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ORIGINAL ARTICLE

Nontyphoidal *Salmonella* bacteremia in patients with connective tissue diseases

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Background/Purpose: Nontyphoidal *Salmonella* (NTS) is a crucial pathogen in immunocompromised patients, especially those with connective tissue disease (CTD) and corticosteroid or immunosuppressant therapy. The aim of this study is to identify the clinical characteristics and outcomes of patients with CTD and NTS bacteremia, and the clinical variations between systemic lupus erythematosus (SLE) and other CTDs.
Methods: During a 15-year study period, from 1994 to 2009, NTS bacteremia patients were reviewed from the database of clinical microbiology laboratory. Medical records were reviewed for clinical information and only patients with underlying CTD were included.
Results: From 1994 to 2009, there were 299 patients with NTS bacteremia. Forty-six (15.4%) patients had certain connective tissue diseases, and SLE was the major CTD, accounting for 73.9% (34) of 46 patients. In comparison with patients without CTD, the patients with CTD were younger ($p < 0.0001$), had a predominance of female gender ($p < 0.0001$), fewer extra-intestinal focal infections ($p = 0.011$), and a lower mortality rate ($p = 0.008$). Overall, there were four fatal cases, accounting for a mortality rate of 8.7% of those afflicted with CTD. The factors of old age ($p < 0.006$), shock at presentation ($p = 0.033$), acute renal failure ($p = 0.001$), and presence of any extra-intestinal focal infection ($p < 0.0001$) were associated with mortality in the univariate analysis.

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Conclusion: Nontyphoidal *Salmonella* bacteremia causes substantial morbidity and mortality in patients with connective tissue disease, especially in the elderly population. The aggressive detection of extra-intestinal infections may be beneficial.

Introduction

Systemic lupus erythematosus (SLE), scleroderma, polymyositis, dermatomyositis, rheumatoid arthritis, and Sjogren's syndrome are a few of the common disease entities of connective tissue diseases (CTDs).[1,2] Steroid and immunosuppressive drugs are effective medications for these diseases. Infection-related morbidity and mortality is a critical issue for patients because of disease-related immune dysregulation and an immunosuppressive treatment regimen.[3] Nontyphoidal *Salmonella* (NTS) is one of the major food-borne pathogens in the world, and may cause severe and widespread infections, especially in immunocompromised patients.[4] Infectious diseases may cause substantial mortality and morbidity in SLE patients.[2] SLE is regarded as the most common underlying disease in patients with *Salmonlla* bacteremia.[2,5] Self-limited gastroenteritis and bacteremia, with or without extra-intestinal focal infections (EFIs), are common clinical presentations of nontyphoidal salmonellosis. Extra-intestinal focal infections include infected aortitis, meningitis, pneumonia, soft-tissue infection, and pyomyositis.[6] However, NTS infections in patients with CTD were rarely reported. Therefore, we studied the clinical characteristics and clinical outcomes of the specific patient population.

Materials and methods

A retrospective study was conducted at a medical center in southern Taiwan. We recruited patients with NTS bacteremia, of which the onset was between 1994 and 2009. Only the first occurrence of NTS bacteremia from each patient was included. The patients with the underlying disease of CTD were specifically concerned as the study population. A number of patients with a broad sense of chronic inflammatory diseases in an immunosuppressed status, not traditional CTD but receiving chronic steroid therapy, were also recruited. The clinical characteristics of patients with CTD and those without CTD were compared. The patients with SLE and those with a CTD other than SLE were compared. Medical records were reviewed for demographic data, underlying diseases, clinical manifestations, laboratory data at admission, microbiological characters, antimicrobial susceptibility, treatment course, and clinical outcomes.

Microbiology and antimicrobial susceptibility

The slide agglutination test was used to determine the serogroups of *Salmonella* isolates by O antisera (Difco Laboratories, Detroit, MI, USA). For serogroup C or D isolates, the identification of *Salmonella typhi* or *Salmonella paratyphi* was screened by Vi antisera (BBL, Cockeysville, MD, USA). For the serogroup C1 isolates, if the citrate test was negative, such an isolate was reported as *Salmonella choleraesuis*. The interpretations of antimicrobial susceptibility were based on the criteria of Clinical and Laboratory Standards Institute.[7]

Definitions

Fever was defined as the axillary temperature of $\geq$ 38°C. Shock was defined by a systolic blood pressure of $\leq$ 90 mmHg or the use of an inotropic agent to maintain blood pressure. Leukocytosis was defined as a leukocyte count of $>$ 10,000 cells/mm^3, and leucopenia $<$ 3000 cells/mm^3. Chronic renal disease was defined as a serum creatinine level of $\geq$ 1.5 mg/dL. Immunosuppressive therapy was defined as the receipt of prednisolone at a daily dose of more than 10 mg, a corticosteroid at the equivalent dosage for at least 2 weeks, chemotherapy for malignancy, or an immunosuppressive agent. Antimicrobial therapy was regarded as appropriate if the pathogen was *in vitro* susceptible to the agent prescribed within 72 hours after admission. Extra-intestinal focal infection (EFI) of salmonellosis was referred to active infection lesions, evidenced by clinical symptoms and signs, or radiological imaging, such as computed tomography or ultrasonography.

