Non-typhoidal *Salmonella* bacteremia among adults: An adverse prognosis in patients with malignancy

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**KEYWORDS**
Malignancy; Mortality; Non-typhoidal *Salmonella* bacteremia

**Background:** Clinical information about non-typhoidal *Salmonella* (NTS) bacteremia in patients with malignancy has rarely been described. This study investigated clinical characteristics and prognostic variables of patients with malignancy while complicated with NTS bacteremia.

**Methods:** The study included demographic data, clinical information, and outcome in adults (≥18 years old) with and without malignancy complicated with NTS bacteremia at a medical center from 2000 to 2009.

**Results:** There were 206 patients with NTS bacteremia. The serogroups of NTS isolates included group B (40.2%), group D (30.9%), group C (26.5%), and group E (1.5%). Extraintestinal infections were noted in 66 (32.4%) patients and were mainly endovascular (26/206, 12.7%) or pleuropulmonary (17/206, 8.3%) infections. On multivariate analysis, independent factors for in-hospital mortality included shock (odds ratio [OR] 9.13; 95% confidence interval [CI] 3.81–21.83; \( p < 0.001 \)), malignancy (OR 8.42; 95% CI 3.12–22.71; \( p < 0.001 \)), and acute renal failure (OR 2.63; 95% CI 1.11–6.22; \( p = 0.028 \)). Different clinical presentations and outcome were noted in 74 (36.2%) patients with malignancy and 130 without malignancy. The former had more leucopenia and thrombocytopenia at initial presentation and fewer extraintestinal infections (20.2% vs. 39.2%, \( p = 0.005 \)), endovascular infections (2.7% vs. 18.5%; \( p = 0.002 \)), and serovar Choleraesuis (10.8% vs. 27.7%; \( p = 0.005 \)). An elevated in-hospital mortality rate was noted in patients with malignancy compared to those without malignancy (40.5% vs. 17.7%, \( p < 0.001 \)). Among patients with malignancy, multivariate analysis revealed that shock was the only independent factor associated with in-hospital mortality (OR 7.52; 95% CI, 2.38–23.80; \( p = 0.001 \)).

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Introduction

Non-typhoidal Salmonella (NTS) is one of the important causes of foodborne infections, resulting in self-limited gastroenteritis, bacteremia, subsequent focal infection, or persistence in endovascular sites. Several extraintestinal infections, including endovascular infections, meningitis, pneumonia, septic arthritis, or osteomyelitis were reported as primary infectious foci or as secondary infections to primary bacteremia. Aside from an elevated incidence of extraintestinal organ involvement, an increased mortality of patients with NTS bacteremia was also reported. NTS bacteremia in children rarely causes fatalities, whereas NTS bacteremia in adults should be considered life-threatening, regardless of primary or secondary bacteremia. Mean bacteremia in adults should be considered life-threatening, whereas NTS bacteremia possesses important clinical significance because affected patients usually have underlying diseases, suggesting an immunocompromised status.

Previous studies have pointed out several conditions associated with salmonellosis, including connective tissue diseases, use of therapeutic immunosuppressants, malignancies, diabetes mellitus, and human immunodeficiency virus (HIV) infection. As mentioned in previous studies, malignancy and HIV infection have been the leading predisposing medical diseases in patients with NTS bacteremia. A study in Spain reported up to 50% mortality among patients with HIV infection complicated with non-typhoidal salmonellosis. In a previous Taiwanese study, solid-organ malignancy, age, and extraintestinal infection were reported as independent predictors for in-hospital death among patients with NTS bacteremia. However, few reports investigated the clinical characteristics and outcome for patients with NTS bacteremia and underlying malignant diseases. This study described the clinical characteristics and prognostic variables at discharge among patients with malignancy and NTS bacteremia.

Materials and methods

Study design

A retrospective study was conducted in a university-affiliated hospital, which is a medical centre with 1,100 beds. Patients aged 18 or older with at least one blood sample positive for NTS species identified by the clinical microbiology laboratory between January 2000 and December 2009 were included. Medical records regarding demographic data, underlying diseases, clinical manifestations, laboratory data upon admission, antimicrobial treatment, clinical outcome and length of hospital stay were reviewed. For patients with recurrent NTS bacteremia, only the first episode was included.

