Original Research

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Clinical manifestations of non-typhoid Salmonella bacteremia in southern Taiwan

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ABSTRACT

Purpose: This study is conducted to investigate the clinical characteristics of patients with bacteremia caused by non-typhoid *Salmonella* (NTS). **Methods:** Patients with bacteremia caused by NTS during the period 2010 to 2014 were identified from a computerized database of a regional hospital in southern Taiwan. The medical records of these patients were retrospectively reviewed. **Results:** A total of the 85 patients with NTS bacteremia were identified and 66% of them were classified as elderly patient with age ≥ 65 years. In addition to 30 (35.3%) cases of primary bacteremia, the most common source of secondary infection is acute gastroenteritis (n = 29, 34.1%). Group B was the most common NTS serogroup, followed by group D and C. More than 75% of the cases of NTS bacteremia developed in patients with immunocompromised conditions, which was defined as the patient had any one of the following conditions – cancer, liver cirrhosis, diabetes mellitus, end-stage renal disease, connective tissue diseases, HIV infections, and receiving immunosuppressant or steroid. Clinical outcomes, including rate of ICU admission, acute respiratory failure, and mortality were 21.2%, 14.1%, and 11.8%, respectively. In-hospital mortality was significantly associated with shock as the initial presentation (odds ratio, 5.25, 95% confidence interval: 1.31-20.97). 94-98% of clinical isolates were susceptible to third-generation cephalosporin, but ciprofloxacin resistant rate was 17.6%. **Conclusions:** NTS bacteremia is not uncommon, especially in immunocompromised and elderly patients, and shock as the initial presentation is significant risk factors for mortality of patients with NTS bacteremia. Third-generation cephalosporin remains good in vitro activity against NTS.

KEY WORDS: Non-typhoid *Salmonella*; bacteremia; outcome

INTRODUCTION

Nontyphoidal *Salmonella* (NTS) is notorious as a major cause of diarrheal disease and it is estimated to affect 93.8 million cases each year in both developing and developed countries [1]. Fortunately, most of the patients with NTS enteric gastroenteritis have self-limited course. In contrast to this mild type of NTS infections, NTS can also cause invasive human infections globally, especially in Africa [2-9]. In Taiwan, there is no exception [10-16]. In this study, we investigated the clinical characteristics and microbiologic features of bacteremia due to NTS in a regional hospital in southern Taiwan over a 5-year period and assessed the risk factors associated with mortality due to this disease.

METHODS

Hospital setting and patient selection

This study was conducted at the Chi Mei Medical Center, a 900-bed hospital located in southern Taiwan. Patients with positive blood cultures for NTS between January, 2010 and December, 2014, were identified from the hospital's computerized database. The medical records of all patients with bacteremia due to non-typhoid *Salmonella* were retrospectively reviewed and the following information was collected: age, gender, underlying conditions (history of immunosuppressant drug use, diabetes mellitus, liver cirrhosis, end-stage renal disease, and active cancer), laboratory data, microbiological findings, antimicrobial susceptibility test results, and patient outcome. The data was collected on a routine basis and the analysis was carried out retrospectively. The records and information of patient were anonymized and de-identified prior to analysis. Therefore, no informed consent was required and it was specifically waived by Institution Review Board. Ethics approval was obtained from Institution Review Board of Chi Mei Medical Center.

Bacterial isolates and antimicrobial susceptibilities

Blood were inoculated into BACTEC culture bottles

using the BACTEC 9240 system (Becton Dickinson, Cockeysville, MD, USA). All strains were identified to the species level by conventional methods, including triple sugar Iron (TSI) agar motility, urease and citrate utilization tests, and were further verified by the API-20E System (bioMérieux Vitek Inc, Hazelwood, MO, USA), the ID 32 GN System (bioMérieux Vitek Inc), or the Vitek 2 ID-GNB identification card (bioMérieux Inc, Durham, NC, USA). The serogroups of Salmonella isolates were determined by O antisera (Difco Laboratories, Detroit,MI, USA) by the slide agglutination test. Susceptibilities of these isolates to a battery of antimicrobial agents were determined using the disk diffusion method as described by the Clinical and Laboratory Standards Institute.

