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Risk Factors and Bacterial Profiles of Urinary Tract Infections in Patients with Systemic Lupus Erythematosus

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SUMMARY Bacteremic urinary tract infection (UTI) is known to carry a high mortality rate, especially in immunocompromised patients. Patients with systemic lupus erythematosus (SLE) have an immunocompromised status, and thus an increased risk of infection. To evaluate the risk factors for UTI in SLE patients and to identify factors associated with bacteremic UTI, we reviewed SLE patients hospitalized for UTI over a 20-year study period. Based on our results we conclude that lupus nephritis is a risk factor for UTI in SLE patients. Clinical symptoms do not significantly distinguish bacteremic from non-bacteremic UTI in hospitalized SLE patients. Although *Escherichia coli* remain the most common bacteria in UTI, *Salmonella* spp. might need particular attention because of their high likelihood for causing bacteremia.

Recently the survival of patients with systemic lupus erythematosus (SLE) has increased significantly. However, infections remain a major cause of morbidity and mortality in SLE patients.[1-6] Different predisposing factors are being proposed. Some authors suggest that SLE activity predisposes patients to infection[7], other studies presume that aggressive lupus therapies, particularly immunosuppressive and cytotoxic therapies, could be causative factors for those infections.[8,9]

Among the infections, urinary tract infection (UTI) has been reported as the most common primary or secondary infection in SLE patients, followed by respiratory tract infection.[10] *Escherichia coli* is the most frequent organism cultured.[8] The clinical manifestations of UTI are variable, ranging from asymptomatic UTI to urosepsis.

Bacteremia is particularly common in SLE patients, occurring in about 16% to 47% of infected cases.[8] When bacteremia resulting from UTI is suspected in SLE patients, appropriate antibiotics should be administered immediately because bacteremic UTI carries a high mortality rate, especially in immunocompromised patients.

The objective of this study was to evaluate the risk factors for UTI in hospitalized SLE patients. We also identified the differences between UTI with and without bacteremia.

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MATERIALS AND METHODS

We retrospectively collected and reviewed the records of 44 patients who had been admitted to Chang Gung Children's and Chang Gung Memorial Hospitals from 1985 to 2004 that carried the dual diagnosis of SLE and UTI. All of the patients fulfilled the 1982 revised American Rheumatism Association criteria for the classification of SLE.[11,12] The inclusion criteria of UTI in this study were as follows:[13] (a) symptoms of acute illness such as fever, dysuria, flank knocking pain or vomiting; (b) bacterial colony count in a urine culture (from midstream voided specimens) greater than or equal to 10^5 colonies per milliliter, or a catheterized specimen with as little as 100 colony-forming units, or growth of identical pathogen both in the blood and in urine cultures; and (c) no known urinary tract abnormality or other severe underlying disease, such as genitourinary tract stones, previous genitourinary tract surgery, or neurogenic bladder.

Demographic features including age, sex, and time elapsed from SLE diagnosis to UTI admission, were collected from medical charts. The use of corticosteroids or immunosuppressive drugs was reviewed, and clinical symptoms and disease activity of SLE at the time of infection were assessed. Treatments with azathioprine, methotrexate, cyclophosphamide, cyclosporine, and mycophenolate mofetil were recorded as immunosuppressive therapy. Lupus nephritis was diagnosed based on biopsy (World Health Organization class II-VI) or according to the renal involvement criteria of the American College of Rheumatology.[11,12] Overall disease activity was calculated according to the SLE Disease Activity Index (SLEDAI).[14] Serologies for antinuclear antibodies (ANA), anti-dsDNA, and complement levels were also documented. Lastly, the mode of UTI therapy and the disease outcome were identified.