Microbiology and antimicrobial susceptibility

All blood isolates were cultured and identified according to standard methods. The serogroups of Salmonella isolates were determined by O antisera (Difco Laboratories, Detroit, MI, USA) first by the slide agglutination test. For serogroup C or D isolates, the presence of Vi antigen in Salmonella Typhi or Salmonella Paratyphi was screened by Vi antisera (BBL, Cockeysville, MD, USA). Salmonella enterica serotype Choleraesuis was identified if the citrate test was negative in isolates of serogroup C. Antimicrobial susceptibilities were determined using the disk-diffusion method. The interpretation of susceptibility data followed the criteria proposed by the Clinical Laboratory Standard Institute.

Definition

The infectious focus of bacteremia was determined clinically by the presence of an active infection site concomitant with NTS bacteremia, or the isolation of an identical organism from clinical specimens other than blood and feces. Patients were considered to have primary bacteremia if there was no clinical evidence of other infectious focuses as well as no identical organism isolated from a clinical specimen other than blood and feces. Patients were assumed to have diabetes mellitus if the fasting serum glucose level was >126 mg/dL. Chronic kidney disease was defined as a serum creatinine >1.5 mg/dL. Liver cirrhosis was defined by abdominal ultrasonography and findings from clinical follow-up. Immunosuppressive therapy was defined as the receipt of corticosteroid (at least 10 mg of prednisolone per day or equivalent dosage for at least two weeks), anti-neoplastic treatment for malignancy, or immunosuppressive agents for organ transplantation within one month prior to admission.

Fever was defined as an axillary body temperature ≥38 C. Shock was defined as a systolic blood pressure ≤90 mmHg or an unstable hemodynamic status requiring inotropic agents to maintain blood pressure. Acute renal failure was defined as a 2-fold increase of the patient’s baseline creatinine level. Antimicrobial therapy was considered appropriate if the etiological pathogen was susceptible in vitro to at least one of the drugs administered within 72 hours after the onset of bacteremia.

Statistical analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 17.0; SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and were compared using the Student’s t test. Categorical variables,

Conclusion: Malignancy is an adverse prognostic factor in patients with NTS bacteremia. Food safety in patients with malignancy should be emphasized to prevent salmonellosis.

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expressed as numbers and percentages, were compared using the chi-squared test or Fisher’s exact test. The odds ratio (OR) and corresponding 95% confidence interval (CI) for mortality were calculated in the unadjusted and multivariable-adjusted models. Multivariate analysis was performed with the stepwise logistic regression model on the variables with a p value < 0.1 as the limit for entering the variable. A Cox proportional hazard model was used to compare the survival in malignancy and non-malignancy groups and was adjusted for age, gender, shock, and acute renal failure.

Results

During the 10-year period, a total of 206 patients with NTS bacteremia were evaluated. Two patients were excluded for analysis due to a loss of medical information from transference to other hospitals. Of 204 patients with NTS bacteremia, 74 (36.2%) had underlying medical illnesses of solid organ malignancy or hematological malignancy. Overall, 53 patients died in the hospital, attributing to an in-hospital mortality rate of 26.0% in patients with NTS bacteremia.

Clinical characteristics and laboratory data

The demographic data of 204 patients are described in Table 1. Of the 204 patients with NTS bacteremia, the mean (± standard deviation) age was 58.4 (±18.3) years with a range of 19–98 years and males predominating (121/204, 59.3%). At least one underlying medical disease was noted in 177 (86.8%) patients. 74 patients had malignant diseases, and 47 had a solid organ tumor, mainly hepatocellular carcinoma (14), gastrointestinal cancer (10), or lung cancer (8). The other 27 patients had hematological malignancies with a predominance of lymphoma (8) and acute leukemia (7). Only 2 patients had cured malignant diseases and 27 (40%) patients received anti-neoplastic treatment within one month prior to onset of NTS bacteremia. Of 77 patients tested for HIV infection, 13 (6.4%) were positive for HIV-1 antibody and the CD4 counts at presentation were ≤ 40 cells/mm³. As a result, all 13 patients were regarded as cases of acquired immunodeficiency syndrome (AIDS). Only one patient had concurrent HIV infection and multiple myeloma. The distribution of serogroups of NTS isolates was in the order of group B (40.2%), group D (30.9%), group C (26.5%), and group E (1.5%). Meanwhile, the majority (81.5%) of serogroup C isolates belonged to serovar Choleraesuis.

