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Comprehensive Investigations of Multiple Factors That Are Related to Refractory Outcome in Urosepsis Patients

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ABSTRACT

Background Urosepsis is an acute life-threating disease, and some cases show refractory outcome to therapy. In an aging society of developed countries, characteristics of urosepsis are becoming complicated. We performed a comprehensive investigation regarding the clinical and social aspects that are related to refractory outcomes in urosepsis patients.

Methods The patient cohort consisted of 66 patients with urosepsis. Multiple factors from clinical and social aspects were reviewed retrospectively. Two categories of refractory outcomes were defined. One was afebrile resistance (AR); fever continued more than 7 days from the initiation of therapy. Another was discharge resistance (DR); hospitalization continued for more than 30 days. Logistic regression analyses were performed to identify significant factors that are related to the AR or DR.

Results Univariate analysis demonstrated that high score of Eastern Cooperative Oncology Group Performance Status (ECOG PS) (≥ 2) and Age-adjusted Charlson comorbidity index (CCI) (≥ 4), high serum C-reactive protein (CRP) level (≥ 14.9 mg/dL), and low serum albumin level (≤ 2.26 g/dL) were significantly related to AR. Univariate analysis results also revealed that high score of ECOG PS (≥ 2), high serum creatinine level (≥ 1.54 mg/dL) and vasopressor administration were significantly related to DR. Multivariate analyses demonstrated that low serum albumin level (≤ 2.26g/dL) was the only significant factor that was related to AR. In contrast, high score of ECOG PS (≥ 2) and high serum creatinine level (≥ 1.54 mg/dL) were significant factors that were related to DR.

Conclusion It is suggested that evaluating serum albumin levels is essential for the therapeutic first step because hypoalbuminemia was the significant factor that was related to obstruction to antipyresis. It is also suggested that the deterioration of patients' activities of daily living and renal dysfunction might be the refractory factors for discharge from the hospital, which was the ultimate therapeutic goal.

Key words sepsis; urinary tract infection; urosepsis

Sepsis is described as a syndrome consisting of complex pathophysiological and biochemical dysregulation, triggered by endogenous factors in response to the bacterial, viral, parasitic, or fungal infections.[1] The pathogenesis of sepsis involves a complex interaction between the host immune system and the infecting microorganisms. Sepsis describes a broad-based syndrome covering many infectious agents, affecting various sites in patients of differing age, gender, and comorbidity.[2] The definition of sepsis has recently been modified and updated, due to advancements in molecular and clinical research. Based on the new definition, sepsis is currently defined as life-threatening organ dysfunction, caused by a dysregulated host immune response to infection.[1, 2] Sepsis has a high mortality rate based on its highly variable clinical manifestations and is the leading cause of death in noncardiac intensive care units (ICUs).[3, 4]

Urosepsis is defined as sepsis caused by infection of the urogenital tract, and is a systemic response to infection.[5] According to worldwide geographic data, the incidence of cases in which the genitourinary tract was considered the infectious origin of sepsis has been reported to be 9–31%.[6] Alternatively, the incidence of bacteremia in symptomatic urinary tract infections, which was considered almost equal to urosepsis was 15% in the emergency department.[7] Failure to early and proper antibiotic treatment of urosepsis early leads to a high risk of fatality.[8] Unlike malignant diseases such as cancer, urosepsis is a benign disease. Therefore, the therapeutic goal is to cure and discharge patients, considering the possibility of mortality throughout the therapy. One of the typical symptoms of urosepsis is

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Abbreviations: ADL, activity of daily living; AR, afebrile resistance; AUC, area under the receiver-operating characteristic curve; CCI, Charlson comorbidity index; CRP, C-reactive protein; DR, discharge resistance; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESBL, extended-spectrum beta-lactamase; HAS, human albumin solution; ICU, intensive care unit; PLT, platelet; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection; WBC, white blood cell

fever. Therefore, the first therapeutic goal in a patient with urosepsis is to achieve an afebrile condition. The final goal is to achieve a complete cure and discharge of the patient. Despite numerous studies concerning urosepsis, there is no report investigating the characteristics refractory to these therapeutic goals. In this study, we originally defined two categories of refractory outcomes. One was afebrile resistance (AR), and another was discharge resistance (DR).

In the aging population of developed countries, many elderly people without self-independence are living. Recently, medical therapy has often been complicated in this situation. A physician must examine not only the disease itself but also a patient as an individual while considering the background of the patient. That way, analyzed factors were extended to the social factors in the study. At any rate, the characterization of refractory therapeutic factors to urosepsis is sought in the actual clinical field. This study was undertaken to comprehensively characterize factors that were related to refractory outcomes in urosepsis using retrospective clinical and social detailed data from our institute.