Patients were divided into two groups according to whether or not they had concomitant bacteremia. Bacteremic UTI was diagnosed when an identical pathogen was isolated from both blood and urine cultures at the same time. Nonbacteremic UTI was defined as positive urine culture only. The demographic data, clinical symptoms, and laboratory studies during admission of those two groups were compared. To identify risk factors for UTI, the data of SLE patients with UTI were compared to the data of 100 SLE patients without UTI. Those control patients were randomly chosen and they were hospitalized over the same time period because of fever from other causes. All of the control group SLE patients were admitted at the same hospital, and the admission date was within 1 month of the admission date of the 44 cases.

Nonparametric Mann-Whitney U test, chi-square test, or Fisher's exact test were used, as appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

We identified 52 episodes of UTI in 44 patients from a total of 3,179 hospitalized SLE patients during the 20-year review period according to the inclusion criteria. Bacteremia was identified in 13 (25%) of these episodes. The sex ratio revealed a female predominance in the bacteremic as well as the nonbacteremic groups (Table 1). The age ranged from 18 to 74 years (mean 44.4 ± 15.8 years). The average age at SLE onset was 33.8 years (SD = 13.6 years). The mean interval between diagnosis of SLE to admission for UTI was 47.6 months (SD = 49.5 months). This interval was longer in the bacteremic UTI group, but the difference was not significant (p = 0.119). Eight patients were diagnosed simultaneously with SLE and UTI. Among the patients with recurrent UTI, 4 patients had 2 episodes of UTI, and 2 patients had 3 episodes of UTI. Forty-one (93%) patients had taken prednisolone (average dose of 24.7 mg daily) before the diagnosis of UTI. There was no significant difference between the 2 groups in the daily corticosteroid dose or the use of other immunosuppressive drugs.

The mean age of the SLE patients with UTI was not significantly different from that of patients without UTI (Table 1). The results of the analysis of potential risk factors are presented in Table 1. The frequency of lupus nephritis was higher in UTI cases (77.30%) than in the controls (57.4%) (p = 0.036; Odds ratio: 2.519; CI: 1.115-5.690). There was no difference between UTI cases and controls in the daily corticosteroid dose or the use of other immunosuppressive drugs.

Table 1 Demographic features and treatment in SLE patients with urinary tract infection (44 cases) and in the control group (100 cases)

	Bacteremic UTI	**Nonbacteremic UTI**				**UTI cases**	**Controls**			
	(n = 9) mean (SD)	(n = 35) mean (SD)	*p*	OR	95%CI	(n = 44) mean (SD)	(n = 100) mean (SD)	*p*	OR	95%CI
Sex (male:female)	1:8	4:31	1.000*	1.371	0.139-13.506	5:39	15:85	0.447*	1.645	0.557-4.858
Age, years	47.8 (14.9)	42.8 (15.6)	0.373	-	-	44.4 (15.8)	43.9 (16.7)	0.452	-	-
Onset age of SLE, years	37.6 (12.4)	32.5 (14.1)	0.306	-	-	33.8 (13.6)	34.5 (14.2)	0.799	-	-
Interval between SLE onset and UTI, months	62.0 (53.4)	35.6 (43.9)	0.119	-	-	47.6 (49.5)	-	-	-	-
Daily corticosteroid dose, mg	22.0 (12.1)	27.0 (19.6)	0.337	-	-	24.7 (17.3)	25.9 (18.1)	0.689	-	-
Immunosuppressive agent use	4	11	0.714*	1.394	0.325-5.972	15	43	0.267*	0.613	0.292-1.219
Lupus nephritis	8	26	0.659*	2.769	0.303-25.313	34	54	0.036*	2.519	1.115-5.690

SD, standard deviation; OR, Odds ratio; CI, confidence interval; *Fisher's exact test.

