-associated infection (OR, 3.491), and liver cirrhosis (OR, 4.609) were independent risk factors responsible for the incidence of septic shock.

Obstructive uropathy of the upper urinary tract that is complicated with infection requires decompression of the renal collecting system with ureteral stenting or PCN. Rapid decompression procedures such as PCN or retrograde double J stent insertion reduce intrarenal pressure and improve renal perfusion. Borofsky et al.<sup>19</sup> reported that 1,712 patients with ureteral calculi and sepsis were from the 2007 to 2009 Nationwide Inpatient Sample. Of the patients with urosepsis, 78% underwent surgical decompression. Mortality was higher in patients who were not treated with surgical decompression (19.2% vs. 8.82%). The lack of surgical decompression was independently associated with an increased OR of mortality even after adjusting for patient demographics, comorbidities, and geographic region of treatment (OR, 2.6). They concluded that the absence of surgical decompression was associated with higher odds of mortality in patients with sepsis and ureteral calculi.

The diagnosis of uroseptic shock is made when a patient with severe urosepsis presents with acute circulatory failure characterized by persistent arterial hypotension (systolic arterial pressure below 90 mmHg, mean arterial pressure < 60 mmHg, or reduction in systolic blood pressure > 40 mmHg compared to the baseline), despite adequate volume resuscitation.<sup>20</sup>

Several researchers have published studies that focused on determining the risk factors associated with uroseptic shock.<sup>9,21-23</sup> Tambo et al.<sup>9</sup> assessed the risk factors for septic shock with obstructive APN associated with upper urinary tract calculi. Multivariate analysis revealed that reduction in platelet count and serum albumin levels were independent risk factors for septic shock. Moreover, Kamei et al.<sup>22</sup> reviewed the records of 48 patients who underwent emergency drainage of the upper urinary tract for sepsis associated with acute obstructive pyelonephritis. Multivariate logistic regression analysis identified that thrombocytopenia and positive blood culture were independent risk factors for septic shock. Platelets and neutrophils are involved in the pathogenesis of urosepsis and work in conjunction to contribute to the inflammatory response. Studies have demonstrated that platelets and neutrophils are recruited to the microvasculature of lung and liver, leading to the production of neutrophil extracellular traps in sepsis.<sup>23</sup> Various factors can be responsible for low serum albumin levels, including increased protein catabolism and decreased hepatic synthesis, which can result in extravasation into the extravascular space because of increased vascular permeability during the inflammatory process. Bossink et al.<sup>24</sup> reported that low serum albumin levels were one of the predictive factors for shock development (as per univariate analysis). Similar to the previous studies, our study showed that previous history of stones and abnormal leukocyte count were significant factors indicating the presence of sepsis. Moreover, thrombocytopenia, abnormal BUN levels, and positive blood culture were proven to be associated with urosepsis. Furthermore, we discovered that underlying hypertension and high ESR had protective effects on the progression to septic shock.

The present study has some limitations, despite these interesting findings. First, this was a retrospective study; therefore, some inflammatory markers such as procalcitonin, serum amyloid A, and cytokines were not investigated, and the collected data might have been missed, which could have affected the results of the study. Moreover, the treatment process was not the same for all patients. The timing of the examination and treatment, which could be related to the risk factors for uroseptic shock, such as urine culture, prescription of antibiotics, and timing or method of drainage, were not the same for all patients. Furthermore, the physician who first met the patient was responsible for the choice of empirical antibiotics. Finally, the sample size was small because this investigation was a single-center study was conducted with the patients from a single institution. Therefore, future multi-center studies are needed to validate the results of this study.

In conclusion, the risk factors associated with the progression from APN to sepsis differ from those associated with the progression from sepsis to septic shock. Several factors should be considered while selecting treatment options, depending on the severity of complicated APN with ureteral stone. The condition should be managed with aggressive treatment and close observation, especially in the presence of risk factors.

