Non-typhoidal *Salmonella* bacteraemia in elderly patients: an increased risk for endovascular infections, osteomyelitis and mortality

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SUMMARY

Non-typhoidal *Salmonella* (NTS) is a common pathogen causing foodborne infections, bacteraemia, and extra-intestinal focal infections (EFIs) in humans. The study compares the clinical characteristics of elderly patients with NTS bacteraemia with those of young adults. Of 272 adults with NTS bacteraemia identified in this study, 162 (59·6%) were aged $\geqslant$55 years. EFIs were observed in 36% of the 162 patients. The most common EFIs in the elderly patients ($\geqslant$55 years) was mycotic aneurysm, followed by pulmonary infections and bone/joint infections. Elderly patients more often had chronic heart, lung, renal and malignant diseases, had more EFIs, and a higher 30-day mortality rate. Independent factors of 30-day mortality in elderly patients were solid-organ tumour [adjusted odds ratio (aOR) 4·4, $P = 0·003$], mycotic aneurysm (aOR 3·7, $P = 0·023$) and shock (aOR 12·1, $P < 0·0001$). HIV infection, autoimmune diseases, and receipt of immunosuppressive therapy were more often observed in young patients.

Key words: Elderly, extra-intestinal focal infection, non-typhoidal *Salmonella* bacteraemia.

INTRODUCTION

Non-typhoidal *Salmonella* (NTS) is a common pathogen causing foodborne infections in humans. Although most patients with NTS infection have self-limiting gastroenteritis, some patients develop invasive NTS infections, such as bacteraemia and extra-intestinal focal infections (EFIs) [1–3]. Invasive NTS infections can be life-threatening, and usually affect infants, the elderly and immunocompromised persons [4]. In the USA, 22% of patients with *Salmonella* infections required hospitalization, while the hospitalization rate in the elderly (>60 years) with NTS infection was even higher [5]. In a population-based study performed in Denmark, Gradel *et al.* found that the incidence rate of NTS bacteraemia increased steadily from age groups 40–49 years to >90 years [6]. Not surprisingly, elderly patients with

Salmonella infection had a higher mortality rate than children and young adults, because of multiple comorbidity [5, 7, 8]. However, previous studies have rarely investigated clinical characteristics of the elderly with NTS bacteraemia, their risk factors of mortality, or the differences of clinical presentations between elderly and young patients. Our study aims to delineate clinical characteristics and outcomes of the elderly with NTS bacteraemia, compared to young adults.

MATERIAL AND METHODS

A retrospective study was conducted between January 1996 and December 2008 at a university hospital, a medical centre with about 1000 beds in southern Taiwan. Patients aged ⩾18 years with NTS isolated from blood cultures were included. For patients with recurrent NTS bacteraemia, only the first episode was included for analysis. Medical charts of these patients were reviewed for demographic characteristics, underlying diseases, clinical presentations, laboratory data upon admission, length of hospital stay, and clinical outcome. The study was approved by the Institutional Review Board (ER-99-093) at the study hospital. Details of a portion of the study subjects from 1999 to 2006 had been analysed and published previously [2].

Definitions

An EFI was defined by the presence of clinical or radiological evidences of any infectious focus other than the gastrointestinal tract, or the isolation of the identical organism from clinical specimens other than bloodstream or faeces, coincident with NTS bacteraemia. Fever was defined as an axillary temperature of at least 38 °C. Renal insufficiency was determined as a serum creatinine of at least 1·5 mg/dl, and acute renal failure as a ⩾twofold increase of the baseline level in serum creatinine. Diagnosis of liver cirrhosis was retrieved from the medical records based on the discharge diagnosis by clinicians. Atherosclerotic conditions were defined as the presence of atherosclerotic diseases such as previous ischaemic stroke, ischaemic heart disease, or peripheral arterial occlusive disease [9]. Immunosuppressive therapy included the receipt of corticosteroids, i.e. prednisolone ⩾10 mg/day or equivalent dosage, chemotherapy for malignancy, or immunosuppressive agents for organ transplantation, within 2 weeks prior to the onset of NTS bacteraemia.

Shock was defined as a systolic blood pressure <90 mmHg, or an unstable haemodynamic condition requiring inotropic agents to maintain blood pressure. Leukopenia and leukocytosis were white blood cell counts <4000 and >10 000/mm³, respectively. Antimicrobial therapy was considered to be appropriate, if the *Salmonella* isolate was susceptible *in vitro* to a drug administered within 3 days after bacteraemia onset.

Microbiology and antimicrobial susceptibility

All blood isolates were cultured and identified according to standard methods [10]. The serogroup of *Salmonella* isolates was determined by methods described elsewhere [2]. Antimicrobial susceptibilities of NTS isolates were determined by the disk-diffusion method and the interpretations of susceptibility data followed the criteria of the Clinical and Laboratory Standards Institute [11].

Statistical analysis

Statistical analysis was performed to compare the differences of variables between elderly and young adults with SPSS v. 15.0 (SPSS Inc., USA). The variables associated with 30-day mortality in elderly patients were also studied. Continuous variables were expressed as medians and interquartile ranges (IQR), and compared using the Mann–Whitney test. Categorical variables, expressed as numbers and percentages, were compared using χ^2 or Fisher's exact tests. Stepwise logistic regression was used for multivariate analysis. Variables with a *P* value ⩽0·1 were selected for the analysis in the model. The trend test was performed to examine the relationship between increasing age and the prevalence of NTS infections based on the Cochran–Armitage trend test.