Table 1. The inherent patient's clinical and social background

Factors	AR (n = 20)	DR (n = 15)	All cases (n = 66)
Age			
Median (range)-yr	85.5 (40–93)	83 (70–93)	78 (31–94)
Sex-no. (%)			
Male	6 (30.0)	8 (53.3)	30 (45.5)
Female	14 (70.0)	7 (46.7)	36 (54.5)
ECOG PS-no. (%)			
0, 1	6 (30.0)	4 (26.7)	33 (50.0)
2, 3	14 (70.0)	11 (73.3)	33 (50.0)
Age adjusted CCI			
Median (range)	4 (0–9)	4 (4–9)	4 (0–9)
Spouse-no. (%)			
Exist	10 (50.0)	10 (66.7)	35 (53.0)
Not exist	10 (50.0)	5 (33.3)	31 (47.0)

yr, years.

MATERIALS AND METHODS

Patients

In our study, urosepsis was defined as sepsis caused by infection of the urogenital tract, and is a systemic response to infection.[5] Eighty-two patients with urinary tract infection (UTI) with bacteremia was determined between April 1, 2015 and March 31, 2020 in our hospital. The definition of UTI with bacteremia is as follows. Patient's blood and urine was collected simultaneously, and their bacterial culture was the same. Of 82 patients with UTI with bacteremia, 66 patients who presented with a systemic response to infection were defined as urosepsis and included in the study. The systemic response to infection was diagnosed by the attending physician using laboratory, radiographic and physical findings. The analyzed data were retrospectively obtained from medical record . This study conformed to the provisions of the Declaration of Helsinki. This study was approved by the Ethics Committee of Matsue City hospital (approval number R1A-0005). All patients provided opt-out consent in accordance with the institutional guidelines.

Definition of two refractory outcomes

Two categories of refractory outcomes were defined to clarify the refractory therapeutic factors in urosepsis patients. One was afebrile resistance (AR); the fever continued more than seven days from the initiation of therapy. The definition of afebrile was that axillary temperature was below 37°C at any time in a day. Axillary temperature measurements were performed at least three times per day. Another was discharge resistance (DR); hospitalization continued for more than 30 days. Twenty and fifteen patients were categorized as AR and DR, respectively.

The analyzed factors

The factors analyzed were age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS),[9] age-adjusted Charlson comorbidity index (CCI),[10] marital status, residence status, urethral catheter, ureteral stent, the origin of UTI, the complexity of UTI, systemic inflammatory response syndrome (SIRS), other infections, peripheral blood laboratory data of white blood cells (WBCs), platelets (PLTs), C-reactive protein (CRP), albumin and creatinine, bacterial culture, the first used anti-biotics, and administration of vasopressor drugs. Concerning peripheral blood laboratory data, the worst blood data (i.e., the maximum values of WBC, CRP and creatinine, and the minimum values of PLT and albumin) within three initial days were selected for analyses because abnormal findings of blood examination were not obvious on the admitted day in some cases. The inherent patient's clinical and social background in AR, DR and all cases is shown in Table 1.

Statistical analyses

Logistic regression analyses indicated the potential factors that were related to AR or DR. First, all analyzed

Table 2. Diagnosis of UTI and patient's condition at the initiation of therapy

Factors	AR ($n = 20$)	DR ($n = 15$)	All cases ($n = 66$)
Diagnosis of UTI-no. (%)			
Pyelonephritis	15 (75.0)	9 (60.0)	42 (63.6)
Pyelonephritis with urinary stone	5 (25.0)	4 (26.7)	15 (22.7)
Prostatitis	0 (0.0)	1 (6.7)	7 (10.6)
Emphysematous cystitis	0 (0.0)	1 (6.7)	1 (1.5)
Urethral injury	0 (0.0)	0	1 (1.5)
Complexity of UTI-no. (%)			
Simple	8 (40.0)	5 (33.3)	23 (34.8)
Complicated	12 (60.0)	10 (66.7)	43 (65.2)
SIRS at first visit-no. (%)			
Yes	15 (75.0)	13 (86.7)	43 (65.2)
No	5 (25.0)	2 (13.3)	23 (34.8)
Other infection diseases-no. (%)			
Yes	3 (15.0)	2 (13.3)	6 (9.1)
No	17 (85.0)	13 (86.7)	60 (90.9)

