Title: Bacteremia in systemic lupus erythematosus patients from RELESSER: risk factors, clinical and microbiological characteristics and outcomes.

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Title: Bacteremia in systemic lupus erythematosus patients from RELESSER: risk factors, clinical and microbiological characteristics and outcomes.

Abstract

Objectives: To describe the incidence of bacteremia in a large multicentric cohort of SLE patients and their clinical characteristics and to identify risk factors.

Methods: All bacteremic episodes from the RELESSER registry were included. Clinical and laboratory characteristics concerning bacteremia and SLE status, as well as comorbidities at the time of infection, were retrospectively collected. A comparison with sex- and age-matched SLE controls without bacteremia was made. A logistic regression was conducted.

Results: A total of 114 episodes of bacteremia in 83 patients were included. The incidence rate was 2.7/ 1,000 patient-years. At the time of bacteremia, the median age was 40.5 (range: 8-90) years, and 88.6 % of patients were female; SELENA-SLEDAI: 4 (IQR:8); 41% had an SLE flare (66% severe); SLICC/ACR DI: 3 (IQR4). A comorbidity was recorded in 64% of cases. At the time of bacteremia, 88.6% received corticosteroids (68.6% >10mg/day) and 57% immunosuppressors. Gram-negative bacilli, most frequently *E. coli* (29.8%), caused 52.6% of the episodes. The bacteremia-related mortality was 14% and bacteremia was recurrent in 27.2% of cases. A dose-response relationship was found between corticosteroids and bacteremia risk. In the multivariate analysis, elevated creatinine [OR 1.31 (95%CI 1.01-1.70), p=0.045], diabetes [OR

6.01(2.26-15.95), p=0.000], cancer [OR 5.32 [2.23-12.70), p=0.000], immunosuppressors (OR 6.35 (3.42-11.77), p=0.000) and damage [OR 1.65(1.31-2.09), p=0.000] were associated with bacteremia.

Conclusions: Bacteremia occurred mostly in active SLE patients and was frequently associated with severe flares and corticosteroid use. Recurrence and mortality were high. Immunosuppressors, comorbidities and disease-related damage were associated with bacteremia.

1. Introduction

Infections remain a major cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients and ~30% will suffer at least one serious infection at some time (1).

Although respiratory infections are the most common severe infection in SLE, according to RELESSER (Spanish Society of Rheumatology Lupus Registry) data, bacteremia has a greater impact on mortality (2). However, the prevalence of bacteremia in SLE patients is not well known, with reports ranging between 7-49% across several studies (3,4,5,6). In fact, according to a recent population-based study, the prevalence of this life-threatening complication is probably increasing (7). Additionally, the incidence of bacteremia of unknown origin was significantly greater in SLE patients than in non-SLE controls in one study (3) and the long-term survival rate of patients with SLE following a bacteremic episode was lower (6). Despite the relevance of bloodstream infections in SLE, few studies have provided detailed information concerning the nature and significance of bacteremia in SLE patients and none has been conducted in a European county.

The aim of this retrospective, case-control study is to describe the cumulative incidence, microbiology and outcomes of bloodstream infections in a wide national SLE cohort from the RELESSER registry, and to examine risk factors associated with bacteremic events.

2. Methods

All centers with bacteremic episodes registered with RELESSER were invited to participate in the study. The RELESSER registry includes data from 3,679 SLE patients (ACR-1997 criteria) (8) from 45 Spanish hospitals. The methodologic and general characteristics of the RELESSER registry have been published previously (9).

New information (i.e., not available in the RELESSER registry) concerning both bacteremia and SLE status at the time of the infection was retrospectively collected, including the etiologic agent, potential sources of bacteremia, antibiogram testing, treatment and bacteremia-related outcomes. SLE activity at the time of bacteremia was estimated using SELENA-SLEDAI, while flares, and flare severity, were defined using SFI criteria (10). Damage at the time of bacteremia was measured using the SLICC/ACR damage index.