Table 2 Clinical manifestations in bacteremic and nonbacteremic SLE patients with urinary tract infection (52 episodes)

	Total, n = 52 (%)	**Bacteremic UTI, n = 13** (%)	**Nonbacteremic UTI, n = 39** (%)	***p***
Fever	41 (78.8)	13 (100.0)	28 (71.8)	0.047
Dysuria	17 (32.7)	5 (38.5)	12 (30.8)	0.735
Frequency	14 (26.9)	6 (46.2)	8 (20.5)	0.086
Urgency	6 (11.5)	2 (15.4)	4 (10.3)	0.632
Flank knocking pain	11 (21.1)	4 (30.8)	7 (17.9)	0.435
Abdominal pain	9 (17.3)	1 (7.7)	8 (20.5)	0.420
Nausea/vomiting	9 (17.3)	3 (23.1)	6 (15.4)	0.674

Chi-square tests

Reviewing the clinical symptoms of these 52 episodes of UTI, fever (≥ 38°C) was the most common symptom for UTI admission (41 episodes, 78.8%). Fever was the major symptom of illness in all patients of the bacteremic group and in 71.8% of the nonbacteremic patients (13/13 *vs.* 28/39, $p = 0.047$), which was statistically significant. Other symptoms such as dysuria, frequency of urination, urgency, flank knocking pain, nausea, or vomiting were reported more often in bacteremic patients, but the difference was not significant. Abdominal pain was more frequent in the nonbacteremic group, but the results were not statistically significant (Table 2).

Table 3 describes the laboratory data at the time of UTI. The difference of the mean white blood cell count (WBC) between bacteremic and nonbacteremic UTI patients was statistically significant (13,862 *vs.* 8,372/μl; $p = 0.035$). Mean C-reactive protein (CRP) concentrations were significantly higher in bacteremic patients (183 *vs.* 46 mg/l; $p = 0.016$). The risk of bacteremia increased when the CRP concentration was greater than 50 mg/l ($p = 0.026$; odds ratio: 10.883; CI: 1.37-85.44). The mean erythrocyte sedimentation rate (ESR) was also higher in the bacteremic group (92 *vs.* 53 mm/h; $p = 0.021$). Hypoalbuminemia was noted in both groups,

Table 3 Laboratory data acquired from patients during urinary tract infection

	Bacteremic UTI (n = 13) mean (SD)	**Nonbacteremic UTI (n = 39)** mean (SD)	***p***
WBC (/μl)	13,862 (10,356)	8,372 (4398)	0.035
Neutrophils (%)	82.9 (9.0)	80.8 (8.9)	0.465
Lymphocytes (%)	8.6 (7.4)	11.0 (10.5)	0.415
Band (%)	1.8 (2.7)	1.2 (3.2)	0.326
Hb (g/dl)	11.2 (2.1)	10.8 (2.4)	0.634
PLT ($\times 10^3/\mu$)	156 (71)	201 (92)	0.125
Alb (g/dl)	2.4 (0.5)	2.9 (0.6)	0.057
CRP (mg/l)	183 (147)	46 (67)	0.016
ESR (mm/h)	92 (28)	53 (34)	0.021
BUN (mg/dl)	22.5 (15.9)	27.7 (34.9)	0.950
Cr (mg/dl)	1.2 (1.0)	1.4 (1.5)	0.680
C3 (mg/dl)	98.2 (33.0)	80.3 (43.7)	0.150
C4 (mg/dl)	20.7 (11.8)	18.4 (12.1)	0.433
Anti-dsDNA (mg/dl)	176 (393)	323 (558)	0.197

Non-parametric Mann-Whitney U tests; SD, standard deviation; WBC, white blood cells; Hb, hemoglobin; PLT, platelets; Alb, albumin; BUN, blood urea nitrogen; Cr, creatine.

Table 4 Bacteria isolated from 52 episodes of bacteremic and nonbacteremic urinary tract infections in our study patients.

