Risk Factors of Mortality for Salmonella Infection in Systemic Lupus Erythematosus

CHING-HSIUNG TSAO, CHUN-YI CHEN, LIANG-SHIOU OU, and JING-LONG HUANG

ABSTRACT. ***Object.*** To investigate the risk factors of mortality for Salmonella infection in patients with systemic lupus erythematosus (SLE).

Methods. Between 1995 and 1999 we reviewed 37 cases of Salmonella infection in 31 patients with SLE from a total of 1191 hospitalized patients with SLE at a medical center in Taiwan. Contrasting cases of patients who died with those who survived, we compared clinical and laboratory characteristics of SLE at the time of Salmonella infection, with special attention to potential risk factors (sex, age, complete blood count and differential count, erythrocyte sedimentation rate, C-reactive protein, complements, Salmonella species, infection site, reinfection, SLE presenting with Salmonella infection, associated non-Salmonella infection, etc.).

Results. The mean age at the onset of SLE in the 8 mortality cases was significantly higher than the 23 cases of survivors ($p < 0.05$). Other factors significantly related to death included associated infections other than Salmonella species, reinfection of Salmonella species, and cases of SLE presenting with Salmonella infection. Reinfection and SLE presenting with Salmonella infection were the most important risk factors of mortality for SLE with Salmonella infections: relative risk (CI) 84 (4.3–1638.8) and 63 (3.1–1296.5), respectively.

Conclusion. Patients with SLE who are older or have associated infections other than Salmonella have an increased mortality rate when they have concurrent Salmonella infection. Patients with Salmonella infection occurring concurrently with the first presentation of SLE and patients with SLE reinfected with Salmonella species are at higher risk of mortality. (J Rheumatol 2002;29:1214–8)

Key Indexing Terms:
MORTALITY
SALMONELLA INFECTION
SYSTEMIC LUPUS ERYTHEMATOSUS
RISK FACTOR

Infections are the main causes of mortality in patients with systemic lupus erythematosus (SLE). Overall, their survival rate improves with early diagnosis and the treatment of patients with kidney or central nervous system problems[1-3]. The main predisposing factors for infection are disease activity, depression of cell mediated and specific antibody mediated immune response, deficient opsonic capacity, the use of immunosuppressive therapy, and complications of SLE such as uremia[4,5]. Among the most common opportunistic bacterial infections seen in SLE are those caused by Salmonella[6,7]. Abramson declared that SLE was the most common underlying disease for Salmonella bacteremia in hospitalized patients[8]. SLE predisposes patients to severe Salmonellosis. Pablos, *et al* found the death of SLE patients with Salmonellosis was significantly associated with renal failure[9]. Rare reports have discussed the relationship of Salmonella infections in SLE patients and mortality in the English literature. We reviewed 37 cases of Salmonella infection found in 31 patients with SLE to propose potential risk factors of mortality in these patients.

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MATERIALS AND METHODS

Thirty-seven cases of Salmonella infection in 31 patients with SLE were reviewed from a total of 1191 hospitalized SLE patients at Chang Gung Children's and Memorial Hospital between 1995 and 1999. All fulfilled the 1982 American Rheumatism Association revised classification criteria for SLE. Eight patients died while infected with Salmonella, and they provide cases for comparison with those who recovered. We compared the clinical and laboratory characteristics of SLE at the time of Salmonella infection, with special attention to potential predisposing factors — i.e., sex, age, complete blood count and differential count (CBC/DC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complements, Salmonella species, infection site, reinfection, SLE presenting with Salmonella infection, associated non-Salmonella infection, etc.

We used the nonparametric Mann-Whitney U test, chi-square test, or Fisher's exact test to analyze the relationships between various risk factors and mortality, when appropriate. The standard deviation was calculated for every mean. Logistic regression was calculated for multivariate analysis to identify variables that related to death. A factor of $p \leq 0.05$ was considered to be statistically significant.

