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Original Article

Non-typhoidal *Salmonella* bacteremia in adults

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Background and Purpose: Very few studies have examined prognostic factors in adult patients with non-typhoidal *Salmonella* (NTS) bacteremia. The purpose of this study was to identify the prognostic factors of these patients.
Methods: A total of 79 episodes of NTS bacteremia were identified in 73 patients between January 2001 and December 2003. Susceptibilities to various antimicrobials were determined using disk-diffusion tests and National Committee for Clinical Laboratory Standards criteria. Multiple logistic regression was used to evaluate the relationship between patients' characteristics and covariates of mortality.
Results: There were only 5 episodes (6%) of gastroenteritis, two of which were due to *Salmonella* septicemia contracted abroad. Potentially predisposing factors were identifiable in 51 episodes (65%). Infections in 24 patients (30%) were due to serogroup B *Salmonella* and in 22 patients (28%), to serogroup C *Salmonella*. A logistic regression analysis selected two variables as independently influencing prognosis: coma (p=0.006) and septic shock (p=0.002).
Conclusions: Thus, most adult patients with NTS bacteremia do not develop gastroenteritis. Patients in shock or coma have poor prognosis, and susceptibility to third-generation cephalosporins, cefepime, and carbapenem is high.

Key words: Bacteremia; Risk factors; *Salmonella* infections; Serotyping

Introduction

The incidence of human infections due to non-typhoidal *Salmonella* (NTS) in industrialized countries has increased at an alarming rate in recent decades [1,2]. Many foods have been implicated as vehicles of salmonellosis transmission to humans, including eggs, beef, pork, poultry, milk, fish, shellfish, fresh vegetables and fruits [3,4]. Although most patients with NTS infection have self-limited gastroenteritis, invasive disease with bacteremia is seen in only 3-8% of patients [5]. Among the most susceptible are renal transplant recipients [6] and patients with acquired immunodeficiency syndrome (AIDS) [7], systemic lupus erythematosus (SLE) [8], malignant diseases [9] or diabetes mellitus [10]. Antibiotics are very important for the treatment of invasive disease or complicated bacteremia. The gradual increase in the prevalence of multidrug-resistant NTS in adult patients with septicemia in the last decade has complicated the choice of invasive salmonellosis treatment [11].

In this study, clinical and microbiological data collected at a medical center in Taiwan from January 2001 to December 2003 were analyzed to identify prognostic factors in patients with NTS bacteremia.

Methods

Patients with at least one blood culture positive for NTS were included. From January 2001 to December 2003, a total of 79 episodes occurred in 73 patients. The hospital is a 2900-bed tertiary referral medical center

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and has specialized units for bone marrow and solid organ transplantation, cardiac monitoring, burn care and intensive care. The following data from these patients' medical records were retrieved and reviewed: demographic characteristics, underlying disease(s), clinical presentations, use of immunosuppressive therapy, origin of the disease (community or hospital), bacteriological characteristics, antibiotic susceptibility of isolates, treatment and outcome.

Immunosuppressive therapy included steroids and immunosuppressive agents for organ transplantation. Steroid use was defined as 30 mg of prednisone taken daily (or an equivalent dosage) for at least 1 week or 20 mg of prednisone daily for at least 2 weeks before the positive blood sample was drawn. Patients were considered immunosuppressed when any of the following conditions were present: malignancy, collagen diseases, cirrhosis of liver, organ transplantation, immunosuppressive therapy, or AIDS. A white blood cell count of $<4 \times 10^9$/L was classified as leukopenia.

Acute respiratory failure was defined as hypoxia (partial pressure of oxygen <60 mm Hg) and/or hypercapnia (partial pressure of carbon dioxide >50 mm Hg) in the room air. Acute respiratory failure was considered to be bacteremia-related if no other obvious explanation was found. Shock was considered to be present if the systolic blood pressure was <90 mm Hg and/or if total urine output was <80 mL in 4 h. Shock was considered to be bacteremia-related (septic shock) if no other explanation was apparent. Coma was defined as a decreased level of consciousness together with a lack of motor and/or verbal response at admission, without evidence of meningoencephalitis or primary brain disease. Acute renal failure was defined as serum creatinine increased by 2 mg/dL within a few days to 2 weeks. Acute renal failure was considered to be bacteremia-related if acute renal failure occurred within one week after NTS bacteremia and no other explanation was apparent.