A comparison was made with sex- and age-at-diagnosis-matched SLE controls (1 case/6 controls) without bacteremia, using the last visit recorded in the RELESSER-T registry database as the reference visit (11).

Only bacteriologically proven bacteremia with sufficient clinical data were ultimately included in the analysis. Clinically significant bacteremia was defined as a positive blood culture and any sign or symptom of sepsis or a systemic inflammatory response. The presence of coagulase-negative *Staphylococcus sp.*, *Streptococcus viridans group*, *Corynebacterium sp*., *Propionibacterium sp*. or *Bacillus sp.* in just one blood culture bottle was considered the result of contamination (12). Bacteremia was classified as

polymicrobial if two microorganisms, not usually considered contaminants, were obtained from blood cultures.

Nosocomial blood-stream infections were defined according to Centers for Disease Control (CDC) criteria (13). The source was considered accurately established if the microorganism was isolated both from blood and the focus at the same time.

The Pitt Bacteremia Score was used as a numerical measure of the bacteremia's severity, with values above 8 having been previously associated with mortality (14).

Common definitions for the main comorbidities (e.g., diabetes, cancer, etc.) were used and a vital prognosis of the comorbidity was assessed using McCabe and Jackson's criteria (15).

Empirical antimicrobial therapy was defined as the initial therapy prior to the availability of blood culture results. Appropriate antimicrobial therapy was defined as the administration of any antimicrobial agent to which the causative organism was considered susceptible according to antibiogram results. Antibiotic multi-resistance was defined as resistance or intermediate sensitivity to one or more antibiotics from three different categories in susceptibility testing.

The length of antimicrobial therapy was defined as the time period from the first to the last day of an appropriate antimicrobial regimen. Total antimicrobial days were calculated on the basis of the length of therapy with each appropriate antimicrobial agent (e.g., 7 days of gentamicin and 7 days of carbapenem would represent 14 total antimicrobial therapy days).

We defined bacteremic-related mortality as any death occurring in a patient without previous disease-related severity and that was temporally related to a bacteremic event.

2.1 Statistical analysis

Each bacteremic episode was considered for analysis, and descriptive analyses were carried out. Numerical variables are expressed as the mean and standard deviation for those having a normal distribution, and as median and interquartile ranges for non-normal distributions (Kolmogorov test). The categorical variables are described by absolute frequencies and percentages.

A bivariate analysis was performed to identify any differences between patients with and without bacteremia, using the chi-square test for qualitative-independent variables (or Fisher's exact test when necessary), and a Student's t test for quantitative-independent variables (or the nonparametric Mann-Whitney U test in the case of non-normal distributions).

A logistic regression was carried out as a multivariate analysis, using a step-wise approach, including variables sequentially, on the basis of likelihood ratio. The following variables were ultimately included in the model: SLE duration, creatinine, diabetes, cancer, immunosuppression use, cyclophosphamide, SLICC damage index, SELENA-SLEDAI, active lupus nephritis, HIV or Hepatitis C seropositivity, splenectomy, hospitalization by SLE, corticosteroids > 10mg/day, antimalarials, mycophenolate, renal transplant and dialysis.

Given the low number of deaths, a multivariable analysis of mortality associated-factors was not considered appropriated.

The IBM-SPSS for Windows statistical software package (v.19.0) was used for all statistical analyses. Significance was defined as $p < 0.05$.

Ethical issues: The study was approved by the Ethics Committee at Doctor Negrín Hospital (board approval number: RELES-SER-2009-01)

3. Results

Comparative clinical and demographic characteristics between patients with and without bacteremia are shown in **Table 1**. The first bacteremic episode was recorded on 1 April 1980 and the last on 3 January 2015; however, 80.5% of the bacteremias took place during the years 2000 to 2015.