Statistical analysis

The Statistical Package for the Social Science for Windows (SPSSWIN; SPSS, Chicago, IL, USA), version 15.0, was used to conduct the data analysis. Categorical variables were illustrated as numbers and percentages, and compared by the Chi-square test or Fisher's exact test. The continuous variables were expressed as a median, interquartile range, and were compared by the Student *t* test or the Wilcoxon rank sum test.

Results

Clinical information

During the study period of 1994 to 2009, a total of 299 patients with NTS bacteremia were found, including 46 patients with CTD, and 253 patients without CTD. The clinical characteristics of 46 adults (≥ 18 years old) with CTD and NTS bacteremia are shown in Table 1. Female gender was predominant in patients with CTD, and the mean age of patients with CTD was younger than those without CTD. The serogroups of 46 NTS isolates from adults

Table 1 Clinical characteristics of patients with or without connective tissue disease complicated by nontyphoidal *Salmonella* bacteremia

Clinical characteristics	Case number (%)				p values[e]
	CTD ($n = 46$)			NonCTD ($n = 253$)	
	SLE[c] ($n = 34$)	Others[d] ($n = 12$)	Total ($n = 46$)		
Female gender	25 (73.5)	9 (75.0)	34 (73.9)	88 (34.8)	<0.0001
Age (y) (median, interquartile range)	35(27-43)	58(49-66)	38 (28-53)	65 (51-73)	<0.0001
Underlying disease					
Atherosclerotic conditions					
Diabetes mellitus	11 (32.4)	4 (33.3)	15 (32.6)	75 (29.6)	0.068
Hypertension	6 (17.7)	4 (33.3)	10 (21.7)	83 (32.8)	0.136
Coronary artery disease	1 (2.9)	0 (0)	1 (2.2)	30 (11.9)	0.062
Stroke	1 (2.9)	0 (0)	1 (2.2)	18 (7.1)	0.327
Chronic renal disease	8 (23.5)	4 (33.3)	12 (26.1)	78 (30.8)	0.519
Liver cirrhosis	0 (0)	1 (8.3)	1 (2.2)	36 (14.2)	0.022
Malignancy	0 (0)	1 (8.3)	1 (2.2)	98 (38.7)	<0.0001
HIV infection[a]	0 (0)	0 (0)	0/43 (0)	18/229 (7.9)	0.087
Serogroups					0.611
B	18 (52.9)	5 (41.7)	23 (50)	115 (45.5)	
C1/C2	9 (26.5)/1 (2.9)	2 (16.7)/1 (8.3)	11 (23.9)/2 (4.3)	66 (26.0)/6 (2.4)	
D	6 (17.6)	4 (33.3)	10 (21.7)	61 (24.1)	
E	0 (0)	0 (0)	0 (0)	3 (1.2)	
Clinical symptoms and signs					
Fever	29 (85.2)	10 (83.3)	39 (84.8	185 (73.1)	0.09
Gastrointestinal symptoms	5 (14.7)	2 (16.7)	7 (15.2)	53 (20.9)	0.372
Shock	2 (5.9)	2 (16.7)	4 (8.7)	72 (28.5)	0.005
Acute renal failure	5 (14.7)	4 (33.3)	9 (19.6)	80 (31.5)	0.091
Leukopenia	8 (23.5)	3 (25.0)	11 (23.9)	158 (62.5)	0.032
Leukocytosis	5 (14.7)	6 (50.0)	11 (23.9)	126 (49.8)	0.001
Immunosuppression	31 (96.9)	9 (75.0)	40 (86.9)	58 (22.9)	<0.0001
Appropriate treatment[b]	19 (55.9)	10 (83)	29 (63.0)	165 (65.2)	0.698
Extra-intestinal focal infections	4 (11.8)	3 (25.0)	7 (15.2)	86 (34.0)	0.011
Mortality	1 (2.9)	3 (25.0)	4 (8.7)	68 (26.9)	0.008

CTD = connective tissue disease; HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus.
[a] Only 272 patients were tested for human immunodeficiency virus infection.
[b] Refer to an *in vitro* active drug prescribed within 72 hours.
[c] Systemic lupus erythematosus.
[d] Others mean other CTD, including polymyositis/dermatomyositis (4), rheumatoid arthritis (3), bullous pemphigoid (1), amyotrophic lateral sclerosis (1), psoriasis (1), erythroderma (1), and Sjögren's syndrome (1).
[e] Comparisons between those with or without CTDs.

with CTD were group B (22 isolates, 47.8%), C1 (11, 23.9%), group D (10, 21.7%), and group C (2, 28.3%). All serogroup C1 isolates were *S. choleraesuis*.