RESULTS

There were 31 patients, aged between 13 and 58 years, among whom 23 were adults and 8 were children. All the pediatric patients were female. The age distribution in the group that died was 19–58 years (mean 37.3 ± 14.1 yrs) and in the group who recovered it was 13–43 years (mean 24.5 ± 9.6 yrs). The mean age at onset of SLE in the 8 mortality cases was significantly higher than the 23 cases of survivors ($p < 0.05$). The sex ratio revealed a female predominance in both groups. The mortality rate for male patients was 50% compared to a rate of 30% for female patients ($p = 0.250$). The interval between the diagnosis of SLE and Salmonella infection was 22.9 months (SD 41.3 mo) in the group that died, and 40.9 months (SD 49.0 mo) in the group that survived. The mortality rate in adult patients (53%) was higher than pediatric patients, but the difference was not significant ($p = 0.076$). The time interval between the age of the onset of SLE and the first Salmonella infection ranged from 0 to 16 years (mean 36.2 ± 41.7 mo). No difference was noted in the time interval between the 2 groups (Table 1).

The results of laboratory examinations were not distinctive and from the laboratory studies we were unable to find any predisposing factors for mortality (Table 2). Although leukopenia was more common in the group of patients who died, no significant difference was found compared with the group who survived. The levels of blood urea nitrogen and creatinine were both higher than normal in most of the 31 patients. Nearly half the patients had proteinuria or hematuria, but again there was no significant difference between the 2 groups. Despite the stress of acute infection, C3 complement levels were depressed in 5 (62.5%) of the patients who died and 13 (61.9%) of the remaining patients (Table 2).

In both groups, all SLE patients received steroid treatments for lupus activity except those cases in whom Salmonella infection was detected at the first SLE presentation, 3 among those who died and one among survivors. Three in the group who died and 9 among the survivors had received either cyclophosphamide or azathioprine. There was no significant difference between the 2 groups concerning the cumulative dose or mean daily dose of prednisolone prescribed prior to Salmonella infection (Table 1), and we found no difference regarding the use of the cytotoxic drugs.

Table 1. Demographic features and steroid use of the 31 patients. Data are mean ± SD unless stated otherwise.

	Total, n = 31	Patients that Died, n = 8	Survivors, n = 23	p
Sex, M:F	4:27	2:6	2:21	0.250
Age ≥ 18 yrs, %	74.2	100	65.2	0.076
Onset age of SLE, yrs	27.8 (12.1)	37.3 (14.1)	24.5 (9.6)	0.033
Age of first Salmonella infection, yrs	30.8 (12.2)	39.5 (13.6)	27.8 (10.3)	0.033
Interval between SLE onset and Salmonella infection, mean (SD) mo	36.2 (41.7)	22.9 (41.3)	40.9 (49.0)	0.091
Steroid dose*				
Total, g	19.0 (26.2)	15.8 (21.5)	21.0 (27.9)	0.411
Daily, mg	20.5 (14.9)	20.4 (19.9)	20.5 (13.3)	0.912

* Cumulative dose of prednisolone prior to Salmonella infection.

Table 2. Laboratory evaluation of the 31 patients.

	Total, n = 31	Patients that Died, n = 8	Survivors, n = 23	p
Leukopenia, %	22.6	25.0	21.7	1.000
Lymphopenia, %	74.2	62.5	78.3	1.000
Anemia, %	87.1	87.5	87.0	1.000
Thrombocytopenia, %	19.4	12.5	23.8	0.519
Hypoalbuminemia, %	35.5	57.4	35.0	0.391
ESR, mm/h, mean (SD)	78.6 (49.9)	87.4 (45.26)	75.0 (53.1)	0.646
CRP, mg/l, mean (SD)	101.8 (100.6)	148.9 (117.7)	88.4 (95.7)	0.327
Low C3, mg/dl, %	58.1	62.5	61.9	1.000
Low C4, mg/dl, %	8.4	62.5	47.6	0.682
Azotemia, %	25.8	50.0	17.7	0.100
Proteinuria, %	41.9	43.4	37.5	0.808
Hematuria, %	48.4	52.2	37.5	0.550
ANA+, %	77.4	100	70	0.706
Anti-dsDNA, mg/dl, mean (SD)	458.4 (633.0)	692.9 (911.8)	359.6 (470.0)	0.218

Leukopenia: count < $4 \times 10^3/\mu l$; lymphopenia: count < $1.5 \times 10^3/\mu l$; anemia: < 12.5 g/dl; thrombocytopenia: < $100 \times 10^3/\mu l$; hypoalbuminemia: < 2.5 g/dl. Low C4: < 17.3 mg/dl; low C3: < 77.4 mg/dl; azotemia: creatinine > 1.4 mg/dl; proteinuria: ≥ 3+ (300 mg/dl); hematuria: > 5 red blood cells/high power field; ANA+: titer ≥ 1:160.