	Total n = 52	**Bacteremic UTI** n = 13	**Nonbacteremic UTI** n = 39
E. coli	39	9	30
G. vaginalis	3		3
S. enteritidis	3	2	1
S. typhimurium	2	2	
K. pneumonia	2		2
Proteus	2		2
E. aerogenes	1		1

without a statistically significant difference. Comparing the 2 groups, the anti-dsDNA level was lower in the bacteremic UTI group, but again, the difference was not statistically significant. The mean complement levels of both groups were above the lower limit of the normal range. The bacteremic UTI group had higher mean complement levels (results not statistically significantly different). The renal function and SLEDAI of those 2 groups were likewise not significantly different. From the 52 urinalysis records, 48 (92.3%) had positive leukocyte esterase concentrations, 26 (50.0%) had a positive nitrite test, and 25 (48.1%) were positive for both. The frequency of positive leukocyte esterase concentrations or positive nitrite tests was not significantly different between the 2 groups (data not shown).

The most common pathogen cultured from urine was *E. coli* (39/52, 75%), followed by 5 cases of *Salmonella* spp., 3 cases of *Gardnerella vaginalis*, 2 cases of *Klebsiella pneumoniae*, 2 cases of *Proteus* spp., and 1 case of *Enterobacter aerogenes* (Table 4).

There were 13 (25%) episodes of UTI with concomitant positive blood cultures, diagnosed as bacteremic UTI. The other 39 (75%) episodes had positive urine cultures only. The most common pathogen isolated from the blood cultures of bacteremic UTI patients was *E. coli* (9 episodes), followed by 4 cases of *Salmonella* spp.

Antimicrobial therapy was started empirically as combined antibiotic therapy in 77% of bacteremic patients and in 49% of nonbacteremic patients. The most frequently used antibiotic combination therapy was a first-generation cephalosporin with an aminoglycoside. Based on the results of susceptibility tests *in vitro*, the antibiotics were switched to ceftriaxone in all *Salmonella* spp. bacteremia patients. The mean duration of parenteral antibiotics was 10.7 ± 4.7 days in patients with bacteremia and 7.1 ± 3.5 days in nonbacteremic patients ($p = 0.222$). All UTI patients recovered completely without any complications after proper antibiotic treatment.

DISCUSSION

Lupus is a disease that predisposes patients to urinary tract infections, yet there is only one outpatient study on UTI in SLE patients.[10] The majority of patients from that study were nonbacteremic. Bacteremic UTI has been reported as carrying a high mortality rate, especially in immunocompromised patients. However, the characteristics and risk factors for bacteremic UTI in SLE patients remained unclear. Our study was the first to investigate the clinical profile of bacteremic and nonbacteremic UTI in hospitalized SLE patients.

In non-SLE patients, the clinical presentation of UTI is variable, ranging from frequent dysuria to full-blown pyelonephritis, and from bacteremia to asymptomatic bacteriuria.[15] Our study revealed that SLE patients with bacteremic UTI are often clinically indistinguishable from those with nonbacteremic UTI. Only fever was reported more often in bacteremic patients. No significant differences were found between the 2 groups regarding clinical manifestations such as dysuria, frequency of urination, urgency, and flank knocking pain. All bacteremic UTI patients experienced fever, however, 71.8% of patients with UTI of nonbacteremic origin also suffered from fever. Even though the difference between the 2 groups was statistically significant, this makes it difficult to use fever or other symptoms in the differential diagnosis between bacteremic and nonbacteremic UTI.

Although initially it may be difficult to differentiate UTI from pyuria with fever associated with underlying SLE, CRP is helpful in differentiating an infectious entity from an exacerbation of the disease.[16] CRP levels during an infection are usually higher than during disease exacerbation; CRP levels greater than 50 mg/l strongly suggest the presence of an infection.[16] All of our patients with UTI had elevated CRP levels, and 82% of the CRP levels were greater than 50 mg/l. We found that bacteremic UTI patients had more severe inflammatory reactions, indicated by significantly higher serum CRP concentrations, higher ESR, and leukocytosis. These inflammatory indices are good predictors of bacteremia in SLE patients, especially when CRP is over 50 mg/l. We found no significant influence on the bacteremic UTI risk concerning complement level, anti-dsDNA level, renal function, and SLEDAI. Taking automated urinalysis into consideration, leukocyte esterase and nitrite concentrations can be helpful in determining whether the urine is infected or not.[13,17] However, the frequency of a positive leukocyte esterase concentration or positive nitrite tests was not different between these 2 groups.