Table 3. Therapeutic agents and patient's outcome

Factors	AR ($n = 20$)	DR ($n = 15$)	All cases ($n = 66$)
First administration antibiotics-no. (%)			
MEPM	7 (35.0)	7 (46.7)	19 (28.8)
CMZ	5 (25.0)	4 (26.7)	14 (21.2)
CTRX	8 (40.0)	3 (20.0)	30 (45.5)
LVFX	0 (0.0)	0 (0.0)	2 (3.0)
PAMP · BP	0 (0.0)	1 (6.7)	1 (1.5)
Use of vasopressor			
Yes	5 (25.0)	6 (40.0)	13 (19.7)
No	15 (75.0)	9 (60.0)	53 (80.3)
Dead due to Urosepsis			
Yes	0 (0.0)	1 (6.7)	1 (1.5)
No	20 (100.0)	14 (93.3)	65 (98.5)
Period until afebrile (days)			
Median (range)	11.5 (9–28)	10 (3–28)	6 (2–28)
Period until discharge (days)			
Median (range)	25.5 (10–169)	39 (31–169)	15 (1–169)

CMZ, cefmetazole; CTRX, ceftriaxone sodium; LVFX, levofloxacin; MEPM, meropenem; PAMP•BP, panipenem•betamipron.

factors were analyzed univariately. Second, the potent factors ($P < 0.1$) in univariate analyses were evaluated using multivariate analyses. The continuous variables of the analyzed factors (peripheral blood laboratory data of WBC, PLT, CRP, albumin and creatinine) were divided into two groups according to the cut off value. The optimal cut off values were determined based on a receiver-operating characteristic curve. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the Statview 5.0 software. Receiver-operating characteristic curve and optimal cut off values were generated using EZR,[11] which is for R. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Diagnosis and patient's condition

The diagnosis of UTI and the patient's condition at the initiation of therapy in AR, DR and all cases are summarized in Table 2. Most diagnoses were pyelonephritis (63.6%). Other infectious diseases, such as pneumonia in which infecting bacteria was different from that of urosepsis, were recognized in a few patients (9.1%).

Therapeutic agents and patient outcomes

The therapeutic agents and patient outcomes in AR, DR and all cases are summarized in Table 3. The most commonly used first-line antibiotics were ceftriaxone sodium (45.5%) that is a narrow-spectrum antibiotic and the third-generation cephalosporin. However, the second most frequently used agent was meropenem (28.8%), which is a broad-spectrum antibiotic and a carbapenem. The physician performed empiric intravenous therapy until the results of bacterial culture were revealed. After that, definitive targeted antibiotic therapy to the bacteria was performed. Vasopressor was used in 13 patients (19.7%) to improve circulatory failure caused by septic shock. One patient died despite intensive treatment. The median period until the patient was afebrile was 6 days. Alternatively, the indicated median period until the patient was discharged from the hospital was 15 days.

Blood laboratory and bacterial culture data

Blood laboratory data and bacterial culture results for each patient in AR, DR and all cases are summarized in Table 4. The median values of peripheral blood WBC, CRP and creatinine per patient were 15,800/μL, 19.1 mg/dL, and 1.22 mg/dL, respectively. The median values of peripheral blood PLT and albumin per patient were 125,500/μL and 2.4 g/dL, respectively. The most frequent bacterial culture was *Escherichia coli* (69.7%), and approximately half were extended-spectrum beta-lactamase (ESBL)-producing.

Table 4. Blood laboratory data and bacterial culture results for each patient

Factors	AR (n = 20)	DR (n = 15)	All cases (n = 66)
WBC (/μL)			
Median (range) ($\times 10^3$)	16.7 (10.5–34.3)	17.5 (10.5–39.3)	15.8 (5.5–39.3)
PLT (/μL)			
Median (range) ($\times 10^3$)	116.5 (14.0–650.0)	100.0 (14.0–650.0)	125.5 (10.9–650.0)
CRP (mg/dL)			
Median (range)	20.8 (6.3–48.4)	21.2 (4.2–48.4)	19.1 (1.4–48.4)
Albumin (g/dL)			
Median (range)	2.1 (1.5–2.5)	1.9 (1.1–2.3)	2.4 (1.1–4.2)
Creatinine (mg/dL)			
Median (range)	1.09 (0.66–10.75)	2.22 (0.66–10.75)	1.22 (0.49–10.75)
Bacterial culture-no. (%)			
Escherichia coli	6 (30.0)	6 (40.0)	24 (36.4)
Escherichia coli (ESBL)	6 (30.0)	3 (20.0)	22 (33.3)
Enterococcus faecalis	3 (15.0)	0 (0.0)	4 (6.1)
Proteus spp	1 (5.0)	1 (6.7)	3 (4.5)
Serratia marcescens	0 (0.0)	0 (0.0)	2 (3.0)
Morganella morganii	1 (5.0)	0 (0.0)	2 (3.0)
Enterobacter cloacae	0 (0.0)	0 (0.0)	2 (3.0)
Others	4 (20.0)	5 (33.3)	7 (10.6)