A total of 114 episodes of bacteremia were recorded in 83 patients. The incidence rate was 2.7/ 1,000 patient-years (N total of the cohort: 3,658). At the time of the bacteremia, the median age was 40.5 (range: 8-90) years, and 88.6% were female. Median disease duration was 9.7 years (IR: 16.7), median SELENA-SLEDAI: 4 (IR:8), 41.2% had a coincident SLE flare, 66% of these severe flares. SLE was serologically active in 50.9% of cases. Active nephritis was present in 19 (16.7%), median SLICC/ACR DI: 3 (IR4). Some comorbidity was recorded in 64% of cases and proved rapidly or ultimately fatal in 28.1% (McCabe-Jackson criteria), the latter more often involving renal failure (15.8%) or diabetes (11.4%). The complete list of comorbidities recorded are provided in **Table 2**.

Regarding SLE treatments at the time of bacteremia, 88.6% of patients received corticosteroids with the following dosage distribution: 31.7% prednisone < 10mg/day or equivalent, 37.6%, 10-30 mg/day and 30.7% > 30mg/day (68.6% >10mg/day). In a total of 10 cases, a bolus of methylprednisolone had been used in the previous month. In 65 episodes (57%), the treatment included immunosuppressors (mycophenolate 17.5%, azathioprine 13.2%, cyclophosphamide 12.3% and others). Only 26.3% were on antimalarials. In 51 (44.7%) of the bacteremic episodes, an invasive procedure was recorded, more often intravascular catheter (24.6%), surgical intervention (8.8%), urinary catheter (3.5%), mechanical ventilation for at least 24 hours (0.95%) and others.

The bacteremia was nosocomial in 35.1% of cases and the source was more frequently urinary (27.2%), followed by respiratory tract (16.7%), intravascular catheter (11.4%),

intestinal (8.8%) and cutaneous (7%). The origin remained undetermined in 25.5% of cases based on the predefined criteria. Fever was present in 78.9 % of the episodes, 64% developed systemic inflammatory response syndrome, (3.5%) endocarditis and 35% required intensive care unit (ICU) admission, with multi-organ failure in 22.8% of patients.

A total of 60 (52.6%) bacteremic episodes were caused by gram-negative bacteria. The most frequent microorganism isolated was *E. coli* (29.8%), followed by *Staphylococcus aureus* (16.7%) (22% methicillin-resistant) and *Salmonella sp.* (10.5%). The bacteremia was polymicrobial in only 4 cases (3.5%). Sixteen percent of the gram-negative enteric bacilli were extended-spectrum b-lactamase (BLEE) positive, while 17.5% proved to be multidrug-resistant.

The distribution of bacteremia's causes, according to the area of acquisition, is shown in **Table 3**. There were greater proportions of *Sstreptococcus pneumoniae* and *Salmonella sp.* in community-acquired bacteremia compared to those acquired in hospital.

As expected, although the percentage of resistance to typical microorganisms were numerically greater in nosocomial bacteremia compared to community-acquired ones, the differences were not statistically significant in any examined cases (see table in supplementary material). However, the prevalence of multi-resistance was significantly higher in nosocomial bacteremia (p=0.005).

E. coli bacteremia was strongly associated with urinary sources (71.0% vs 14.5%, p=0.000), although no associations between *E. coli* and active nephritis or *E. coli* and elevated creatinine were found.

In 68.4% of cases (78/114), antibiotherapy was started before blood culture results were available. This antibiotherapy resulted ultimately active in susceptibility testing in 56

cases (71.8%), which indicated that the appropriate empirically-based antibiotic therapy had been carried out in only 49% (56/114) of the episodes.

The median number of antibiotics used was 2 (1-5), while monotherapy was administered in 67/114 episodes (58.8%). The median duration of antibiotic therapy was 15 days (IQR:10).

Bacteremia-related mortality was 14%. As expected, the risk of death was higher in patients with severe sepsis or septic shock (Pitt Bacteremia Score >8) (OR: 13 (95%CI: 3.71-45.17). Bacteremia was recurrent in 31 patients (27.2%); 18.1% suffered a second bacteremia episode and seven (8.4%) at least three episodes.