Complement levels and SLEDAI indicated that both groups were not in an active stage of SLE. This finding was comparable to that of Hidalgo-Tenorio *et al.* in 2004.[10] Duffy *et al.*[7] found that hospitalized patients are more likely to have an infection if their disease is active, but this condition was not found in our study population. In addition, neither corticosteroids nor other immunosuppressive drugs given to the patients affected the occurrence of bacteremic UTI in this study. In non-SLE patients, the predisposing factors for UTI were urinary tract obstruction, vesicoureteral or intrarenal reflux and instrumentation of the urinary tract. After excluding these underlying issues, we found that lupus nephritis was a risk factor for UTI. Lupus nephritis is a common renal involvement in SLE. SLE patients with lupus nephritis usually present with proteinuria and hypoalbuminemia. This could result in decreased serum immunoglobulin concentrations; thus, these patients are susceptible to a variety of infections.[18]

In non-SLE patients, *E. coli* is the most common organism causing UTI and more than 95% of UTIs develop through the ascending route. However, bacteremia with hematogenous seeding is another route for UTI. Hematogenously derived infections of the urinary tract are particularly common in instances of *Salmonella* spp. sepsis.[15] In our study, the most frequently isolated pathogen was *E. coli*, which was found in 75% of the urine cultures in our study population. This finding was similar to that described previously.[7,8,10] After *E. coli*, *Salmonella* spp. was the second most common pathogen. SLE has a propensity for *Salmonella* spp. infections.[2] Urinary tract infections caused by nontyphoidal salmonellae present as either cystitis or pyelonephritis, usually in association with malignancy, urolithiasis, structural abnormalities, or immunosuppression.[19] Among the immunosuppressed patients, SLE was the most common disease entity vulnerable to *Salmonella* spp. UTI.[20] Moreover, we noticed that 4 of the 5 *Salmonella* spp. UTI cases were associated with concurrent bacteremia. These five patients did not have gastrointestinal symptoms and the stool cultures were all negative for *Salmonella* spp. Abramson *et al*.[21] declared that SLE is the most common underlying disease for *Salmonella* spp. bacteremia in hospitalized patients, and most striking was an inability to confine the organism to the extravascular space. Patients with bacteremia were treated longer parenterally, but the outcomes of our patients were good in both groups. We suggest that aggressive antibiotic treatment with ceftriaxone should be considered in *Salmonella* spp. bacteremia patients.

Our study had limitations. Outpatients were not studied because they were treated with oral medications and with outpatient clinic follow-up. We only focused on hospitalized patients who were usually immunocompromised and needed careful treatment by their clinicians. To determine the predisposing factors for UTI related directly to the underlying SLE disease entity, we excluded patients with underlying genitourinary tract disease. We know that the small number of cases will affect the statistical relevance of this study, but the impressive results still provide opinions when dealing with hospitalized SLE patients who initially present with fever without definite cause and are eventually diagnosed with bacteremic or nonbacteremic UTI.

In summary, lupus nephritis is a risk factor for UTI in SLE patients. Clinical symptoms do not distinguish bacteremic UTI from nonbacteremic UTI in SLE patients. However leukocytosis and high CRP and ESR levels are good predictors for bacteremic UTI. Although *E. coli* remains the most common bacteria in bacteremic and nonbacteremic UTI, *Salmonella* spp. UTI might need particular attention because of its potential likelihood for causing bacteremia. Bacteremic and nonbacteremic UTI in hospitalized SLE patients are both curable diseases but warrant early diagnosis and intervention.

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