

Prognostic Factors and Clinical Features of Non-typhoid *Salmonella* Bacteremia in Adults

Yung-Fong Yen¹, Fu-Der Wang^{2*}, Chien-Shun Chiou³, Yin-Yin Chen⁴, Mei-Lin Lin²,
Te-Li Chen², Cheng-Yi Liu²

¹Section of Infectious Diseases, Taipei Municipal Yang-Ming Hospital, ²Division of Infectious Diseases, Taipei Veterans General Hospital and National Yang-Ming University, ³Central Region Laboratory, Research and Diagnostic Center, Centers for Disease Control, and ⁴Committee of Nosocomial Infection Control, Taipei Veterans General Hospital and Community Medicine Research Center and Institute of Public Health, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Background: Infections caused by non-typhoid *Salmonella* (NTS) have increased, and the increasing incidence of multidrug-resistant NTS bacteremia in adult patients has also been noted. This study aimed to investigate the clinical and microbiological characteristics of NTS bacteremia.

Methods: A total of 71 episodes of NTS bacteremia among 65 patients were identified between 2004 and 2006. Clinical characteristics were collected from medical records. The agar dilution method described by the Clinical and Laboratory Standards Institute was used to determine the *in vitro* activities of each antibiotic. Multiple logistic regression analysis was used to evaluate the relationship between patient characteristics and all other covariates studied for prognosis.

Results: *Salmonella enteritidis* was isolated in 30 cases (42.3%), *Salmonella typhimurium* in 22 (31.0%), and *Salmonella choleraesuis* in 19 (26.7%). Thirty-two (45.1%) isolates of 71 NTS bacteremias were susceptible to chloramphenicol, 37 (52.1%) to ampicillin, 47 (66.2%) to trimethoprim/sulfamethoxazole (TMP/SMX), 56 (78.9%) to moxifloxacin, 57 (80.3%) to ciprofloxacin and levofloxacin, and 71 (100%) to ceftriaxone. The crude 30-day mortality rate was 19.7%. In multiple logistic regression analysis, the following variables were independent and significant predictors of mortality: coma (odds ratio, 12.03) and inadequate antibiotic treatment (odds ratio, 6.63).

Conclusion: *S. enteritidis* was the most frequently isolated serotype. High resistance rates of NTS to some readily available antimicrobials (ampicillin, chloramphenicol, TMP/SMX, fluoroquinolones) were found. Patients with the factor of coma or inadequate antibiotic treatment had poor prognosis. [*J Chin Med Assoc* 2009;72(8):408–413]

Key Words: bacteremia, non-typhoid *Salmonella*, prognosis

Introduction

In developing countries, non-typhoid *Salmonella* (NTS) accounts for a steadily increasing proportion of human infections in recent decades.¹ Most patients with NTS infection have self-limited gastroenteritis, but invasive diseases with bacteremia are found in 5% of patients,² especially in renal transplant recipients,³ patients with acquired immunodeficiency syndrome (AIDS),^{4–6} systemic lupus erythematosus (SLE),^{6,7} diabetes mellitus

(DM)⁶ and malignant diseases.⁸ Antibiotic treatment is very important in cases with invasive diseases or complicated bacteremia, but the prevalence of multidrug-resistant NTS bacteremia in adult patients has gradually increased in the last decade, which has made the treatment of invasive salmonellosis a clinical dilemma.^{9–11}

In related literature, very few studies have focused on analyzing the prognostic factors in NTS bacteremia. In this study, we collected 71 cases of NTS bacteremia to analyze the prognostic factors and clinical features.



*Correspondence to: Dr Fu-Der Wang, Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: fdwang@vghtpe.gov.tw • Received: December 29, 2008 • Accepted: July 10, 2009

Methods

All adult patients, older than 18 years, admitted during the study period (January 2004 to December 2006) to the hospital were considered eligible if they had had at least 1 blood set positive for NTS. The hospital is a 2,900-bed tertiary referral medical center and has specialized units for solid organ and bone marrow transplantation, cardiac monitoring, burns and intensive care units. The medical records of eligible patients were reviewed, including their demographic characteristics, underlying diseases, clinical presentations, use of steroids, bacteriological characteristics, antibiotic susceptibility, treatment and outcome.

Steroid use was defined as having taken 30 mg prednisone daily (or an equivalent dosage) for at least 1 week or 20 mg prednisone daily for at least 2 weeks before the positive blood sample was drawn. Patients were considered to be immunosuppressed in the presence of any of the following conditions: collagen disease, liver cirrhosis, malignancy, organ transplantation, steroid use, or AIDS. A white blood cell count of $<4 \times 10^9/L$ was classified as leukopenia.