## REFERENCES

1. Foxman B, Klemstine KL, Brown PD. Acute pyelonephritis in US hospitals in 1997: hospitalization and in-hospital mortality. *Ann Epidemiol* 2003;13(2):144-50.  
[PUBMED](#) | [CROSSREF](#)
2. Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. *Clin Infect Dis* 2007;45(3):273-80.  
[PUBMED](#) | [CROSSREF](#)
3. Kim B, Myung R, Kim J, Lee MJ, Pai H. Descriptive epidemiology of acute pyelonephritis in Korea, 2010–2014: population-based study. *J Korean Med Sci* 2018;33(49):e310.  
[PUBMED](#) | [CROSSREF](#)
4. van Nieuwkoop C, van't Wout JW, Spelt IC, Becker M, Kuijper EJ, Blom JW, et al. Prospective cohort study of acute pyelonephritis in adults: safety of triage towards home based oral antimicrobial treatment. *J Infect* 2010;60(2):114-21.  
[PUBMED](#) | [CROSSREF](#)
5. Nicolle LE. Urinary tract infection: traditional pharmacologic therapies. *Dis Mon* 2003;49(2):111-28.  
[PUBMED](#) | [CROSSREF](#)
6. Danuser H, Ackermann DK, Studer UE. Urological emergencies. *Schweiz Med Wochenschr* 1993;123(15):749-55.  
[PUBMED](#)
7. Lee JH, Lee YM, Cho JH. Risk factors of septic shock in bacteremic acute pyelonephritis patients admitted to an ER. *J Infect Chemother* 2012;18(1):130-3.  
[PUBMED](#) | [CROSSREF](#)
8. 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(1):4.  
[PUBMED](#) | [CROSSREF](#)
9. Tambo M, Okegawa T, Shishido T, Higashihara E, Nutahara K. Predictors of septic shock in obstructive acute pyelonephritis. *World J Urol* 2014;32(3):803-11.  
[PUBMED](#) | [CROSSREF](#)
10. Cawcutt KA, Peters SG. Severe sepsis and septic shock: clinical overview and update on management. *Mayo Clin Proc* 2014;89(11):1572-8.  
[PUBMED](#) | [CROSSREF](#)
11. Efstathiou SP, Pefanis AV, Tsioulos DI, Zacharos ID, Tsiakou AG, Mitromaras AG, et al. Acute pyelonephritis in adults: prediction of mortality and failure of treatment. *Arch Intern Med* 2003;163(10):1206-12.  
[PUBMED](#) | [CROSSREF](#)

12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315(8):801-10.  
[PUBMED](#) | [CROSSREF](#)
13. 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(6):1644-55.  
[PUBMED](#) | [CROSSREF](#)
14. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med* 2003;31(4):1250-6.  
[PUBMED](#) | [CROSSREF](#)
15. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358(2):111-24.  
[PUBMED](#) | [CROSSREF](#)
16. Annane D, S ebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288(7):862-71.  
[PUBMED](#) | [CROSSREF](#)
17. Wagenlehner FM, Lichtenstern C, Rolfes C, Mayer K, Uhle F, Weidner W, et al. Diagnosis and management for urosepsis. *Int J Urol* 2013;20(10):963-70.  
[PUBMED](#)
18. Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Intensive Care Med* 2000;26 Suppl 1(Suppl 1):S64-74.  
[PUBMED](#) | [CROSSREF](#)
19. Borofsky MS, Walter D, Shah O, Goldfarb DS, Mues AC, Makarov DV. Surgical decompression is associated with decreased mortality in patients with sepsis and ureteral calculi. *J Urol* 2013;189(3):946-51.  
[PUBMED](#) | [CROSSREF](#)
20. Vincent JL. Clinical sepsis and septic shock--definition, diagnosis and management principles. *Langenbecks Arch Surg* 2008;393(6):817-24.  
[PUBMED](#) | [CROSSREF](#)
21. Sharaf A, Amer T, Somani BK, Aboumarzouk OM. Ureteroscopy in patients with bleeding diatheses, anticoagulated, and on anti-platelet agents: a systematic review and meta-analysis of the literature. *J Endourol* 2017;31(12):1217-25.  
[PUBMED](#) | [CROSSREF](#)
22. Kamei J, Nishimatsu H, Nakagawa T, Suzuki M, Fujimura T, Fukuhara H, et al. Risk factors for septic shock in acute obstructive pyelonephritis requiring emergency drainage of the upper urinary tract. *Int Urol Nephrol* 2014;46(3):493-7.  
[PUBMED](#) | [CROSSREF](#)
23. Clark SR, Ma AC, Tavener SA, McDonald B, Goodarzi Z, Kelly MM, et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. *Nat Med* 2007;13(4):463-9.  
[PUBMED](#) | [CROSSREF](#)
24. Bossink AW, Groeneveld AB, Koffeman GI, Becker A. Prediction of shock in febrile medical patients with a clinical infection. *Crit Care Med* 2001;29(1):25-31.  
[PUBMED](#) | [CROSSREF](#)