Logistic regression analyses for potential factors that are related to AR or DR

Univariate analyses demonstrated that high scores of ECGG PS (≥ 2) and age-adjusted CCI (≥ 4), high serum CRP level (≥ 14.9 mg/dL), and low serum albumin level (≤ 2.26 g/dL) were significantly related to AR (Table 5). In contrast, high score of ECOG PS (≥ 2), high serum creatinine level (≥ 1.54 mg/dL) and vasopressor administration were significantly related to DR (Table 6). The factors that showed $P < 0.1$ were evaluated using multivariate analyses. The results of the multivariate analyses are shown in Tables 7 and 8. The low serum albumin level (≤ 2.26 g/dL) was the sole independent factor that was related to AR. The area under the receiver-operating characteristic curve (AUC) was 0.78. In contrast, the high scores of ECGG PS (≥ 2) and the high serum creatinine level (≥ 1.54 mg/dL) were the independent factors that were related to DR. In the analysis of serum creatinine level, the AUC was 0.833.

DISCUSSION

The special features of our study cohort were a high ratio of patients with advanced age and deteriorated activity of daily living (ADL). The cohort's median age was 78 years, and 33 out of 66 (50%) patients were categorized as having an ECGG PS greater than 2. In the clinical real world, the issue of patient's independence is important. For example, the length of hospital stay varies according to patient's independence because patients who lack independence need rehabilitation programs during hospitalization. Because patient's independence is closely associated with social factors, social factors might be related to the refractory outcome of urosepsis. Therefore, social factors were added to the factors analyzed. These were not significant in our study. However, regarding residence, nursing homes tended to be related to AR in the univariate analysis, although statistical significance was not reached (P = 0.0546). Alternatively, an ECOG PS greater than 2 was the significant factor that was related to AR and DR in univariate analysis and was the independent factor that was related to DR in multivariate analysis. Kino et al. demonstrated that poor PS was a great risk factor for urosepsis induced by transurethral lithotripsy of kidney and ureteral stones.[12] Although the patient cohort characteristics differed between our study and Kino et al., ECGG PS was suggested to be the crucial factor in managing urosepsis. Similar to the ECOG PS, the CCI is often employed to evaluate the patient's general condition. An age-adjusted CCI greater than 4 was the

Table 5. Univariate logistic regression analysis for factors that were related to with AR

Factors	Odds ratio (95 % confidence interval)	*P* value
Age (≥ 80)	2.333 (0.798–6.822)	0.1216
Sex (Male)	0.393 (0.128–1.201)	0.1014
ECOG PS (≥ 2)	3.316 (1.079–10.185)	0.0363*
Age adjusted CCI (≥ 4)	4.359 (1.120–16.965)	0.0337*
Spouse (Not exist)	1.19 (0.416–3.406)	0.7451
Residence (Nursing home)	3.167 (0.977–10.259)	0.0546
Urethral catheter (Yes)	0.569 (0.175–1.843)	0.3467
Ureteral stent (Yes)	0.754 (0.074–7.73)	0.8123
Region of UTI (Upper urinary tract)	775326.734 (0.00–N/A)	0.9748
Complexity of UTI (Complicated)	0.726 (0.245–2.151)	0.5632
SIRS at first visit (Yes)	1.929 (0.597–6.231)	0.2723
Other infection diseases (Yes)	2.529 (0.464–13.792)	0.2835
WBC (/μL) (≥ 14,300)	1.5 (0.517–4.352)	0.4556
PLT (/μL) (≤ 148,000)	1.534 (0.526–4.471)	0.433
CRP (mg/dL) (≥ 14.9)	4.359 (1.12–16.965)	0.0337*
Albumin (g/dL) (≤ 2.26)	16.056 (3.988–64.642)	< 0.0001***
Creatinine (mg/dL) (≥ 1.54)	2.121 (0.691–6.516)	0.189
Bacterial culture (E. coli)	0.529 (0.174–1.608)	0.2617
First administration antibiotics (MEPM)	1.526 (0.493–4.724)	0.4638
Use of vasopressor (Yes)	1.583 (0.446–5.623)	0.4772

significant factor that was related to AR in the univariate analysis of our study. A systematic review demonstrated a higher CCI as a significant predictive factor of urinary tract infection and urosepsis after ureteroscopy although the patient cohort characteristics differed from ours.[13] Therefore, in addition to the assessment of medical information such as physical findings, laboratory data and radiographic findings, evaluating the patient's functional status that refers to ECOG PS and CCI is essential in managing urosepsis.

