

Original Article

Bacteremia in female Chinese patients with systemic lupus erythematosus: a case-control study

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*Department of Dermatology, Southwest Hospital, Third Military Medical University, Chongqing, China***Abstract**

Introduction: Bacteremia is a common complication in systemic lupus erythematosus (SLE) patients, causing high morbidity and mortality. We investigated characteristics, pathogens, and sites of infection using a cohort of 64 female adults from a single university hospital in China. **Methodology:** SLE patients who had at least one episode of bacteremia ($n = 16$) were compared with non-bacteremia SLE patients ($n = 48$) in a case-control fashion, matching for age at SLE diagnosis and time of admission. Demographic characteristics, clinical and laboratory data, and bacteriologic examinations were collected and reviewed.

Results: A series of parameters were found to be significantly different between controls and cases at bacteremia diagnosis, including an SLE disease activity index, multiple major organ involvement (> 2), active renal disease, leukocytes, neutrophils, 24-hour urine protein, erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), creatinine, hemoglobin, lymphocyte, platelets, and albumin. Eighteen episodes of bacteremia were analyzed, with *Escherichia coli* and *Staphylococcus aureus* being the most frequent isolates. Additionally, *Listeria monocytogenes*, *Rhodotorula mucilaginosa*, and *Salmonella choleraesuis*, which were very rare in the general population, were isolated from the bloodstreams of the cases. Apart from bacteremia without focus, respiratory tract, gastrointestinal tract, urinary tract, skin, and soft tissue were the major origins of infection.

Conclusions: The present study depicts the nature of a cohort of female Chinese SLE patients with bacteremia, revealing that bacteremia is a critical factor contributing to the aggravation of SLE. Our findings provide useful information regarding the control and prevention of bacteremia in female SLE patients in China.

Key words: bacteremia; systemic lupus erythematosus; pathogen; infection sites.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease characterized by a wide range of laboratory and clinical manifestations. Infection is one of the major causes of morbidity and mortality in patients with SLE. It has been demonstrated that patients with SLE are especially prone to developing pneumonia, urinary tract infections, and bacteremia without a specific focus [1], which is caused by endogenous immune deficiency and the use of corticosteroids and immunosuppressive agents [2].

As reported by Chen *et al.*, patients with SLE are more likely to develop bacteremia, with an incidence as high as 92.7 cases/1,000 hospital admissions [3]. Moreover, episodes of bacteremia in both European [4] and Asian [3] patients with SLE are associated with an unfavorable long-term outcome.

So far, few studies have provided detailed information regarding the nature of bacteremia in SLE

patients. Furthermore, the nature of complications in SLE patients varies among ethnic and geographic groups [5], and even fewer data regarding Chinese SLE patients with bacteremia have been reported. Therefore, the aims of this study were to describe the characteristics of bacteremia in a case-control design, including demographic and clinical characteristics at the time of bacteremia diagnosis, species of microorganisms identified in the bloodstream, and sites of infection, using a single cohort of 64 female Chinese adults with SLE.

Methodology*Patients and setting*

A retrospective medical records review was performed in female inpatients admitted to Southwest Hospital of the Third Military Medical University in China, from January 2000 to December 2013. A total of 16 patients who experienced at least one episode of bacteremia throughout their entire SLE evolution were

recruited as cases; 18 episodes of bacteremia were recorded. Three controls (SLE patients without relevant bacteremia episodes), matched for time of admission and age at SLE diagnosis, were selected for each case. The research protocol of the study was approved by the ethics committee of Southwest Hospital of the Third Military Medical University. Patients' informed consent was not required by the review board, as this study did not interfere with the patients.

Definition of terms

Inclusion criteria of SLE were based on the updated American College of Rheumatology classification criteria for the classification of SLE (1997), while bacteremia was diagnosed as at least one positive blood culture and clinically apparent signs or symptoms of sepsis [4]. As for bacteremia caused by coagulase-negative staphylococci, two consecutive positive cultures were required for diagnosis. Major organ involvement of SLE was defined as renal, neuropsychiatric, gastrointestinal, pulmonary, hematological, and cardiovascular involvement.