Complications due to NTS bacteremia (i.e. acute respiratory failure, shock, coma) were defined as follows. Acute respiratory failure was defined as the development of hypoxia ($PaO_2 < 60$ mmHg) and/or hypercapnia ($PaCO_2 > 50$ mmHg) in room air, and was considered to be bacteremia-related if no other obvious cause was found. Shock was defined as systolic blood pressure <90 mmHg and/or if total urine output was <80 mL over a period of 4 hours, and was considered to be bacteremia-related (septic shock) if there was no other obvious cause. Coma was defined as the presence of impaired responsiveness (or unresponsiveness) to external stimulation and the patient was difficult to arouse or unarouseable.¹²

Cure was defined as the disappearance of clinical symptoms and signs as well as negativity of blood cultures posttreatment. Thirty-day mortality was defined as death occurring within 30 days of septicemia.

Any microbiologically or clinically documented infection was considered to be septic metastasis due to NTS if it developed ≥ 2 days after the first positive blood sample was drawn. Inadequate antibiotic therapy was defined as either (1) the antibiotic was not sensitive to *Salmonella* species isolated from blood culture or (2) the antibiotic had not been proven to have good penetration into cells.

NTS isolates were identified by serotyping according to the Kauffmann-White scheme utilizing *Salmonella* agglutination antisera. *In vitro* activities to various antimicrobials were determined by measuring minimum

inhibitory concentrations (MICs) using agar dilution methods (Clinical and Laboratory Standards Institute, 2006),¹³ and susceptible or resistant isolates were defined according to the criteria suggested by the Clinical and Laboratory Standards Institute.¹⁴

Univariate analysis was used to identify the risk factors associated with the outcome of salmonellosis. Fisher's exact or χ^2 test was used for the comparison of proportions. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for the statistical analysis of odds ratios and 95% confidence intervals. A p value <0.05 was considered significant.

Multiple logistic regression analysis was used to evaluate the relationship between patients' characteristics and all other covariates studied for prognosis. We built the model using a stepwise selection strategy, and the covariates that were found to be significant ($p < 0.05$) were included in the final model.

Results

During the 3-year period, a total of 71 cases of NTS were collected. Forty-eight (67.6%) patients were males. The mean age was 60 years (range, 24–93 years). Underlying diseases were identified in 46 (64.8%) cases (Table 1). The most common underlying disease was solid tumor (18 cases, 25.4%), followed by DM (16 cases, 22.5%), AIDS (9 cases, 12.7%) and SLE (5 cases, 7.0%).

Fifty-eight (81.7%) cases manifested with fever, and 16 (22.5%) cases were accompanied or preceded by symptoms of acute gastroenteritis. Eight (11.3%) cases presented with septic metastases including osteomyelitis (2 cases), central nervous system infection (1 case), mycotic aneurysm (4 cases), and soft tissue infection (1 case).

Salmonella enteritidis was isolated in 30 (42.3%) cases, *Salmonella typhimurium* in 22 (31.0%), and *Salmonella choleraesuis* in 19 (26.7%).

In vitro activities are shown in Table 2. Thirty-two (45.1%) isolates were susceptible to chloramphenicol, 37 (52.1%) to ampicillin, 47 (66.2%) to trimethoprim/sulfamethoxazole (TMP/SMX), 56 (78.9%) to moxifloxacin, 57 (80.3%) to ciprofloxacin and levofloxacin, and 71 (100%) to ceftriaxone.

The crude 30-day mortality rate was 19.7% (Table 1). The clinical, epidemiological and laboratory variables, and the underlying diseases studied and their relative influence on mortality are shown in Table 3. Age ≥ 65 years, immunosuppressed status, septic shock, coma, acute respiratory failure and inadequate antibiotic treatment were significantly associated with high

Table 1. Characteristics of 71 cases of non-typhoid *Salmonella* bacteremia

	Serotype			n (%)
	<i>S. typhimurium</i>	<i>S. choleraesuis</i>	<i>S. enteritidis</i>	
Number of cases	22	19	30	71 (100)
Male	13	16	19	48 (67.6)
Mean age (yr)	60	60	62	60
Age range (yr)	32–80	32–89	24–93	24–93
Age ≥ 65 yr	13	9	9	31 (43.7)
Clinical presentations				
Diarrhea	4	5	7	16 (22.5)
Fever	18	16	24	58 (81.7)
Septic metastasis*	1	4	3	8 (11.3)
Steroid use	5	1	7	13 (18.3)
Underlying diseases				
Solid tumor	6	2	10	18 (25.4)
Diabetes mellitus	11	0	5	16 (22.5)
AIDS	2	4	3	9 (12.7)
SLE	2	0	3	5 (7.0)
Hematological malignancy	1	1	2	4 (5.6)
Organ transplantation	0	1	0	1 (1.4)
None	7	10	8	25 (35.2)
Deaths (within 30 d)	6	4	4	14 (19.7)

*Includes osteomyelitis (2 cases), central nervous system infection (1 case), mycotic aneurysm (4 cases), and soft tissue infection (1 case). AIDS = acquired immunodeficiency syndrome; SLE = systemic lupus erythematosus.