Hospital-acquired bacteremia was defined as fever with a positive blood culture over 72 h after admission. Episodes of NTS bacteremia were considered to be distinct if separated by 2 or more weeks and the *Salmonella* serogroups in each episode were different. Relapse of bacteremia was defined as recurrence of bacteremia with the same organism (same species and susceptibility) after 2 weeks of appropriate antibiotic therapy resulting in complete clinical response. Cure was defined by the disappearance of clinical symptoms and signs as well as the post-treatment negativity of blood cultures. Death was considered due to NTS bacteremia if it occurred during therapy or within 1 week after treatment was stopped, and other causes of death were ruled out by the clinical or pathological data.

Any microbiologically or clinically documented infection was considered an instance of septic metastasis due to *Salmonella* spp. if it developed ≥2 days after the first positive blood sample was drawn. Appropriate antibiotic therapy was defined if: (1) the *Salmonella* was proved to be susceptible in vitro to the antibiotic used for treatment; and (2) this antibiotic had been proved to be effective in vivo in treating salmonellosis.

Blood isolates of *Salmonella* were first identified according to previously described criteria [12] and the serogrouping of *Salmonella* was checked with O antisera using the slide agglutination method. Susceptibilities to various antimicrobials were determined using disk-diffusion tests, and susceptible or resistant isolates were defined according to the criteria suggested by the National Committee for Clinical Laboratory Standards [13]. Isolates in the "intermediate" category were considered to be resistant.

Univariate analysis was used to identify the risk factors associated with the prognosis of salmonellosis. Fisher exact 2-tailed tests were used to examine nominal data. Statistical Package for the Social Sciences (SPSS) for Windows (Version 14.0; SPSS, Chicago, IL, USA) software and Epi Info™ 6.02 (Centers for Disease Control and Prevention, Atlanta, GA, USA) were used for the statistical analysis of the odds ratio and the 95% confidence interval. p Values of ≤0.05 were considered significant.

Multiple logistic regression was used to evaluate the relationship between patient characteristics and covariates of mortality. We built the model using a stepwise selection strategy. Those covariates found to be significant (p<0.05) were included in the final model.

Results

In total, 79 episodes in 73 patients were collected from January 2001 to December 2003. Forty seven patients were males. The mean age was 61 with range of 24 to 93 years (median, 63 years). The distribution of age for these 73 patients and 79 episodes is shown in Fig. 1.

Twenty eight episodes (35%) were nosocomial (Table 1) and the time of infection was 3 to 88 days (median, 12 days) after admission.

The factors predisposing to NTS were identified in 51 episodes (65%; Table 1). The most common