Study design and collection of data

Baseline data for the subjects included in the case-control study were analyzed in order to prevent a selection bias. Age at diagnosis of SLE was excluded from the analysis due to the age-matched case-control design of the study. The study point was defined as the moment of suffering the first bacteremia in the cases and the most comparable time point in the controls. The following patient data were collected at the study point: age; SLE activity assessed by SLE disease activity index (SLEDAI); pertinent clinical and biological information, such as blood routine test, routine urine test, 24-hour urine protein quantity, serum complement, anti-dsDNA; administration and doses of glucocorticoid; pulse steroid ever; use of immunosuppressive therapy prior to bacteremia; type of microorganisms; and site of infection. Throughout the study period, all febrile patients with SLE had at least a blood culture, a urine culture, a sputum culture, and a chest radiograph to diagnose the sites of infection. Stool culture was performed when necessary.

Statistical analysis

Variables are expressed as mean and standard deviation (SD), or as numbers and proportions, as appropriate. Normally distributed variables were compared using the unpaired Student's t test, while categorical variables were compared by Chi-squared test with Yates' correction, or Fisher's exact test, as appropriate. A two-tailed p value of less than 0.05 was regarded as significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 13.0 (IBM, Armonk, USA).

Results

Baseline characteristics of patients at the study point

A total of 64 female SLE patients (16 cases and 48 controls) were selected for inclusion in the case-control analysis. The mean (SD) age at the study point was 37.1 (17.3) years for cases and 35.7 (11.1) years for controls ($p = 0.762$). The mean (SD) disease duration was 45 (16) and 21.4 (5.1) months, respectively ($p = 0.186$). The number (percentage) of patients with disease durations less than 36 months was 10 (62.5%) for cases and 41 (85.4%) for controls ($p = 0.106$). Thus, the study groups were similar with respect to baseline characteristics (Table 1).

Clinical and biological characteristics

Table 2 summarizes the clinical and biological characteristics of SLE patients with and without bacteremia. The mean (SD) SLEDAI at the time of SLE diagnosis was 13.3 (3.8) for cases and 10.5 (4.8) for controls ($p = 0.087$), indicating similar SLE activity between two groups. However, the SLEDAI of the bacteremia group was significantly higher than that of the non-bacteremia group at the study point ($p = 0.006$). The bacteremia and non-bacteremia groups differed in number of major organs involved (renal, neuropsychiatric, gastrointestinal, pulmonary, hematological, and cardiovascular involvement). A significant difference was noted in the number of patients with active renal disease between two groups, whereas no difference was found in cardiovascular and neuropsychiatric diseases.

Table 1. Baseline characteristics of the patients.

	SLE with bacteremia (cases) N = 16	SLE without bacteremia (controls) N = 48	P value
Age (years)	37.1 ± 17.3	35.7 ± 11.1	NS
Disease duration (months)	45 ± 16	21.4 ± 5.1	NS
Disease duration < 36 months	10 (62.5%)	41 (85.4%)	NS

SLE: systemic lupus erythematosus; NS: not significant.

Table 2. Clinical and biological characteristics of patients at the study point.