Comparisons of patients with and without CTD, complicated by NTS bacteremia

Patients with CTD were younger and had fewer metastatic infections than those without CTD (Table 1). The patients without CTD commonly had liver cirrhosis (14.2% vs. 2.2%, $p = 0.022$), malignancy (38.7% vs. 2.2%, $p < 0.0001$), shock at presentation (28.5% vs. 8.7%, $p = 0.005$), and EFI (34% vs. 15.2%, $p = 0.011$). The patients with CTD complicated by NTS bacteremia had a superior prognosis (mortality rate: 8.7% vs. 26.9%, $p = 0.008$).

To explore the potential impact of underlying CTD, immunocompetent adults without chronic underlying illness and those with only CTD as the underlying illness were compared in Table 2. The factors of older age (57.9 vs. 35.8 years; $p < 0.0001$), more EFI (56.5% vs. 5.6%; $p = 0.001$), and a higher mortality rate (13% vs. 0%, $p = 0.24$), were noted in the immunocompetent patients with NTS bacteremia.

SLE and other CTD patients

The most common disease among the 46 patients with CTD was SLE (34 patients) (Table 1). As the distinguishing feature among patients with CTD, females predominated in patients with SLE and those with other CTD. However, SLE patients were younger than those with other CTD (36.6 vs. 55.3 years). No significant difference was observed in the clinical presentations of NTS bacteremia and concurrent underlying disease, or the development of EFI in both groups. However, the survival rate of SLE patients with NTS

Table 2 Comparisons of the patients with connective tissue disease only and immunocompetent patients complicated by nontyphoidal *Salmonella* bacteremia

Clinical characteristics	Case number (%)[a]		*p* values
	NonCTD ($n = 23$)	CTD[b] ($n = 18$)	
Female gender	6 (26.1)	11 (61.1)	0.02
Age (y) (median, interquartile range)	63 (48—72)	32.5 (27.5—41.0)	<0.0001
Clinical symptoms and signs			
Fever	22 (95.6)	14 (77.8)	0.15
Gastrointestinal symptoms	6 (26.1)	3 (16.7)	0.71
Shock	4 (17.4)	1 (5.6)	0.36
Acute renal failure	4 (17.4)	3 (16.7)	1.00
Leukopenia	2 (8.7)	3 (16.7)	0.64
Leukocytosis	13 (56.5)	3 (16.7)	0.009
Immunosuppression	2 (8.7)	17 (94.4)	<0.0001
Extra-intestinal focal infection	13 (56.5)	1 (5.6)	0.001
Primary bacteremia	10 (43.5)	17 (94.4)	0.001
Appropriate treatment	16 (69.6)	12 (66.7)	0.84
Mortality	3 (13.0)	0 (0)	0.24

CTD = connective tissue disease.
[a] Only patients tested for human immunodeficiency virus infection were included.
[b] CTD included systemic lupus erythematosus (15) and dermatomyositis (3).

bacteremia was 97.1% (33/34), while that of patients with other CTD was 75% (9/12).

Fatal cases of CTD and NTS bacteremia

Four fatal cases occurred during our study (Table 3). The mean age was 61.8 years (range 43—76 years). Three of the four patients received immunosuppressant therapy. All patients had another underlying disease, and EFI, such as pneumonia (one case) or skeletal soft-tissue infections (three cases), and received appropriate antibiotics within 72 hours. However, three patients presenting with acute renal failure, shock and thrombocytopenia died within 5 days after the onset of NTS bacteremia.

Table 3 Clinical summary of four adult deaths with connective tissue disease complicated with nontyphoidal *Salmonella* bacteremia

Case no.	1	2	3	4
Connective tissue disease	Systemic lupus erythematosus	Bullous pemphigoid	Dermatomyositis	Rheumatoid arthritis
Age (y)	43	76	63	65
Gender	Female	Female	Female	Female
Infection site	Pneumonia	Left forearm cellulites and subscutaneous abscess	Right thigh necrotizing fasciitis and pyomyositis	Psoas pyomyositis
Salmonella serogroup	B	D	B	B
Comorbidity	Diabetes mellitus	Liver cirrhosis	Diabetes mellitus, chronic pulmonary disease, chronic kidney disease	Diabetes mellitus, chronic kidney disease
Immunosuppression[a]	Yes	No	Yes	Yes
Clinical symptoms and signs				
Fever	Yes	No	Yes	No
Shock	No	No	Yes	Yes
Acute renal failure	Yes	Yes	Yes	Yes
Thrombocytopenia	No	No	Yes	Yes
Leukocytosis	Yes	No	No	Yes
Hospitalization before death (d)	30	5	2	3
Appropriate antibiotic within 72 h	Yes	Yes	Yes	Yes
Surgical intervention	—	No	No	No

[a] Receipt of prednisolone daily dose more than 10 mg or corticosteroid at the equivalent dosage for at least 2 wk, chemotherapy for malignancy, or immunosuppressive agent.