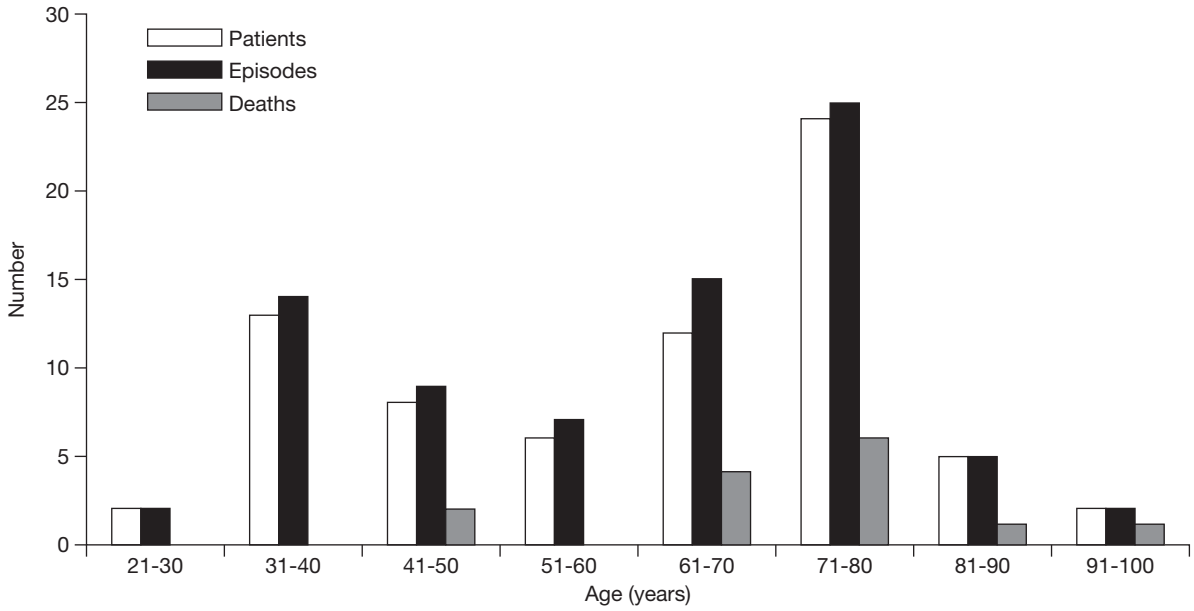

Fig. 1. Age distribution among 73 patients suffering 79 episodes of non-typhoidal *Salmonella* bacteremia.

predisposing factors were solid tumor (20 episodes [25%]) followed by diabetes mellitus (18 episodes [23%]), human immunodeficiency virus/AIDS (10 episodes [13%]), and SLE (6 episodes [8%]).

Fever occurred in 66 episodes (84%) and was accompanied or preceded by symptoms of acute gastroenteritis in 5 episodes (6%). In one of these episodes, fever and gastroenteritis were associated with

Table 1. Characteristics of 79 isolates of non-typhoidal *Salmonella* bacteremia

Characteristics	*Salmonella* group				Total no. (%)
	A	B	C	D	
Isolates	2	24	22	31	79 (100)
Gender (male)	2	14	17	20	53 (67)
Age (years)					
Mean	79	61	62	62	61
Range	73-85	35-80	24-90	27-93	24-93
>65	2	14	8	12	36 (46)
Nosocomial infection	2	8	7	11	28 (35)
Clinical presentations					
Fever	2	20	19	25	66 (84)
Diarrhea	0	1	0	4	5 (6)
Septic metastasis[a]	1	1	3	4	9 (11)
Immunosuppressive therapy	0	7	4	10	21 (27)
Underlying diseases					
Hematological malignancy	0	0	3	1	4 (5)
Solid tumor	1	5	2	12	20 (25)
HIV/AIDS	0	1	4	5	10 (13)
Systemic lupus erythematosus	0	0	2	4	6 (8)
Organ transplantation	0	0	0	1	1 (1)
Diabetes mellitus	2	9	4	3	18 (23)
None	0	10	10	8	28 (35)
Deaths	1	6	2	5	14 (18)
Relapse	0	0	0	1	1 (1)

Abbreviations: HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome

[a]Includes mycotic aneurysm (1), osteomyelitis (2), buttock abscess (2), arthritis (1), epidural abscess (1), meningitis (1), and lung abscess (1).

Table 2. Antimicrobial susceptibilities of 79 isolates of non-typhoidal *Salmonella* bacteremia

Antibiotic	Group A (n = 2) No. (%)	Group B (n = 24) No. (%)	Group C (n = 22) No. (%)	Group D (n = 31) No. (%)	Total (n = 79) No. (%)
Ampicillin	0	9 (38)	5 (23)	31 (100)	45 (57)
Trimethoprim-sulfamethoxazole	1 (50)	20 (83)	7 (32)	26 (84)	55 (70)
Chloramphenicol	0	9 (38)	1 (5)	29 (94)	39 (49)
Ceftriaxone	2 (100)	23 (96)	22 (100)	30 (97)	77 (97)
Cefotaxime	2 (100)	23 (96)	22 (100)	31 (100)	78 (99)
Cefepime	2 (100)	24 (100)	22 (100)	31 (100)	79 (100)
Ciprofloxacin	1 (50)	24 (100)	14 (64)	31 (100)	70 (87)
Imipenem	2 (100)	23 (96)	22 (100)	31 (100)	78 (99)

international travel. One episode occurred during a trip to West Africa and the other shortly after returning from Thailand.