	SLE with bacteremia (cases) N = 16	SLE without bacteremia (controls) N = 48	P value
SLEDAI at SLE diagnosis	13.3 ± 3.8	10.5 ± 4.8	NS
SLEDAI	14.4 ± 8.8	7.23 ± 5.06	0.006
SLEDAI ≥ 10	11 (68.8%)	5 (10.4%)	0.000
Major organ involvement > 2	6 (37.5%)	2 (4.2%)	0.002
Active renal disease	11 (68.8%)	12 (25.0%)	0.004
Cardiovascular	5 (31.3%)	4 (8.3%)	NS
Neuropsychiatric	2 (12.5%)	0 (0.0%)	NS0
High fever > 39°C	9 (56.3%)	2 (4.2%)	0.000
Hemoglobin, g/L (± SD)	95.38 ± 18.65	113.30 ± 20.44	0.003
Leukocytes × 10 ⁹ /L (± SD)	9.98 ± 6.21	6.25 ± 3.39	0.034
Neutrophils × 10 ⁹ /L (± SD)	8.59 ± 5.59	4.40 ± 2.65	0.010
Lymphocytes × 10 ⁹ /L (± SD)	0.87 ± 0.56	1.34 ± 0.84	0.049
Platelets × 10 ⁹ /L (± SD)	149.25 ± 65.98	169.54 ± 66.53	0.409
24-hour urine protein (g/day) 24 uP	1.5 ± 2.1	0.7 ± 1.1	0.045
Low complement, n (%)	7 (43.8%)	33 (68.8%)	NS
Serum C3 levels	0.82 ± 0.40	0.69 ± 0.22	NS
Serum C4 levels	0.33 ± 0.32	0.15 ± 0.07	NS
Anti-DNA positive, n (%)	4 (25.0%)	11 (22.9%)	NS
ANA positive, n (%)	15 (93.8%)	41 (85.4%)	NS
ANA titer	221.33 ± 154.82	213.33 ± 125.69	NS
ESR	86.54 ± 39.81	43.65 ± 36.74	0.002
Albumin (g/dL)	30.52 ± 4.48	36.54 ± 5.82	0.001
Aspartate aminotransferase (AST, U/L)	52.64 ± 47.02	21.77 ± 8.47	0.030
Alanine aminotransferase (ALT, U/L)	43.00 ± 56.34	18.77 ± 8.46	NS
Gamma-glutamyl transpeptidase (γ-GT, U/L)	60.08 ± 70.27	27.80 ± 31.35	NS
Alkaline phosphatase (ALP)	67.83 ± 17.42	57.93 ± 31.35	NS
Blood urea nitrogen (BUN)	8.66 ± 5.88	5.70 ± 3.20	NS
Creatinine	97.67 ± 55.12	61.24 ± 19.13	0.029

SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; ANA: antinuclear antibodies; ESR: erythrocyte sedimentation rate; NS: not significant.

Table 3. Treatment prior to bacteremia.

Treatment	SLE with bacteremia (cases) N = 16	SLE without bacteremia (controls) N = 48	P value
Current steroid dose ^a (mg)	34.06 ± 16.95	31.19 ± 10.99	NS
Current steroid dose > 30 mg	7 (43.8%)	23 (47.9%)	NS
Pulse steroid ever	8 (50.0%)	26 (54.2%)	NS
Pulse steroid ever < 3 months	2 (12.5%)	14 (29.2%)	NS
Pulse steroid ever < 6 months	3 (18.8%)	17 (35.4%)	NS
Pulse CTX ever	5 (31.3%)	18 (37.5%)	NS
Pulse CTX ever < 3 months	1 (6.3%)	13 (27.1%)	NS
Pulse CTX (cumulative dose in mg)	5.12 ± 4.16	3.87 ± 2.65	NS

^a Expressed in milligrams of prednisolone or equivalent; SLE: systemic lupus erythematosus; CTX: cyclophosphamide; NS: not significant.

Significantly more patients were found with high temperature and low levels of total serum complement in cases compared to controls. Substantially higher levels of leukocytes, neutrophils, 24-hour urine protein, erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), and creatinine and lower levels of hemoglobin, lymphocyte, platelets, and albumin were detected in cases than in controls. The use of steroid and cyclophosphamide (CTX) is depicted in Table 3 and showed no difference between two groups of patients.

Recurrent bacteremia

Two of the 16 cases had recurring bacteremia. The microorganisms isolated from patients with recurrent bacteremia were the same species as previously isolated. The pathogens of the two cases were *S. choleraesuis* and *S. aureus*. One recurrence happened two weeks after discharge, while the other occurred three months after discharge.