Table 2. Antimicrobial susceptibility of 71 isolates of non-typhoid *Salmonella* bacteremia

	MIC (mg/L)			Percentage of isolates susceptible
	Range	MIC ₅₀	MIC ₉₀	
Ampicillin	1 to >128	4	>128	52.1
TMP/SMX	0.06 to >128	0.25	>128	66.2
Chloramphenicol	4 to >128	32	>128	45.1
Ceftriaxone	0.03 to 0.5	0.12	0.12	100
Ciprofloxacin	0.015 to 16	0.03	16	80.3
Levofloxacin	<0.015 to 16	0.12	16	80.3
Moxifloxacin	<0.015 to 32	0.12	16	78.9

MIC = minimum inhibitory concentration; TMP/SMX = trimethoprim/sulfamethoxazole.

mortality. Values for all variables were available in all episodes and were included in the logistic regression analysis. Coma and inadequate antibiotic treatment were identified as independent risk factors for outcome (Table 4).

Discussion

Most previously reported cases of NTS bacteremia in adults were described as having symptoms of gastroenteritis not developed at presentation.⁸ Sixteen (22.5%)

cases presented with symptoms of gastroenteritis in this study. The rate of septic metastasis of 11.3% in our series was similar to the 15.7% and 12.5% in earlier reports.^{15,16} Four cases with *S. choleraesuis* developed the complication of mycotic aneurysm in this study. This serious complication often occurs in elderly or arteriosclerotic patients with salmonellosis, particularly in *S. choleraesuis* bacteremia.^{17–19}

It is well documented that certain patient groups are at increased risk of acquiring NTS bacteremia.^{3–8} In our study, 64.8% of patients had underlying diseases, including malignant diseases, DM, AIDS, and SLE.

Table 3. Univariate analysis of risk factors influencing the outcome in 71 cases of non-typhoid *Salmonella* bacteremia

	No. of patients who died/total no.	OR (95% CI)	<i>p</i>
Sex			
Male	11/48	1.98 (0.50–7.94)	0.328
Female	3/23	1	
Age (yr)			
≥65	11/31	6.78 (1.69–27.17)	0.003
<65	3/40	1	
Fever			
Yes	11/58	0.78 (0.18–3.32)	0.736
No	3/13	1	
Leukocyte count (10 ⁹ /L)			
<4	5/17	2.08 (0.59–7.38)	0.249
≥4	9/54	1	
Septic metastasis			
Yes	1/8	0.55 (0.06–4.87)	0.586
No	13/63	1	
Immunosuppressed			
Yes	12/41	5.79 (1.19–28.25)	0.018
No	2/30	1	
Septic shock			
Yes	7/13	8.50 (2.21–32.67)	0.001
No	7/58	1	
Coma			
Yes	7/12	10.40 (2.58–41.87)	<0.001
No	7/59	1	
Acute respiratory failure			
Yes	6/11	7.80 (1.92–31.66)	0.002
No	8/60	1	
Inadequate antibiotic treatment			
Yes	6/12	6.38 (1.64–24.71)	0.004
No	8/59	1	

OR = odds ratio; CI = confidence interval.

Table 4. Multivariate logistic regression model for the analysis of factors predicting prognosis in 71 episodes of non-typhoid *Salmonella* bacteremia

	High-risk category	OR of death (95% CI)	<i>p</i>
Coma	Present	12.03 (2.59–55.89)	0.002
Inadequate antibiotic treatment	Present	7.63 (1.60–36.30)	0.011

OR = odds ratio; CI = confidence interval.

S. enteritidis and *S. typhimurium* contributing to over 75% of all NTS infections have been reported,²⁰ and certain serotypes such as *S. choleraesuis*²¹ and *S. virchow*²² have also been reported to be associated with a higher incidence of septicemia. In this study, the most commonly isolated serotype was *S. enteritidis*, followed by *S. typhimurium* and *S. choleraesuis*.

Resistance of NTS to some common antimicrobials (ampicillin, chloramphenicol, TMP/SMX) has been increasing gradually.²³ Our study also found poor susceptibility to chloramphenicol, ampicillin, and TMP/SMX. Isolates of fluoroquinolone-resistant *Salmonella* have increased steadily in the last decade.^{24–29} In our study, 14 (19.7%) isolates were resistant to ciprofloxacin

and levofloxacin and 15 (21.1%) to moxifloxacin. Additionally, the MIC₉₀ of fluoroquinolones in this study was high. According to previous reports,^{30,31} *Salmonella* species have excellent sensitivities to third-generation cephalosporins, including ceftriaxone. In our study, all NTS isolates were susceptible to ceftriaxone.

Coma, immunosuppressed status and septic shock were independent risk factors of death in a previous study.¹⁶ In this study, a patient was more likely to die of *Salmonella* bacteremia when they had ≥ 1 of the following factors: age ≥ 65 years, immunosuppressed status, inadequate antibiotic treatment, and presence of septic shock, coma or acute respiratory failure. Coma and inadequate antibiotic treatment were identified as independently influencing prognosis.

In conclusion, most cases of NTS bacteremia in adults did not have the presenting symptoms of gastroenteritis. *S. enteritidis* was the most frequently isolated serotype. A high rate of NTS resistant to some readily available antimicrobials (ampicillin, chloramphenicol, TMP/SMX, fluoroquinolones) was found. Patients with coma or inadequate antibiotic treatment had poor outcome.

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