With regard to peripheral blood laboratory data in our study, univariate analysis demonstrated that high serum CRP level (≥ 14.9 mg/dL) and low serum albumin level (≤ 2.26g/dL) were significantly related to AR. On the other hand, multivariate analysis demonstrated that low serum albumin level (≤ 2.26g/dL) was significantly related to AR. CRP is an acute inflammatory protein that is increased up to 1,000 -fold at sites of infection or inflammation.[14–16] It is well known that CRP level rises above normal limits within 6 hours, and peaks at 48 hours. Because the maximum values of CRP within three initial days were adopted in our study, it is suggested that these data represented the worst inflammatory condition in each case. Because universal relationship between serum CRP level and severity of inflammation, it is reasonable that severe inflammation with high serum CRP level prolonged febrile period, consequently was related to AR in our study. Hypoalbuminemia is a complex pathophysiological condition. It is caused by damage to hepatocytes, which decreases albumin synthesis, causes deficiency in the ingestion of amino acids and increases albumin excretion, all of which are influenced by inflammation.[17] Hypoalbuminemia is deteriorated rapidly by various mediators of septic inflammatory reactions.[18, 19] These mediators reduce albumin synthesis, and increase vascular permeability that leads to transcapillary leakage of albumin.[19–21] Sepsis is the leading cause of mortality in the ICU, and hypoalbuminemia in the acute phase related to increased risks of severity and death.[22–25] Similar to these reports that hypoalbuminemia was related to severity and poor prognosis in sepsis, our study indicated that hypoalbuminemia was the independent factor that was related to AR. However, we did not conclude whether hypoalbuminemia caused AR, or AR cases had a characteristic of hypoalbuminemia. Growing evidence of the efficacy of human albumin solution (HAS) recently received more attention.[26] There were three famous trials in which the

Table 6. Univariate logistic regression analysis for factors that were related to DR

Factors	Odds ratio (95 % confidence interval)	*P* value
Age (≥ 80)	2.143 (0.662–6.932)	0.2032
Sex (Male)	1.506 (0.474–4.786)	0.4871
ECOG PS (≥ 2)	3.625 (1.016–12.929)	0.0471*
Age adjusted CCI (≥ 4)	N/A (N/A–N/A)	0.9721
Spouse (Not exist)	0.481 (0.144–1.606)	0.2339
Residence (Nursing home)	1.818 (0.514–6.436)	0.3539
Urethral catheter (Yes)	1.458 (0.443–4.796)	0.5344
Ureteral stent (Yes)	1.143 (0.11–11.869)	0.911
Region of UTI (Upper urinary tract)	0.867 (0.156–4.817)	0.8701
Complexity of UTI (Complicated)	1.091 (0.323–3.686)	0.8886
SIRS at first visit (Yes)	4.55 (0.928–22.309)	0.0618
Other infection diseases (Yes)	1.808 (0.297–10.994)	0.5203
WBC (/μL) (≥ 15,800)	3.094 (0.869–11.014)	0.0812
PLT (/μL) (≤ 108,000)	3.281 (0.998–10.791)	0.0504
CRP (mg/dL) (≥ 14.99)	4.55 (0.928–22.309)	0.0618
Albumin (g/dL) (≤ 2.26)	N/A (N/A–N/A)	0.963
Creatinine (mg/dL) (≥ 1.54)	25.143 (5.634–112.199)	< 0.0001***
Bacterial culture (E. coli)	0.568 (0.171–1.889)	0.3558
First administration antibiotics (MEPM)	2.844 (0.854–9.473)	0.0887
Use of vasopressor (Yes)	4.19 (1.136–15.456)	0.0314*

Table 7. Multivariate logistic regression analysis for factors that were related to AR