Definitions

The diagnosis of infection focus of bacteremia was made based on clinical, bacteriological, and radiological investigations. Biliary tract infections were diagnosed in patients with clinical hepatobiliary tract inflammation plus positive bile cultures. The bile specimens were collected by percutaneous transhepatic cholangiodrainage, percutaneous gallbladder drainage, or operation. Catheter-related bloodstream infection was defined as a positive semi-quantitative tip culture (≧15 colony-forming units), bacteremia, and/or high clinical suspicion; pneumonia was defined as a positive culture for NTS. in purulent sputum samples and the presence of newly developed lung infiltrates; Genitourinary tract infection (GUTI) was defined as positive urine culture with growth of 10^5 CFU/ml and pyuria; and skin and soft tissue infection (SSTI) was defined as clinical soft tissue inflammation plus positive soft tissue or pus culture and bacteremia. If no primary focus could be identified, the bacteremia was classified as primary. Septic shock was diagnosed in septic patients with a systolic blood pressure < 90 mm Hg or in patients who required inotropic agents to maintain blood pressure. In-hospital mortality was defined as death due to any cause during hospitalization. Polymicrobial infections were classified if the patients whom had other non-NTS pathogens grew from blood samples. Inappropriate usage of antibiotics was defined as that the clinical isolates were in vitro resistant to used antimicrobial agents.

Statistical analysis

Continuous variables are expressed as means ± standard deviations. Comparisons between each variable/category were using the chi-square test or one-way analysis of variance, as appropriate. A multivariate stepwise logistic regression model was used to identify risk factors for mortality. All statistical analyses were conducted using the statistical package SPSS for Windows (Version 19.0, SPSS, Chicago, Il, USA), and a P value < .05 was considered to show statistical significance.

RESULTS

Clinical characteristics

The clinical characteristics and biochemical findings of the 85 patients with NTS bacteremia are summarized in Table 1 and 2. The patients ranged in age from 30 to 91 years (mean, 68.8. years) and 66% of them were classified as elderly patient with age ≥ 65 years. In addition to 30 (35.3%) primary bacteremia, the most common source of secondary infection is acute gastroenteritis (n = 29, 34.1%), followed by genitourinary tract infection (n = 9, 10.6%), pneumonia (n = 5, 5.9%), SSTI (n = 3, 3.5%), catheter-related bloodstream infection (n= 3, 3.5%), mycotic aneurysm (n = 3, 3.5%), psoas muscle abscess (n =2, 2.4%), and biliary tract infection (n = 1, 1.2%). Group B was the most common NTS serogroup, followed by group D and C. Hypertension (n= 40, 47.1%) was the most common underlying disease, followed by diabetes mellitus. Among twenty-nine patients having underlying cancer, hepatocellular cell carcinoma was the most common type of cancer (n = 10), followed by lung cancer (n = 5). Fever, diarrhea, and shock was the initial presentation in 56 (65.9%), 31 (36.5%) and 17 (20.0%) patients, respectively. Of three patients who had polymicrobial bacteremia, *E. coli* and Enterococcus were the co-pathogens in two and one patient, respectively.

Outcome analysis

Clinical outcomes, including rate of ICU admission, acute respiratory failure, and mortality were 21.2%, 14.1%, and 11.8%, respectively. In-hospital mortality was significantly associated with shock as the initial presentation (odds ratio, 5.25, 95% confidence interval: 1.31-20.97). In contrast, overall mortality was not associated with age, gender, or other underlying conditions, such as diabetes mellitus, end-stage renal disease, polymicrobial infection or primary bacteremia (table 3).

Antimicrobial susceptibilities

The results of in vitro susceptibility testing of clinical NTS isolates against various antimicrobial agents are shown in Table 4. More than 98% of clinical isolates were susceptible to ceftazidime, and more than 90% of clinical isolates were susceptible to ceftriaxone. As for ciprofloxacin, the overall resistant rate was 17.6%. The antimicrobial susceptibilities vary according to different serogroup.

DISCUSSION

This study investigating 85 patients with NTS bacteremia at a regional hospital in southern Taiwan during a 5-year period had several significant findings. We found that most of patients had various underlying diseases, such as diabetes mellitus, cancer and liver cirrhosis. Moreover, more than 75% of the cases of NTS bacteremia developed in patients with immunocompromised conditions, which was defined as

the patient had any one of the following conditions – cancer, liver cirrhosis, diabetes mellitus, end-stage renal disease, connective tissue diseases, HIV infections, and receiving immunosuppressant or steroid. In addition to primary bacteremia, and acute gastroenteritis associated secondary NTS bacteremia, NTS bacteremia can be secondary to other type of infection including genitourinary tract infection, pneumonia, SSTI, catheter-related infection, mycotic aneurysm, psoas muscle abscess, and biliary tract infection.