Bivariate analysis revealed several factors associated with bacteremia (114 bacteremias vs 688 controls), as are shown in **Table 4**. Splenectomy was strongly associated with encapsulated microorganism bacteremia [OR 17.79 (95%CI: 4.38-72.28)]. Anti-malarials showed some protective effects. Interestingly, a dose-response relationship was found between corticosteroids and bacteremia; that is, the risk of bacteremia increased proportionally with the dose of corticosteroids (**Table 5**).

The use of mycophenolate or cyclophosphamide was not associated with neutropenia at the time of a bacteremic event (data not shown).

In the multivariate analysis (adjusted for disease duration), only elevated creatinine [OR 1.31 (95%CI 1.01-1.70), p=0.045], diabetes [OR 6.01(95%CI 2.26-15.95), p=0.000], cancer [OR 5.32 [95%CI 2.23-12.70), p=0.000], immunosuppressors (OR 6.35 (3.42-11.77), p=0.000), cyclophosphamide use [OR 9.37 (5.12-17.14), p=0.000] and damage [OR 1.65(1.31-2.09), p=0.000] remained statistically significant.

4. Discussion

The rate of bacteremia in SLE widely surpasses that reported in the general population, where rates between 80 and 189 per 100,000 per year have been estimated (16). With the exception of *Salmonella sp.*, the distribution of the most important etiologic agents in our study matched the data reported on community-acquired bloodstream infections in the general population (16). This is consistent with the predominance of non-nosocomial bacteremia found in this cohort. As in the present study, gram-negative bacilli were the microorganisms most commonly responsible for bacteremia in Asian SLE patients, which was also the case in a monocentric cohort in Spain (6, 17). The predominance of *E. coli* (29.8% in this cohort) as an etiologic agent of bacteremia in SLE has similarly been reported by other researchers (3,4). As expected, in our study *E. coli* bacteremia was associated with the urinary tract, which is consistent with the fact that such infections remain the most common type suffered by SLE patients (18). Although this finding could be put in the context of active nephritis as an independent factor associated with bacteremia, unfortunately this variable did not retain significance in the multivariable analysis in our study. This is in contrast to Lim et al, who found that bacteremia was associated with lupus nephritis relapse in their monocentric SLE cohort (19). Furthermore, in another retrospective study the frequency of lupus nephritis was higher in urinary tract infection (UTI) cases than in SLE controls without UTI, as was a high frequency of bacteremia, affecting up to 25% of cases (20). The high rate of *Salmonella sp.* isolates in this study is not a surprise, since SLE is a well-known risk factor for bacteremia in cases of *Salmonella sp*. infection (21). In fact, Abramson et al. point out that SLE is the most common underlying disease for *Salmonella sp.* bacteremia in hospitalized patients. In their study, these authors demonstrated the inability of SLE patients to confine the microorganism to the extravascular space (22).

The association with damage, as measured by SLICC/ACR DI, in our multivariable analysis warrants further consideration. In our previous study, which took into account the total number of severe infections in the entire SLE-RELESSER cohort, we also found a significant association with damage (2). It is tempting to speculate that renal damage could facilitate the dissemination of the microorganism throughout the bloodstream. The finding that elevated creatinine is also linked to bacteremia in the multivariable model, in the absence of "active nephritis" variable in the same model, reinforces this assumption.

The use of oral corticosteroids has been previously recognized as a risk factor in SLE patients who developed bacteremia (6). Our observations reinforce the relationship between corticosteroids and bloodstream infections, showing a strong, not previously reported, dose-dependent effect; i.e., the higher the corticosteroid dose, the greater the risk. It is possible that the combination of azotemia and high doses of corticosteroids favor the spread of infection, as has been previously suggested (23). Unfortunately, in our multivariable analysis, neither of these variables retained statistical significance when included together in the same model. Furthermore, a group of researchers found that prednisone doses during bacteremic episodes represented an independent risk factor for acquiring drug-resistant bacteria in patients with SLE (23). A strong trend was found when the possible association between microbial resistance and corticosteroid doses was tested (p=0.07).