Discussion

Nontyphoidal salmonellosis is a food-borne infection that occurs in patients throughout the world, especially in immunocompromised patients. The common risk factors of salmonellosis include old age, malignancy, diabetes, rheumatological disorders and immunosuppressive therapy.[3,8,9] Among our patients without CTD, the elderly, and adults with underlying liver cirrhosis or malignancy, are the susceptible population for NTS bacteremia. A characteristic higher mortality rate and more extra-intestinal focal infections in patients without CTD may be, at least partially, related to the presence of underlying medical illness.

The common underlying disease in the patients presenting with *Salmonella* bacteremia is SLE.[10] As young age is the specific character of patients with SLE, we observed a higher incidence of shock, acute renal failure, and extra-intestinal infections in patients with other CTD. The patients with SLE are less likely to receive appropriate antimicrobial therapy within the initial 72 hours as the initial presentations of NTS bacteremia are easily overlapped by the flare-up of the disease activity of SLE, such as lupus fever, leucopenia or thrombocytopenia. The mortality rate of patients with other CTD is higher than those with SLE, even though 83% of these patients received an appropriate antimicrobial agent within 72 hours. It is assumed that the host factor, most likely age, plays an important role in the clinical outcome of adults with CTD complicated with NTS bacteremia.

Graciela et al (2006) reported that the common species in SLE patients with *Salmonella* bacteremia were *S. choleraesuis, Salmonella enteritidis, Salmonella typhimurium* and *Salmonella arizona*.[2] The groups B, D and C were the three major serogroups among the serogroup distribution of NTS obtained from SLE patients in Taiwan.[10] In our study, the most common NTS bacteremic isolates are the serogroups B, C and D, regardless of the patient subgroups, without CTD, with SLE, or with other CTD. This serogroup distribution reflects the frequent exposure to certain serogroups in the community or the variable invasiveness of these serogroups. Further serovar or serotype determination of these bacteremic isolates may be useful in the delineation of the cause of the predominance of serogroup B.

In a systemic review of infection-related mortality in patients with CTD, the overall median mortality rate was 20% with a range of 2.1—79%. In major types of CTD, the mortality rates were similar, 4.7% in SLE, 6.5% in rheumatoid arthritis and 5% in polymyositis or dermatomyositis.[11] In our study, the crude mortality rate was 8.7% in patients with CTD, 2.9% in SLE, and 25% in other CTD. However, the limited case number and heterogeneous population in the types of CTD between different studies make the comparisons of clinical outcomes difficult.

Severe soft-tissue infections with abscess formation or necrotizing fasciitis may cause high mortality, especially in immunocompromised patients.[12] Two studies reported that necrotizing fasciitis caused a mortality rate of 20—50% in patients with underlying SLE or rheumatic diseases.[13,14] The causative pathogens of necrotizing fasciitis among patients with underlying rheumatic diseases are *Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas fluorescens, Morganella morganii, Aeromonas caviae* and *Escherichia coli*.[14] Few severe soft-tissue infections, caused by NTS species, were reported in patients with CTD. In our study, three of the four fatal cases with CTDs complicated with NTS bacteremia had soft-tissue infections, including psoas muscle abscess, necrotizing fasciitis, and cellulitis with abscess formation. Therefore, physicians should consider NTS as one of the causative pathogens of invasive soft-tissue infections in patients with CTD.

There are a number of limitations in our study. The case number of patients with CTD is small, and not all patients fulfilled the traditional criteria of CTD. However, the vast majority of our case patients had SLE, polymyositis/dermatomyositis, rheumatoid arthritis or Sjögren's syndrome, accounting for 91.3% (42/46) of those categorized as having CTD. A number of patients were not tested for HIV infection, and it is likely that the impact of underlying HIV infection was underestimated, especially those grouped as being immunocompetent.

In summary, nontyphoidal *Salmonella* bacteremia causes substantial morbidity and mortality in patients with connective tissue disease, especially in the elderly population. The aggressive detection of extra-intestinal infections may be beneficial, and soft-tissue infections may be associated with in a grave prognosis.

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