Antibiotics were started empirically with intravenous first generation cephalosporin and aminoglycoside drugs when the patients were suspected to have infection. Based on the results of susceptibility tests *in vitro*, we switched the antibiotics to the most appropriate antibiotherapy with one of the following antibiotics for 2 to 3 weeks: ampicillin (2 cases), ceftizoxime (17 cases), ceftriaxone (11 cases), or ceftazidime (one case). No significant difference was found concerning the type or duration of antibiotic regimen between the deceased group and survivors. These patients had various clinical manifestations, including fever and chills (83.8%), abdominal pain (29.0%), diarrhea (29.0%), pulmonary signs (including cough, sputum or dyspnea, 35.5%), arthritis (32.3%), and urinary signs (including dysuria, frequency or urgency, 19.4%). There was no significant difference between these 2 groups (Table 3).

In the group that died, the coexisting underlying systemic diseases included chronic viral hepatitis, pulmonary tuberculosis infection, diabetes mellitus, splenectomy, and chronic renal failure (all on case each). Hypertension (3 cases), hyperthyroidism (2), chronic obstructive lung disease (one case), asthma (one case), splenectomy (one case), viral hepatitis (2), chronic renal failure (3), and transverse myelitis (one case) were observed in the other group.

All the diagnoses of Salmonella infection were based on the isolation of the organisms from blood (24 cases), feces (4), urine (3), synovial fluid (3), ascites (one case), and abscess (one case) (Table 4).

Table 3. Clinical manifestations and characteristics of SLE patients with Salmonella infection.

Clinical Symptom/Sign	Patients that Died, n (%)	Survivors, n (%)	p
Fever and chill	5 (62.5)	21 (91.3)	0.093
Abdominal pain	3 (37.5)	6 (26.1)	0.660
Diarrhea	5 (62.5)	4 (17.4)	0.540
Arthritis	2 (25.0)	8 (34.8)	1.000
Respiratory signs*	5 (62.5)	6 (26.1)	0.095
Urinary signs**	2 (25.0)	4 (17.4)	0.643
Associated infection***	6 (75.0)	7 (30.4)	0.043
SLE presenting as Salmonella infection†	3 (37.5)	1 (4.3)	0.043
Recurrence††	4 (50.0)	1 (4.3)	0.010

* Cough with/without sputum, chest pain, or dypsnea. ** Frequency, dysuria, or urgency. *** Concurrent diagnosis of non-Salmonella infection and Salmonella infections. † Salmonella infection occurring concurrently with first presentation of SLE. †† Reinfection of Salmonella species.

Table 4. Sites of isolation of Salmonella species.

Infection Site	Patients that Died, n (%)	Survivors, n (%)	p
Blood	6 (75.0)	18 (78.3)	0.656
Synovial fluid	1 (12.5)	2 (8.7)	1.000
Stool	1 (12.5)	3 (13.0)	1.000
Urine	0 (0.0)	3 (13.0)	0.550
Abscess	1 (12.5)	0 (0.0)	0.258
Ascities	1 (12.5)	0 (0.0)	0.258

A total of 98 gram negative bacteremias were recorded from a group of 1191 inpatients with SLE. The incidence of Salmonella infection in gram negative bacteremias was 32%. Among the group who survived, the most common serotype was group B (22 cases); other serotypes included C1 (3 cases) and D1 (6 cases). Twenty-five percent of the group of patients who died had group D1 serotype compared to 17.4% of surviving group patients (Table 5). Of the 8 patients who died, 4 (50%) had more than one recurrent Salmonella infection, while there was only one (4.3%) in the other group. The difference between these 2 groups was statistically significant ($p < 0.05$) (Table 3).