Up to 73.5% of patients presented with fever at admission and only 12.2% had gastroenteritis symptoms. About one-fourth (27%) of patients experienced a shock episode and 31.4% had acute renal failure at the onset of NTS bacteremic events. Generally, primary bacteremia without obvious infectious focus was reported, accounting for 67.6% of patients. Among those with extraintestinal focal infections, 26 (39.4%) patients had invasive endovascular infections as the most common extraintestinal infection followed by pleuropulmonary infections (17, 25.8%) and spinal osteomyelitis (6, 9.1%).

In the present study, 144 (70.6%) of 204 patients have been empirically treated by appropriate antimicrobial agents, such as third-generation cephalosporins, fourth-generation cephalosporins, or fluoroquinolones, according to the in vitro susceptibility data.

Mortality among patients with NTS bacteremia

Overall, 53 (26.0%) patients died during hospitalization and 27 (13.2%) could not survive for 14 days. Univariate analysis showed that several variables associated with in-hospital mortality included old age (p < 0.007), congestive heart failure (p = 0.003), connective tissue diseases (p = 0.022), malignancy (p < 0.001), absence of fever (p = 0.001), gastroenteritis symptoms (p = 0.001), shock (p < 0.001), leukocytosis (p = 0.036), thrombocytopenia (p = 0.004), acute renal failure (p < 0.001), and presence of extraintestinal infections (p < 0.001), as shown in Table 2. However, multivariate logistic regression analysis revealed that only shock (adjusted odds ratio [aOR] 9.13; 95% CI 3.81–21.83; p < 0.001), malignancy (aOR 8.42; 95% CI 3.12–22.71; p < 0.001), and acute renal failure (aOR 2.63; 95% CI 1.11–6.22; p = 0.028), were independently associated with in-hospital mortality. As for clinical manifestations, mycotic aneurysm, the most common extraintestinal infection, has shown a borderline significance (p = 0.080) in association with in-hospital mortality rates (Table 3).

Differences of clinical characteristics between NTS bacteremic patients with and without malignancy

The comparison of clinical characteristics between patients with malignancy and without malignancy is shown in Table 1. Patients with malignancy were less likely to have hypertension (p = 0.001), connective tissue disease (p < 0.001), and HIV infection (p = 0.034), but more likely to have liver cirrhosis (p = 0.023). Concerning initial clinical presentations, leukopenia and thrombocytopenia were present more often in patients with malignancy (p = 0.009 and 0.034, respectively). However, patients with malignancy had less extraintestinal infections (p = 0.005), including invasive endovascular infections (p = 0.002), serogroup C bacteremia (p = 0.013), and especially serovar Choleraesuis (p = 0.005).

Mortality among patients with malignancy and NTS bacteremia

An elevated in-hospital mortality rate was noted in patients with malignancy compared to 130 patients without malignancy, (40.5%, 30/ 74 vs. 17.7%, 23/130; p < 0.001). The Cox proportional hazard model was applied after adjusting for confounding variables of age, gender, shock, and acute renal failure. The survival rate of patients with NTS bacteremia and malignancy compared to those without malignancy was significantly different (p = 0.02), with a relative hazard of death of 2.08 (95% CI, 1.11–3.88) (Fig. 1).

Absence of fever (p = 0.024) or shock (p < 0.001) and the presence of extra-intestinal infections (p = 0.021) were significant risk factors associated with unfavorable outcomes in patients with malignancy complicated with NTS bacteremia in the univariate analysis. Active status of
cancer, appropriate antimicrobial therapy within 72 hours, or anti-neoplastic treatment one month prior to the bacteremic episode, was not related to in-hospital mortality for this patient group. Multivariate logistic regression analysis revealed shock as the only independent factor associated with in-hospital mortality (aOR 7.52; 95% CI, 2.38–23.80; p < 0.001).

Discussion

Malignancy is a common underlying medical condition in patients with NTS bacteremia in previous reports and in our study. Prior to this study, the association of malignancy and mortality in patients with NTS bacteremia was rarely described. On the basis of univariate analysis, a higher mortality rate was seen in patients with underlying congestive heart failure and malignancy, especially with solid organ tumor(s). Multivariate analysis revealed that only malignancy is a significant predictor for in-hospital mortality. In our study, patients with malignancy had a worse prognosis than those without malignancy (40.5% vs. 17.7%, p < 0.001).