Factors	Odds ratio (95 % confidence interval)	*P* value
ECOG PS (≥ 2)	1.129 (0.185–6.901)	0.8957
Age adjusted CCI (≥ 4)	1.812 (0.301–10.919)	0.5165
Residence (Nursing home)	1.03 (0.196–5.415)	0.9723
CRP (mg/dL) (≥ 14.9)	2.524 (0.489–13.01)	0.2686
Albumin (g/dL) (≤ 2.26)	10.343 (2.061–51.907)	0.0045**

Table 8. Multivariate logistic regression analysis for factors that were related to DR

Factors	Odds ratio (95 % confidence interval)	*P* value
ECOG PS (≥ 2)	13.298 (1.124–157.28)	0.0401*
SIRS at first visit (Yes)	7.765 (0.611–98.724)	0.1141
Creatinine (mg/dL) (≥ 1.54)	58.101 (4.606–732.852)	0.0017**
First administration antibiotics (MEPM)	1.179 (0.147–9.435)	0.8763
Use of vasopressor (Yes)	0.567 (0.053–6.128)	0.6406
WBC (/μL) (≥ 15,800)	8.674 (0.618–121.722)	0.1089
PLT (/μL) (≤ 108,000)	1.941 (0.252–14.92)	0.524
CRP (mg/dL) (≥ 14.99)	4.013 (0.282–57.155)	0.3052

usefulness of HAS was investigated.[27–29] Although the results were somewhat different among the studies, decreased mortality is suggested by HAS usage in sepsis patients in the ICU. Other results of note were reduced catecholamine requirement, lower cumulative fluid balance and quicker resolution of shock.[27, 29] HAS may benefit over other intravenous fluid therapies; however, this has never been definitely proven in a large-scale randomized controlled trial. HAS was administered in 5 out of 66 (7.5%) patients in our study, and the therapeutic purpose of HAS was to increase blood pressure. The therapeutic contribution of HAS in urosepsis is unclear in our study because of the low incidence of HAS usage. However, the usefulness of HAS should be investigated in the future.

ICU treatment of urosepsis is a common scenario because it is an acute and lethal disease. Acute kidney injury frequently arises as a common complication of septic shock in ICU patients.[30–32] In our study, a serum creatinine level greater than 1.54 mg/dL within three initial days was significantly related to DR in multivariate analysis. It might reflect the initial sign of acute kidney injury caused by severe urosepsis or patient's intrinsic renal insufficiency. Renal insufficiency is an obstacle in treating urosepsis, consequently prolong the therapeutic duration. It takes several weeks to restore renal function in urosepsis cases that require renal-replacement therapy. In our study, continuous hemodialysis was performed in 7 of 66 (10.6%). In these cases, a longer duration of hospitalization was required periods (median 51, range 20–99 days). However, afebrile condition was achieved within 7 days in all seven cases because of the speculation that cytokine-adsorbing hemofilter used in all cases suppressed cytokine storm in sepsis, consequently improved fever. Another problem in treating urosepsis with renal insufficiency is determining the proper dosing of antibiotics. Adequate antibiotics are required for effective treatment, but it is necessary to reduce the dose of antibiotics due to decreased renal function. This dilemma might result in inefficient bacterial removal, consequently prolong the hospitalization period. The clinical outcome in renal insufficiency cases depends on the level of the attending physician experience because it is difficult to evaluate the optimal blood antibiotic concentration and timing for treatment in each case.

Our study has certain limitations. First, several attending physicians participated in the study. The choice of antibiotics and the therapeutic management of patients during septic shock depended on each physician's treatment methodology. Concerning types of antibiotics, physician performed empiric intravenous therapy considering the site of origin, underlying diseases, pretreatment history, and whether the sepsis was primary or secondary. Although physicians made a great effort to initiate therapy as soon as possible, the first antibiotics were not necessarily administered in the ideal first hour. The physicians' varying clinical experience influenced the treatment duration and time afebrile or hospital discharge goals. Other limitations include the study's retrospective nature and the small sample size. External validation of our findings and further exploration of the potent factors that were related to refractory outcomes in urosepsis patients will help to further improve the treatment of urosepsis.

In conclusion, evaluating serum albumin levels is essential as the therapeutic first step because hypoalbuminemia was the significant factor that was related to obstruction to antipyresis. It is also suggested that the deterioration of patients' ADL and renal dysfunction might be the refractory factors for discharge from the hospital that was the ultimate therapeutic goal. The attending physician should be mindful of prolonged therapeutic periods, and take appropriate measures for patients experiencing these therapeutic obstacles.

The authors declare no conflicts of interest.

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