Table 1. Clinical characteristics of 85 patients with bacteremia caused by non-typhoidal *Salmonella*

	No (%) of all patients (n = 85)
Age, years (mean±SD)	68.8 ± 14.3
Age ≥ 65 years, no. (%)	56 (65.9)
Male, no. (%)	54 (63.5)
Underlying disease or condition, no. (%)	
Hypertension	40 (47.1)
Diabetes mellitus	32 (37.6)
Cancer	29 (34.1)
Liver cirrhosis	23 (27.1)
Hepatobiliary stone	19 (22.4)
Stroke	10 (11.2)
End stage renal	7 (8.2)
Coronary artery disease	7 (8.2)
HIV infection	2 (2.4)
Autoimmune disease	2 (2.4)
Peripheral artery occlusive disease	1 (1.2)
Receiving immunosuppressant	16 (18.8)
Receiving steroid	14 (16.5)
Serogroup	
Group B	48 (56.5)
Group C	8 (9.4)
Group D	29 (34.1)
Primary bacteremia	30 (35.3)
Secondary bacteremia	
Acute gastroenteritis	29 (34.1)
Urinary tract infection	9 (10.6)
Pneumonia	5 (5.9)
Skin and soft tissue infection	3 (3.5)
Central line-associated infection	3 (3.5)
Mycotic aneurysm	3 (3.5)
Psoas muscle abscess	2 (2.4)
Biliary tract infection	1 (1.2)
Initial presentation	
Fever	56 (65.9)
Diarrhea	31 (36.5)
Shock	17 (20.0)
Polymicrobial infection, no. (%)	3 (2.8)
Outcome, no. (%)	
Intensive care unit admission	18 (21.2)
Acute respiratory failure	12 (14.1)
In-hospital mortality	10 (11.8)

Table 2. Biochemical findings of 85 patients with bacteremia caused by non-typhoidal *Salmonella*

Variables	Mean value ± SD
White blood cell count (cell/uL)	11517.6 ± 14752.0
Neutrophil cell count (cell/uL)	9473.0 ± 1185.4
Hemoglobin (g/dL)	12.1 ± 2.6
Platelet cell count (cell/uL)	164000 ± 87700
Aspartate transaminase (IU/L)	70.1 ± 82.3
Total-bilirubin (mg/dL)	1.8 ± 2.8
Albumin (g/dL)	2.7 ± 0.6
Urea nitrogen (mg/dL)	39.0 ± 32.6
Serum creatinine (mg/dL)	2.4 ± 2.4
C-reactive protein (mg/L)	70.5 ± 63.4

In this study, we found that approximately two-thirds of the patients with NTS bacteremia were older than 65 years. This is consistent with two previous studies in Taiwan – Yen et al showed that elderly patients 71-80 years of age was the most common group among 73 patients with NTS bacteremias [15], and Lin et al showed that patients with age greater than 60 years compromised 45 (68.2%) of 66 cases of NTS bacteremia [8]. In contrast, the finding in Taiwan is different from one recent global study [2] that young adult was the second most common affected population followed by children in Africa. The differences between Taiwan and Africa may be due to the significant difference of HIV prevalence. In Africa with high prevalence of HIV, HIV infections may frequently develop in young adults and make them get invasive NTS diseases. In Taiwan with low prevalence of HIV, elderly patients may have more immunocompromised conditions than young adults, and further have more NTS bacteremia than young adult patients. Therefore, it indicates that every country may have different epidemiological characteristics and should conduct its own epidemiological investigation.

Of the 85 patients who developed bacteremia due to NTS during the study period, about 21% and 14% of patients required ICU admission and the use of mechanical ventilation, respectively. Furthermore, the in-hospital mortality rate was 11.8%. Our finding regarding mortality is relative lower than previous studies [8,14,15] in Taiwan. The in-hospital mortality was 26.0% and 15.2% in Li's study[14] and Lin's study [8], respectively. Another study using attributable mortality as outcome measurement by Yen et al [15] showed that there were a total of 14 death (18%) of 79 episodes of NTS bacteremia. In contrast to the small difference regarding mortality between the present and previous studies [8,14,15], we have the similar finding as previous reports [8,14,15] that found that shock as the initial presentation was one of risk factors associated with the mortality.