The leading pathogens for bacteremia were Escherichia coli, followed by Klebsiella pneumoniae and Pseudomonas species, while Salmonella bacteremia remained a low incidence. Whether underlying malignancy adversely affects the clinical outcome of patients with bacteremia...
Non-typhoidal *Salmonella* bacteremia and malignancy

is controversial. In a study of *K pneumoniae* bacteremia, malignancy served as an independent variable for mortality.22 Conversely, some studies failed to identify malignancy as an independent risk factor for mortality in patients with *K pneumoniae*23 or *Pseudomonas aeruginosa*20 bacteremia. In the present study, malignancy was significantly associated with mortality in patients with NTS bacteremia. Such an unfavorable outcome might be multifactorial and difficult to define in the present study of retrospective characteristics but could potentially be related to underlying malignant diseases, anti-neoplastic treatment, or NTS septicemia itself.

The prevalence of NTS species varies in different areas. In a study conducted in Malaysia, which included 55 cases of NTS bacteremia, serogroup D was most common and demonstrated the highest blood invasiveness.8 A study in Taiwan demonstrated a high prevalence of serogroups B and C17 while another study in Thailand reported

### Table 2 Univariable analysis of risk factors of mortality among patients with non-typhoidal *Salmonella* bacteremia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Fatal (n = 53)</th>
<th>Surviving (n = 151)</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (standard deviation; range), y</td>
<td>64.2 (15.3; 19-98)</td>
<td>56.4 (18.9; 19-98)</td>
<td>1.06</td>
<td>0.56–2.01</td>
<td>0.873</td>
</tr>
<tr>
<td>Male gender</td>
<td>32 (60.4)</td>
<td>89 (58.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comorbidities**

- Immunosuppressive therapy: 20 (37.7) | 52 (34.4) | 1.12 | 0.60–2.21 | 0.739 |
- Diabetes mellitus: 14 (26.4) | 47 (51.1) | 0.79 | 0.39–1.60 | 0.602 |
- Chronic kidney diseases: 17 (32.1) | 43 (28.5) | 1.19 | 0.60–2.33 | 0.607 |
- Hypertension: 18 (34.0) | 51 (33.8) | 1.01 | 0.52–1.95 | 1.000 |
- Liver cirrhosis: 10 (18.9) | 14 (9.3) | 2.28 | 0.94–5.49 | 0.082 |
- Coronary artery diseases: 8 (15.1) | 12 (7.9) | 2.06 | 0.79–5.36 | 0.177 |
- Congestive heart failure: 12 (22.6) | 10 (6.6) | 4.13 | 1.66–10.24 | 0.003 |
- Chronic lung diseases: 5 (9.4) | 15 (9.9) | 0.94 | 0.33–2.74 | 1.000 |
- Connective tissue diseases: 4 (7.5) | 33 (21.9) | 0.29 | 0.10–0.87 | 0.222 |
- Human immunodeficiency virus infection: 2 (3.8) | 11 (7.3) | 0.50 | 0.11–2.33 | 0.521 |

**Clinical presentations at bacteremic onset**

- Fever: 30 (56.6) | 120 (79.5) | 0.32 | 0.16–0.62 | 0.001 |
- Gastroenteritis symptoms: 27 (50.9) | 38 (25.2) | 3.09 | 1.61–5.93 | 0.001 |
- Shock: 35 (66.0) | 20 (13.2) | 12.74 | 6.09–26.64 | <0.001 |
- Leukocytosis: 30 (56.6) | 59 (39.1) | 2.03 | 1.08–3.83 | 0.036 |
- Leukopenia: 10 (18.9) | 20 (13.2) | 1.52 | 0.66–3.51 | 0.368 |
- Thrombocytopenia: 23 (43.3) | 33 (21.9) | 2.74 | 1.41–5.34 | 0.004 |
- Acute renal failure: 30 (56.6) | 34 (22.5) | 4.49 | 2.31–8.72 | <0.001 |
- Extra-intestinal infections: 28 (52.8) | 38 (25.2) | 3.33 | 1.73–6.40 | <0.001 |
- Mycotic aneurysm: 13 (24.5) | 12 (7.9) | 3.77 | 1.59–8.90 | 0.003 |
- Pleuropulmonary infections: 5 (9.4) | 12 (7.9) | 1.21 | 0.40–3.6 | 0.774 |