Three (37.5%) patients in the group that died and one (4.3%) survivor were diagnosed as Salmonella infection with the initial presentation of SLE. It showed a statistically significant difference ($p < 0.05$) (Table 3).

Six patients from the group that died and 7 survivors had associated non-Salmonella infections concomitantly. Urinary tract infections with *Escherichia coli* were found in 2 patients in the group that died and 2 survivors. One patient from each group had herpes zoster. In the mortality group, there were cytomegalovirus viremia (one case), Pseudomonas pneumonia (one case) and Micrococcus bacteremia (one case). Cellulitis (one case), *Staphylococcus aureus* bacteremia (one case), E. coli urinary tract infection (one case), and Listeria meningitis (one case) were diagnosed in the group who survived. Comparing the 2 groups, there were more non-Salmonella associated infections among the group that died than the survivors ($p < 0.05$) (Table 3).

Table 5. Serotypes of Samonella species.

Serotype	Patients that Died, n (%)	Survivors, n (%)	p
B	6 (75.0)	16 (69.6)	1.000
C1	0 (0.0)	3 (13.0)	0.550
D1	2 (25.0)	4 (17.4)	0.643

To detect which factors had a significant influence on mortality, multivariables were entered into a logistic regression analysis using SPSS 8.0 for Windows. We found that recurrent Salmonella infection in patients with SLE showed a higher risk of mortality (relative risk 84, CI 4.3–1638.8). Patients diagnosed with Salmonella infection upon first presentation of SLE concurrently also had a greater risk for death (relative risk 63, CI 3.1–1296.5) (Table 6).

DISCUSSION

Infection has been known as a major factor in morbidity in patients with SLE[10,11]. A multicenter study of the outcomes of SLE showed that 33% of patients died from infection[12]. Hellmann, *et al* stated that infections were present in 55% and these were judged to be a cause of death in 30% of all cases of death; opportunistic organisms are common causes of death in SLE[13]. Salmonella is among the most common opportunistic bacterial infections seen in fatal SLE. Among studies evaluating Salmonella infections in SLE, Pablos, *et al* found that death in patients with Salmonellosis and SLE was significantly associated with renal failure[9]. Despite the effect of infection on the survival of patients with SLE, there are few reports that discuss their relationship to each other.

We reviewed 31 SLE patients with 37 cases of Salmonella infections among 1191 SLE patients hospitalized at a medical center in Taiwan between 1995 and 1999. Salmonella infections were the most frequent gram negative species of infection among the patients, accounting for 31.6% of all gram negative bacteremias. The occurrence of Salmonella bacteremia in lupus patients who had bacteremia was 17.3% in our cases, similar to a previous report[8].

Table 6. Risk factors of mortality for SLE patients with Salmonella infection (n = 31) by logistic regression analysis.

Variable	Relative Risk (CI)	p
Recurrent Salmonella infection	84.0 (4.3–1638.8)	0.0035
SLE presenting as Salmonella infection	63.0 (3.1–1296.5)	0.0073

Adult patients, who account for 74.2% of our patients, had a high mortality rate. With regard to duration of disease, we found no significant influence on occurrence or mortality of Salmonella infection. The mean age of onset of SLE in the group that died was significantly higher than in the group that survived. If we compared the age of Salmonella infection in SLE cases among those who died to survivors, it also showed a statistically significant difference.

The coexisting underlying systemic diseases in these 2 groups of patients were also evaluated. Most of these diseases appeared to be concomitant with rather than specifically associated with Salmonella infections. They seemed to have no influence on the incidence of death.