Distribution of microorganisms isolated from blood

A total of 18 episodes of bacteremia, all of which were mono-microbial, occurred in 16 cases. Species of microorganisms isolated from blood of bacteremia group are listed in descending order by number in Table 4. Of the 18 microorganisms identified, 10 (55.6%) were Gram-negative bacteria, 7 (38.9%) were Gram-positive bacteria, and 1 (5.6%) was fungi. *E. coli* (6; 33.3%) and *S. aureus* (4; 22.2%) were the leading Gram-negative and Gram-positive pathogens, respectively, which was in agreement with an earlier report [4], followed by *S. choleraesuis* (2; 11.1%), *Staphylococcus epidermidis* (1, 5.6%), *Acinetobacter spp* (1; 5.6%), *Salmonella typhi* (1; 5.6%), *Streptococcus pneumoniae* (1; 5.6%), *L. monocytogenes* (1; 5.6%), and *R. mucilaginosa* (1; 5.6%).

Origins of infection

Table 5 shows the origins of infection. Seven cases were diagnosed with a single site of infection, while six cases reported multiple sites of infection. Four cases of bacteremia were without focus. Respiratory tract, gastrointestinal tract, and urinary tract were the most common infection sites found in this study. Pulmonary infection was the most frequently found infection site, which constituted 61.1% (11 cases) of all bacteremia, followed by gastrointestinal tract infection (5; 27.8%) and urinary tract infection (3; 16.7%).

Discussion

Our study provides detailed information regarding the nature of bacteremia in a cohort of 64 female patients with SLE from a university hospital in China. The mean age of onset of SLE observed in this study is

Table 4. Microorganisms isolated from blood.

Microorganisms	Number
<i>Escherichia coli</i> -	6
<i>Staphylococcus aureus</i> +	4
<i>Salmonella choleraesuis</i> -	2
<i>Staphylococcus epidermidis</i> +	1
<i>Acinetobacter spp</i> -	1
<i>Salmonella typhi</i> -	1
<i>Streptococcus pneumoniae</i> +	1
<i>Listeria monocytogenes</i> +	1
<i>Rhodotorula mucilaginosa</i>	1

Table 5. Origins of infection.

Infection site	Number
Respiratory tract	11
Gastrointestinal tract	5
Urinary tract	3
Skin and soft tissue	2
Bacteremia without focus	3

consistent with that in a previous study of a Chinese population [6]. We employed a case-control strategy matched for age at SLE diagnosis and the time of admission. No statistically significant difference was found in age and disease duration at the study point, as shown in Table 1.

SLE activity (quantified by the SLEDAI) is regarded as one of the most important risk factors for infection [7,8], since patients with higher SLEDAI score tend to have more severe endogenous immune deficiency and use more corticosteroids and immunosuppressive agents. Our data suggest that patients with similar SLEDAI scores at SLE diagnosis and using comparable doses of steroid before bacteremia showed a significant difference in SLEDAI at the time of bacteremia diagnosis, with a much higher SLEDAI score in the bacteremia group than the control group, suggesting a reciprocal effect of infection on aggravating SLE. This is in agreement with a previous finding, indicating that infection is significantly associated with overall SLE activity [9]. Number of disease manifestations and decreased renal function have been associated with infection in SLE in previous studies as well [7,9-11]. In this study, a larger percentage of patients with multiple major organ involvement and active renal disease were found in the bacteremia group at the study point. Cases had significantly higher levels of 24-hour urine protein and creatinine. Renal involvement at the study point has previously been identified as a variable related to infection in SLE patients by univariate analysis [8]. In addition to abnormal parameters indicating infection, such as body temperature, leukocytes, neutrophils, and ESR, aberrant levels were also found in some indicators for SLE severity and general condition (*e.g.*, total serum complement, lymphocyte, AST, hemoglobin, platelets, and albumin). These results indicate a complicated interaction in which bacteremia and SLE contribute to each other's development, thus aggravating the patient's condition.