In 9 episodes (11%), patients presented with septic metastases, including mycotic aneurysm (1), osteomyelitis (2), buttock abscess (2), arthritis (1), epidural abscess (1), meningitis (1) and lung abscess (1).

Two isolates (3%) were serogroup A *Salmonella*, 24 (30%) were serogroup B *Salmonella*, 22 (28%) were serogroup C *Salmonella*, and 31 (39%) were serogroup D *Salmonella* (Table 1). In one patient with human immunodeficiency virus infection admitted four times within a 6-month period, blood culture was positive for serogroup C, D, C, and B, respectively. In one healthy patient admitted twice within a 6-month period, blood culture was positive for serogroup D and C, respectively. In two patients each having two episodes within four months, blood culture was positive for serogroup D and C, respectively. The median white blood cell count, platelet count, and C-reactive protein were $8.8 \times 10^3/mm^3$ (range, 1.1-35.8), $162 \times 10^3/mm^3$ (range, 10-466), and 10.2 mg/dL (range, 0.2-37.3), respectively.

Susceptibility (Table 2) to chloramphenicol was shown in 39 isolates (49%), to ampicillin in 45 isolates (57%), to trimethoprim-sulfamethoxazole in 55 isolates (70%), to ciprofloxacin in 70 isolates (87%), to ceftriaxone in 77 isolates (97%), to cefotaxime and imipenem in 78 isolates (99%), and to cefepime in 79 isolates (100%). Thirty two isolates (41%) were susceptible to every antimicrobial agent tested.

1 (1%) relapsed and 14 (18%) died of NTS bacteremia (Table 1). Death in all cases occurred within 30 days after the septicemia. Two deaths occurred within 24 h after the positive blood culture result and a further 6 occurred within 10 days. The remaining 6 patients died between 11 and 25 days and no patient younger than 48 years died.

Table 3 shows the influence of clinical features, epidemiological features, underlying diseases, and laboratory variables on mortality. Age >65 years (p=0.015), shock (p<0.0001), acute respiratory failure (p<0.0001), acute renal failure (p<0.0001), coma (p<0.0001) and inappropriate or lack of antibiotic treatment (p=0.047) were significantly associated with mortality.

When values for all variables were included in a stepwise logistic regression analysis, septic shock (p=0.002) and coma (p=0.006) were identified as independent risk factors for predicting outcome (Table 4).

Discussion

Five episodes (6%) were marked by symptoms of gastroenteritis. In a previously reported study, NTS bacteremia in adult patients had not always presented with the symptoms of gastroenteritis [9]. The rate of septic metastasis of 11% in our series was similar to the rates of 15.7% and 12.5% in earlier reports [7,14]. Musculoskeletal infection was treated with prolonged antibiotic therapy, localized abscess was treated with a combination of antibiotics and surgical drainage, and those with endovascular infection did not receive vessel grafts because of their underlying diseases.

Mycotic aneurysm developed in one patient in this study. The ability of *Salmonella* to invade both undamaged intima and preformed artherosclerotic lesions during *Salmonella* bacteremia has been previously shown [15]. This serious complication of aneurysm formation often occurred in elderly or arteriosclerotic patients and should be kept in mind when salmonellosis is diagnosed in these patients.

Certain patient groups are at increased risk of contracting *Salmonella* bacteremia. These include

Table 3. Univariate analysis of risk factors for case-fatality due to non-typhoidal *Salmonella* bacteremia