Table 3. Prognostic factors associated with in-hospital mortality

Variables	No (%) of mortality (n = 10)	No (%) of survivor (n = 75)	Univariate		
			Odds Ratio	95% CI	P value
Elderly (Age≧ 65 years)	7 (70.0)	49 (65.3)	1.238	0.295 – 5.193	0.770
Male	6 (60.0)	48 (64.0)	0.844	0.219 – 3.255	0.805
Female	4 (40.0)	27 (36.0)	1.185	0.307 – 4.573	0.805
Diabetes mellitus	1 (10.0)	31 (41.3)	0.158	0.019 – 1.309	0.087
Liver cirrhosis	4 (40.0)	19 (25.3)	1.965	0.500 – 7.717	0.333
ESRD	2 (20.0)	5 (6.7)	3.500	0.581 – 21.081	0.172
Cancer	3 (30.0)	26 (34.7)	0.808	0.193 – 3.388	0.770
Steroid	3 (30.0)	11 (14.7)	2.494	0.559 – 11.133	0.231
Immunosuppressant	3 (30.0)	13 (17.3)	2.044	0.466 – 8.968	0.343
Diarrhea	3 (30.0)	28 (37.3)	0.719	0.172 – 3.010	0.652
Initial shock	5 (50.0)	12 (16.0)	5.250	1.314 – 20.969	0.0189
Hepatobiliary stone	4 (40.0)	15 (20.0)	2.667	0.667 – 10.663	0.165
Polymicrobial infection	1 (10.0)	2 (2.7)	4.056	0.333 – 44.327	0.272
Primary bacteremia	6 (60.0)	24 (32.0)	3.188	0.822 – 12.357	0.094

Table 4. Antimicrobial resistant rates of non-typhoidal *Salmonella*

	All (%) (n = 85)	Group B (%) (n = 48)	Group C (%) (n = 8)	Group D (%) (n = 29)
Ampicillin	25 (29.4)	19 (39.6)	2 (25.0)	4 (13.8)
Ceftazidime	1 (1.2)	1 (2.1)	0 (0.0)	0 (0.0)
Ceftriaxone	5 (5.9)	4 (8.3)	0 (0.0)	1 (3.4)
Ciprofloxacin	15 (17.6)	11 (22.9)	2 (25.0)	2 (6.9)
Trimethoprim-sulfamethoxazole	15 (17.6)	9 (18.8)	2 (25.0)	4 (13.8)
Chloramphenicol	23 (27.1)	19 (39.6)	3 (37.5)	1 (3.4)

In this study, serogroup B (56.5%) was the most common NTS serogroup, followed by serogroup D (34.1%) and C (9.1%). In Li's study in southern Taiwan [14], the distribution of serogroup was serogroup B (40.2%), serogroup C (26.5%), serogroup D (30.9%), and serogroup E (1.5%). In north Taiwan, Lin's study[8] showed the serogroup distributions were serogroup B (23.4%), serogroup C1 (1.6%), serogroup C2 (6.3%), and serogroup D (68.8%). Another study in north Taiwan by Yen et al [15] found that serogroup D (39.2%) was the most common serogroup, followed by serogroup B (30.3%), and C (27.8%). Based on the above finding, we can observe that serogroup B was the most common in southern Taiwan but serogroup D was the most common in north Taiwan. Although we may see that different serogroup distribution between different sites of Taiwan, more epidemiological studies are warranted to investigate the distribution of different serogroup of NTS disease in different regions.

The antibiotic susceptibility patterns of the clinical isolates in this study were similar to those reported previously in Taiwan [15]. We found that a total of 15 isolates (18%) were resistant to fluoroquinolones. In US, the percentage of NTS isolates resistant to ceftriaxone increased from 0.2% to 3.4%, and the rate of nonsusceptibility to ciprofloxacin also increased from 0.4% to 2.4% from 1996 through 2009 [17]. In China, one recent study showed that the ciprofloxacin resistance rate was 8.05% among 1826 isolates [18]. Thus, we can find that ciprofloxacin-resistant rate of NTS in Taiwan seems to be higher than other countries [4,7,18]. However, 94-98% of our isolates were susceptible to third-generation cephalosporin and this is consistent with previous Taiwan's study [15] that the third-generation cephalosporin susceptible rate was 97-99%. Based on these in vitro finding, third-generation cephalosporin may be recommended as the drug of choice for management of NTS disease in Taiwan.

This study had one major limitation. Serogroups are comprised of different serovars and standard microbiological techniques can be used for serotyping of the bacterial isolates [19]. Different serovars are found to be responsible for NTS bacteremia in different locations [20, 21]. Therefore, it would be of great importance to have knowledge about the prevalent serovars associated with NTS bacteremia in Taiwan. However, we cannot identify Salmonella serovars in our laboratory.

CONCLUSION

NTS bacteremia is not uncommon, especially in immunocompromised and elderly patients, and shock as the initial presentation is significant risk factors for mortality of patients with NTS bacteremia. In Taiwan, ciprofloxacin-resistant rate of NTS seems to be higher than other countries, but third-generation cephalosporin may be considered as the drug of choice for management of NTS disease based on the in vitro studies.

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