It is worth noting that in regard to immunosuppressors, only the use of cyclophosphamide, and not mycophenolate, was ultimately linked to bacteremia in our multivariable analysis. In contrast, the other study that analyzed this topic in SLE patients with bacteremia did not note any differences (6). Despite the fact that most studies found that cyclophosphamide produces more leukopenia compared with mycophenolate, most of these studies were unable to detect any differences in the prevalence of severe infection

between the two drugs (24-29). The dose of cyclophosphamide, not usually recorded in studies of SLE-associated bacteremia, could be an important point to consider when addressing this question (30).

Our study replicates the high rate of recurrent episodes of bacteremia in SLE that have been previously reported (6,17), a rate notoriously higher than that observed in the general population (31,32). These results probably reflect the chronic character of SLE, damage, immunosuppressive treatments and associated comorbidities.

We believe the bacteremia-related mortality rate exhibited in this cohort to be an important finding, since it nearly duplicates that previously reported in a monocentric cohort from our country (17). The inclusion of patients from a wider temporal spectrum could also have some impact, taking into account the fact that antibiotic armamentarium has improved in recent years, with a consequent reduction in sepsis-related mortality (3). Moreover, our rate of bacteremia-related mortality was higher when comparing any type of organ transplant, including bone marrow, in patients that underwent these procedures and who were included in the Spanish national registry of severe infections (33). One additional explanation for such high mortality rates could be that patients with SLE are less likely to receive appropriate antimicrobial therapy within the initial 72 hours, when the first symptoms of bacteremia can be easily mistaken for SLE disease activity flare-ups. The finding that antibiotherapy was started in only 68% of cases before blood culture results were available supports this hypothesis. In this sense, it is pertinent to remember that a delay in the starting of antibiotherapy in patients with bacteremia is perhaps the most important risk factor for mortality (34-36). Interestingly, some researchers have reported a high mortality rate from Sal*monella sp.* infection (ranging from 8.7% to 28.5%) in SLE patients, despite having received appropriate antimicrobial treatment (37,38). Furthermore, reinfection, which frequently occurs in such patients, was the most

important risk factor of SLE-related mortality in those suffering from Salmonella infections in one study (39).

Taking into account these data, including the association with high mortality, some recommendations for the empirical treatment of bacteremia in SLE patients can be advanced. Regarding nosocomial bacteremia, at least for Spanish SLE patients, we suggest using a carbapenem, perhaps meropenem or imipenem, to ensure proper coverage of *Pseudomonas aeruginosa* and extended spectrum betalactameses (ESBL)-producer *Enterobacteriaceae sp.* The use of β-lactamase inhibitors (such as the combination ceftazidime-avibactam) (40) could represent an interesting new alternative. An antibiotic active against methicillin-resistant *Staphylococcus sp.* should always be added. For community-acquired bacteremia, given the low prevalence of *Pseudomonas aeruginosa*, we would recommend ertapenem, avoiding the use of wide-spectrum carbapenems. Moreover, ertapenem is also active against *Streptococcus pneumoniae*, a microorganism that should always be considered in community-acquired bacteremia. Of course, before any decision can be taken, one must always consider the local epidemiology.

Our study has further limitations that need to be pointed out. The limitations of the RELESSER registry have been previously described (15). The most important of these concerns its retrospective design, which renders it susceptible to a higher likelihood of measurement mistakes and which lacks sufficient information regarding confounding variables.