Uremia has been proposed as a risk factor for Salmonella infections in SLE[8,14-16]. It was reported to be one of the most frequent primary causes of death in lupus[12]. Ginzler and Berg reported that the survival rate of patient subsets with normal serum creatinine (Cr < 1.3 mg/dl) was significantly better than that of patients with mild azotemia (Cr 1.3–3.0 mg/dl) and severe azotemia (Cr > 3.0 mg/dl)[2]. The mean blood urea nitrogen and creatinine levels were higher than normal in our study, perhaps caused by 4 cases with renal failure in each group. Both hematuria and proteinuria were recorded in 37.5% of the deceased patients, compared to 52.2% with hematuria and 43.4% with proteinuria among survivors. There was no significant effect of renal involvement in the group that died, in contrast to the results of Pablos, *et al*[9]. In addition to azotemia, we found no significant influence on mortality risk concerning levels of complements, ESR, CRP, CBC/DC, albumin, or renal failure.

A multicenter study reported deaths caused by SLE were significantly associated with the maximum steroid dose received, but not with use of other cytotoxic therapy[12]. All patients we analyzed, except for cases presenting with Salmonella infections, had been taking steroids, and 12 patients had additional cytotoxic drugs. Neither cumulative doses nor the mean daily dose of steroid that patients received affected the occurrence of mortality in our cases. The duration of use of steroid was also not statistically different between these 2 groups.

Clinical diagnosis of Salmonella infection may be delayed because SLE and Salmonellosis share a wide range of clinical manifestations including fever, rash, pleurisy, abdominal pain, and synovitis. From our data it is uncertain whether infections induce SLE flares or mimic the clinical manifestations of SLE. Patients within our 2 groups showed no significant differences regarding these manifestations. Nevertheless, a high index of suspicion should still be taken in patients with SLE when the symptoms and signs described above are observed.

All cases were diagnosed by isolation of organisms, not by serology. As in previous reports, Salmonella isolated from our patients had a high prevalence of group B species (71%)[1,15,17]. In the beginning patients were treated with intravenous first generation cephalosporin and aminoglycoside when they were suspected to have bacterial infection. A higher resistance rate to ampicillin was noted in 27 cases (87%), 7 in the group that died and 20 in the survivors. We switched the antibiotics soon after to the most appropriate antibiotherapy for 2 to 3 weeks according to *in vitro* susceptibility. There was no significant difference regarding duration and type of antibiotic therapy between the 2 groups.

Since SLE has a propensity for Salmonella infection, it is not surprising that concurrent infection with non-Salmonella species was observed. The conditions predispose patients to different bacterial, fungal, and viral infections. The incidence of associated infections in the group that died (75%) was significantly higher than in the group that survived (30.4%). The presence of a second concurrent infection may have reflected their generalized debilitated status, a change in bacterial flora secondary to antibiotics, underlying defects leading to impaired resistance, or an underlying immune system defect. These may partly explain why concurrent infection with non-Salmonella pathogens increases mortality in SLE.

Most reports of Salmonella infection in SLE described patients who developed infection after the diagnosis of SLE. Salmonella infection that occurred concurrently with the first presentation of SLE is rare[7,18]. We found that 3 (37.5%) cases in the group that died and one (4.3%) survivor were the cases with co-occurrence of Salmonella infection with the first SLE presentation. The difference between the 2 groups was statistically significant. This finding supports the hypothesis that immunological malfunction seen in SLE predisposes patients to infection and makes death more likely. Thus early detection and aggressive treatment for concurrent SLE and Salmonellosis should be initiated immediately in any cases where they are suspected.

Defective immune functions may play a part in the high recurrence rate of infection (29%) despite the standard antibiotic therapy[1,19]. It may similarly account for the high mortality rate in patients with SLE. Comparing patients with and without recurrence of infections, we found there were significantly higher rates of recurrence among the group that died.

We know that the limited data and the small number of cases, 8 patients in one group and 23 in the other, will affect the statistical relevance of this study, but the impressive result still reveals a trend. For SLE patients with Salmonella infection with the risk factors described, if earlier intervention and treatment is provided there is lower likely incidence of death.

According to our study, when Salmonella infection in SLE or the onset of SLE is diagnosed, the older the patient the higher the mortality rate. If there is an associated non-Salmonella species infection the patient is also prone to death. It seems that patients with SLE presenting with Salmonella infection or with reinfection of Salmonella species have greater risk of mortality. As advances are made in early detection and treatment of SLE, more studies concerning the risk factors of mortality will be needed.

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