Risk factor category	Number of patients dying/total patients (%)	Odds ratio (95% CI)	*p*
Gender			
Male	11/53 (20.8)	2.01 (0.45-10.17)	NS
Female	3/26 (11.5)	1	-
Age (years)			
>65	11/36 (30.6)	5.87 (1.32-29.67)	0.015
≤65	3/43 (7)	1	-
Place of infection			
Nosocomially acquired	7/28 (25)	2.1 (0.56-7.82)	NS
Community acquired	7/51 (13.7)	1	-
Fever			
Yes	11/66 (16.7)	1	-
No	3/13 (23.1)	1.5 (0.27-7.45)	NS
Septic metastases			
Yes	1/9 (11.1)	1	-
No	13/70 (18.6)	1.82 (0.20-42.27)	NS
Leukocyte count			
$<4 \times 10^9$/L	5/18 (27.8)	2.22 (0.53-9.08)	NS
$\geq 4 \times 10^9$/L	9/61 (14.8)	1	-
Steroid use			
Yes	1/18 (5.6)	1	NS
No	13/61 (21.3)	4.6 (0.55-101.2)	-
HIV infection			
Yes	2/10 (20)	1. 19 (0.15-7.37)	NS
No	12/69 (17.4)	1	-
Malignancy			
Yes	7/24 (29.2)	2.82 (0.75-10.79)	NS
No	7/55 (12.7)	1	-
DM			
Yes	5/18 (27.8)	2.22 (0.53-9.08)	NS
No	9/61 (14.8)	1	-
Immunosuppression			
Yes	11/45 (24.4)	3.34 (0.76-16.79)	NS
No	3/34 (8.8)	1	-
Shock			
Yes	9/11 (81.8)	56.7 (7.87-537.46)	<0.0001
No	5/68 (7.4)	1	-
Acute respiratory failure			
Yes	9/12 (75)	37.2 (6.24-264.66)	<0.0001
No	5/67 (7.5)	1	-
Acute renal failure			
Yes	8/11 (91.7)	27.56 (4.75-186.00)	<0.0001
No	6/68 (7.6)	1	-
Coma			
Yes	9/13 (69.2)	27.45 (5.14-168.15)	<0.0001
No	5/66 (7.6)	1	-
Antibiotic treatment			
Appropriate	9/66 (13.6)	1	-
Inappropriate or lacking	5/13 (38.5)	3.96 (0.88-17.89)	0.047

Abbreviations: CI = confidence interval; HIV = human immunodeficiency virus; DM = diabetes mellitus; NS = not significant

renal transplant recipients [6], and patients with AIDS [7], SLE [8], malignant diseases [9] or diabetes mellitus [10]. The severity of infection in these high-risk persons is also increased [5,16], and thus the medical care of such patients should include food counseling [17].

Table 4. Multivariate analysis of factors predicting prognosis (survival or death) in 79 episodes of non-typhoidal *Salmonella* bacteremia

Variable	High-risk category	Coefficient	Standard error	Odds ratio of death (95% CI)	*p*
Septic shock	Present	4.06	1.33	57.66 (4.28-776.14)	0.002
Coma	Present	3.6	1.30	36.43 (2.83-467.76)	0.006

Abbreviation: CI = confidence interval

Twenty eight episodes of infection (35%) were hospital acquired and occurred between 3 days and 88 days (median, 14 days) after admission. No clustering of cases was observed and no documented outbreaks of *Salmonella* infection had occurred within the hospital during the duration of the study.

Relapse developed in one patient with underlying lung cancer in this study. The rate of relapse was higher among patients with persistent underlying immunosuppression, particularly those with AIDS [14,18].

In blood isolates from patients with *Salmonella* septicemia, the rate of resistance to readily available antimicrobial agents (i.e., ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) has been increasing progressively [19]. Our study also found poor susceptibility of all isolates to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole. A fluoroquinolone resistance-related outbreak of *Salmonella* septicemia has also been reported [20]. In our study, 9 isolates (13%) were resistant to ciprofloxacin. However, 97-100% of our isolates were susceptible to third-generation cephalosporins, cefepime and imipenem.

A previous study found that death due to NTS bacteremia was more likely when coma, shock, and/or immunosuppression were present, or when inappropriate or no antibiotic treatment was provided [14]. In our study, patients with NTS bacteremia had poor prognosis when age was >65 years, and/or coma, acute respiratory failure, acute renal failure, or septic shock was present, or inappropriate or no antibiotic treatment was provided. However, development of septic metastasis has been shown not to be associated with higher crude mortality rate [14]. A previous report used univariate techniques to identify prognostic factors in NTS bacteremia [21], but our study used multivariate analysis to identify septic shock and coma as independently influencing prognosis, which had been previously reported (14).

In conclusion, gastroenteritis does not occur in most cases of NTS bacteremia in adults. Patients in shock or coma have poor prognosis, and susceptibility to the third-generation cephalosporins, cefepime and carbapenem remains high.

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