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Table1: Comparative clinical and demographic characteristics between SLE patients with and without bacteremia

	SLE with bacteremia (n=114)	SLE without bacteremia (n=686)	*p*-value
Male sex (%)	13 (11.4)	57 (8.3)	0.367
Age diagnosis, years *	29.8 (21.9)	31.2 (18.4)	0.596
Age at RELESSER inclusion, years*	36,2 (15.5)	36.6 (14.4)	0.790
Ethnicity (% Caucasian)	106 (95.5)	619 (91.7)	0.662
ACR-97 SLE criteria accrual since diagnosis**			
Malar rash	51 (44.7)	356 (52.1)	0.174
Discoid rash	22 (19.6)	145 (21.5)	0.752
Photosensitivity	60 (53.1)	386 (57.3)	0.468
Oral ulcers	55 (49.1)	314 (46.3)	0.655
Arthritis	90 (78.9)	509 (74.6)	0.384
Serositis	49 (43.0)	182 (26.8)	0.001
Renal disorder	74 (64.9)	277 (41.2)	0.001
Neurologic disorder	26 (22.8)	65 (9.6)	0.001
Hematologic disorder	103 (90.4)	567 (82.7)	0.054
Immunologic disorder	106 (99.1)	598 (92.4)	0.019
Antinuclear antibody	113 (99.1)	681 (99.3)	1.000

* Median (IR)
**Number (%)

Table 2: Comorbidities at the time of bacteremia

	N	**%**
Renal insufficiency	18	15.8
Diabetes	13	11.4
Cardiomyopathy	11	9.6
Cancer	8	7.0
Kidney transplant	8	7.0
Chronic obstructive bronchial disease	7	6.1
Chronic liver disease	7	6.1
Other cardiovascular diseases	7	6.1
Leukemia or Lymphoma	7	6.1
Respiratory insufficiency	3	2.6
Osteomyelitis	3	2.6
Kidney stones	2	1.8
Morbid obesity	2	1.8
Dialysis	2	1.8
Others	20	17.5

Table 3: Factors associated with bacteremia in the bivariate analysis

	OR (95%CI)	p-value
SELENA-SLEDAI	1.10 (1.06-1.14)	<0.001
SLICC/ACR DI	1.27 (1.16-1.38)	<0.001
Elevated creatinine	2.08 (1.66-2.61)	<0.001
Active nephritis	3.52 (1.94-6.37)	=0.001
Hepatitis C	4.82 (1.89-12.27)	=0.002
Diabetes	3.87 (2.06-7.26)	=0.0001
Cancer	3.60 (2.01-6.42)	=0.000
Splenectomy	6.66 (2.44-18.13)	< 0.001
Hospitalization by SLE	26.3 (6.40-107.6)	=0.000
Corticosteroids (Prednisone >10mg/day)	1.81 (1.07-3.09)	=0.023
Immunosuppressors	11.44 (7.31-17.92)	=0.000
Anti-malarials	0.39 (0.25-0.61)	=0.000
Renal Transplant	5.64 (2.63-12.1)	=0.000
Dialysis	7.04 (3.33-14.88)	<0.001

Table 4 : Microorganism according to area of acquisition

Microorganism N (%)	Community-acquired	Hospital-acquired	Total
Enterococcus sp	6 (8.1%)	3 (7.5%)	9 (7.9%)
Escherichia coli	19 (25.7%)	15 (37.5%)	34 (29.8%
Salmonella sp.	10 (13.5%)	2 (5%)	12 (10.5%)
Other enterobacteriae sp.	2 (2.7%)	4 (10%)	6 (5.3%)
Pseudomona aeuruginosa	3 (4.1%)	3 (7.5%)	6 (5.3%)
Staphylococcus aureus	12 (16.2%)	7 (15%)	19 (16.7%)
Coagulase-negative staphylococcus sp.	5 (6.8%)	5 (12.5%)	10 (8.8%)
Streptococcus pneumoniae	10 (13.5%)	1 (2.5%)	11 (9.6%)
Other	9 (12.1%)	2 (5%)	11 (9.6%)
Total	74 (100%)	40 (100%)	114 (100%)

Table 5: Prednisone dose (or equivalent) and odds ratio of bacteremia

Glucocorticoid dose	OR (95%CI)
Prednisone < 10 mg	2.34 (1.25-4.36)
Prednisone 10-30 mg	9.31(5.16-16.78)
Prednisone 30-60 mg	13.33 (7.13-24.9)
Prednisone > 60 mg	16.47 (9.00-30.13)