### Table 3 Multivariable analysis of factors associated with in-hospital mortality determined by stepwise logistic regression analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted odds ratioa</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>9.13</td>
<td>3.81–21.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8.42</td>
<td>3.12–22.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
<td>3.30</td>
<td>0.87–12.53</td>
<td>0.080</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2.63</td>
<td>1.11–6.22</td>
<td>0.028</td>
</tr>
<tr>
<td>Extraintestinal infections</td>
<td>2.51</td>
<td>0.89–7.08</td>
<td>0.083</td>
</tr>
</tbody>
</table>

a Adjusted variables include underlying liver cirrhosis, congestive heart failure, connective tissue disease, the presence of fever, gastrointestinal symptoms, leukocytosis, and thrombocytopenia.
a predominance of serogroup C among NTS bacteremic patients.\textsuperscript{11,24} We found peculiar trends in serogroups in the 10-year period of this study. Decreasing proportions of \textit{Salmonella Choleraesuis} and increasing proportions of \textit{Salmonella} serogroup D could be detected. \textit{S Choleraesuis} was less frequently found in patients with malignancy than in patients without malignancy (10.8% vs. 27.7%, \textit{p} = 0.005). \textit{S Choleraesuis} has been reported to cause invasive extraintestinal infections in humans.\textsuperscript{15,26} Patients with solid-organ tumor(s) are considered less likely to develop endovascular infections,\textsuperscript{13} as noted in the present study. In addition to a possible explanation that patients with malignancy are regularly cared for in hospitals and more likely to seek medical advice if feeling sick, fewer \textit{S Choleraesuis} infections may contribute to a reduced number of endovascular infections.

Previous reports have demonstrated that \textit{S Choleraesuis} was more resistant to certain antimicrobials than serogroup B or D isolates in Taiwan.\textsuperscript{6,27} Up to 70% of \textit{S Choleraesuis} isolates were resistant to fluoroquinolones.\textsuperscript{15} Thus, fluoroquinolones might not be used empirically for invasive salmonellosis in Taiwan unless these drugs can be proven to be \textit{in vitro} active against the causative \textit{Salmonella} isolates. A multistate study conducted in the United States from 1996–2007 reported that 2.5% of invasive \textit{S enterica} isolates were resistant to ceftriaxone.\textsuperscript{28} On the other hand, cefepime and carbapenem remain active against non-typhoid \textit{Salmonella} isolates from Taiwan.\textsuperscript{6} Therefore, appropriate antimicrobial agents should be prescribed according to local susceptibility data for severe NTS infections, such as invasive endovascular infections.

NTS \textit{Salmonella} infections in healthy younger adults might be self-limited without requiring routine antimicrobial treatment. However, among patients with an immunocompromised condition such as malignancy, \textit{Salmonella} infections could be fatal, as compared with immunocompetent patients. Since the acquisition of \textit{Salmonella} species is mainly from contaminated food products associated with certain animals (e.g., chicken and pigs), healthcare providers should advise patients with malignancy not to eat raw or undercooked eggs, meat, poultry, and unpasteurized dairy products. Once the diagnosis of \textit{Salmonella} bacteremia is suspected or confirmed, aggressive antimicrobial treatment should be undertaken, especially in patients with malignancy.

Our study had some limitations. Because this study was retrospective and with limited information obtained from medical records, the mortality directly related to sepsis was difficult define. In addition, antimicrobial minimal inhibitory concentration (MIC) studies or serovars of bacteremic NTS isolates were not routinely performed. However, \textit{in vitro} disk diffusion tests following the recommendations of Clinical Laboratory Standard Institute (CLSI) were completed. Finally, the extent of immunocompromisation posed by underlying malignancy was heterogeneous and not able to be qualified for various types of malignancy. Thus, underlying malignancy for each patient may contribute variably to the clinical outcome.

In conclusion, malignancy is a variable associated with an unfavorable outcome in patients with NTS bacteremia. Therefore, patients with malignancy and with suspected or documented NTS bacteremia should receive antimicrobial treatment as soon as possible. Also, food hygiene is critical for preventing severe NTS infections in immunocompromised patients.

References