It has been demonstrated that Gram-negative bacilli are the most common microorganisms responsible for bacteremia in Asian SLE patients [12]. The present study supports this notion, as Gram-negative bacteria accounted for 55.6% of the overall bacteremia rate. *E. coli* was the leading cause of Gram-negative bacteremia in the general population [13] and the most common causative organism for infections in SLE patients in a Spanish study [14]. *E. coli* [4] and *S. aureus* [3,4] were reported to be the leading Gram-negative and Gram-positive pathogens, respectively, leading to bloodstream infections among lupus patients. The

current findings are in accordance with these reports. However, some other studies regarded nontyphoidal *Salmonella* as the most common Gram-negative pathogen causing bacteremia in SLE patients [3,15,16], whereas *E. coli* ranked second [3]. This inconsistency may be due to various ethnic and geographic cohorts enrolled in different studies and distinct sample sizes. Because of the incidence and the potential severity of *E. coli* and *S. aureus* bacteremia, treatment with antibiotics active against these bacteria should be started promptly.

In this study, *S. choleraesuis* was responsible for two episodes of bacteremia that occurred in one patient. It has been reported that *S. choleraesuis* is one of the least commonly reported nontyphoidal salmonellae [17]. However, patients with SLE are at high risk of infection caused by this very rare species of bacterium [18] and prone to develop into *S. choleraesuis* bacteremia, the recurrence of which is a feared clinical scenario [19]. Accordingly, the prevention of *S. choleraesuis* infection in SLE patients and the recurrence of *S. choleraesuis* bacteremia should be taken seriously in clinical practice. Besides this case, another case had recurrent bacteremia caused by *S. aureus*. A previous report indicated that half of the recurrent episodes of bacteremia were caused by the same species of microorganisms isolated in the previous episodes [3]. Consequently, administration of an antibiotic which covers the same pathogens as those identified in the previous episode is suggested if a recurrence is suspected.

L. monocytogenes infection is a relatively rare complication in SLE patients [20]. One case of *L. monocytogenes* bacteremia was found in our cohort of 18 episodes of bacteremia in patients with SLE. One case of *R. mucilaginosa* infection was observed. No other fungal infections or parasitic diseases were noted. Thus, additional attention should be paid to these bacteremia caused by opportunistic pathogens in heavily immunosuppressed patients with lymphopenia, such as SLE patients. Identifying pathogens of bacteremia in Chinese female SLE patients is crucial for empirical use of antibiotics to further improve the likelihood of survival of these patients.

Similar to infections in the general population, infections in SLE include common infectious diseases such as pneumonia, urinary tract infection, and cellulitis [21]. This study shows that most major infections in SLE patients involved the respiratory tract, while most minor infections were skin and soft-tissue infection, which compares favorably with previous studies. It is worth noting that positive blood cultures were found in

three episodes of bacteremia (16.7%) without clear sites of infection, with *S. aureus*, *S. epidermidis*, and *Acinetobacter spp* as the pathogen, respectively, indicating that female Chinese SLE patients are prone to developing bacteremia without focus, in accordance with results from others [1].

Conclusions

This study describes the main characteristics of a sample of SLE patients with bacteremia and shows a spectrum of pathogens and sites of infection, which may have clinical significance in guiding prophylaxis and empirical use of antibiotics. Our findings underscore the need for close surveillance on the deterioration of SLE, especially on renal function, if an SLE patient is diagnosed with bacteremia. Appropriate precautions should be employed in preventing infections in the respiratory tract, gastrointestinal tract, and urinary tract.

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Authors' contributions

FRC and ZFZ conceived and designed the experiments. FRC, FH, QQC, TQ, YC, and HW collected and analyzed the data. FRC and ZFZ drafted and revised the manuscript.

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