RESULTS

The development of EFI in different age groups

During the 13-year study period, 272 adults (⩾18 years) with NTS bacteraemia were included for analysis. Males predominated (58·5%, age range 19–98 years), with a median age of 63 years (IQR, 45–72 years). About 60% (162) of the patients were aged ⩾55 years. The median hospital stay was 15 days (IQR 7–27 days). Thirty-day mortality rate was 19·1%. A total of 83 (30·5%) patients developed

Table 1. *Serogroups and extra-intestinal focal infections in patients aged ⩾55 years with non-typhoidal* Salmonella *bacteraemia*

| Focal infections	Case number (%)		
	B ($n=78$)	Choleraesuis ($n=33$)	D ($n=40$)
Extra-intestinal focal infections	27 (34·6)	21 (63·6)	14 (35·0)
Mycotic aneurysm	12 (15·4)	11 (33·3)	7 (17·5)
Other than mycotic anuerysm	15 (19·2)	10 (30·3)	7 (17·5)
Intra-abdominal infection	7 (9·0)	—	—
Liver abscess	2 (2·6)	—	—
Spleen abscess	2 (2·6)	—	—
Spontaneous bacterial peritonitis	2 (2·6)	—	—
Cholecystitis	1 (1·3)	—	—
Bone and joint infection	3 (3·8)	7 (21·2)	1 (2·5)
Spinal osteomyelitis	2 (2·6)	7 (21·2)	1 (2·5)
Septic arthritis	1 (3·7)	—	—
Pneumonia/empyema	2/2 (2·6/2·6)	2/– (6·1/–)	5/– (12·5/–)
Cellulitis	—	—	1 (2·5)
Anal fistula	—	1 (3·0)	—
Infective endocarditis	1 (1·3)	—	—
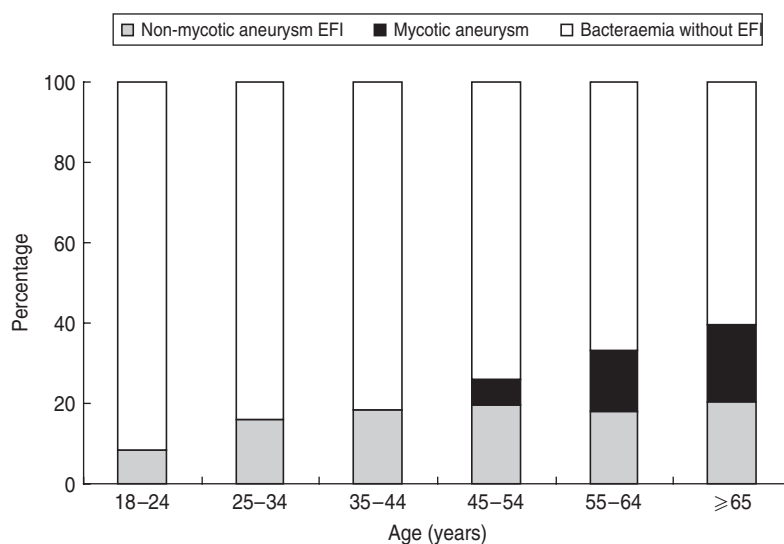
Fig. 1. Percentages of extra-intestinal focal infections (EFIs) by age groups in adults with non-typhoidal *Salmonella* bacteraemia. The prevalence of mycotic aneurysm increased with age ($P < 0.0001$), but the trend in the development of EFIs other than mycotic aneurysm over age was not significant ($P = 0.38$).

EFIs. The percentages of EFIs increased with age (Fig. 1). Of note, mycotic aneurysm developed exclusively in patients aged >45 years, and the rates of mycotic aneurysm increased with the age of patients with NTS bacteraemia ($P < 0.0001$). The highest percentage (19·5%) of mycotic aneurysm was observed in patients aged ⩾65 years. However, the percentage of non-mycotic aneurysm EFIs did not change with increasing age ($P = 0.38$).

Characteristics of EFIs in the elderly

The most common serogroups of NTS bacteraemic isolates in the elderly were serogroups B (78, 48·1%), D (40, 24·7%) and Choleraesuis (33, 20·4%), which were similar in young (<55 years) and elderly (⩾55 years) patients. Serogroups and sites of EFIs in 62 patients aged ⩾55 years with NTS bacteraemia are summarized in the Table 1. The rate of EFIs in

patients with *S.* Choleraesuis bacteraemia was 63·6%, which was higher than those with serogroups B and D bacteraemia ($P = 0.012$). Mycotic aneurysm was the most common EFI, accounting for 30/62 (48·4%) patients with EFI. Similarly, patients with *S.* Choleraesuis bacteraemia had an increased trend to develop mycotic aneurysm than those with other serogroups ($P = 0.087$). The locations of aneurysms were abdominal aorta (60·5%), thoracic aorta (31·6%) and ilio-femoral artery (7·9%). Other EFIs included bone and joint infections (11, 17·7%), pneumonia/empyema (11, 17·7%), liver abscess (two, 3·2%), splenic abscess (two, 3·2%), spontaneous bacterial peritonitis (SBP; two, 3·2%), cellulitis (one, 1·6%), anal fistula (one, 1·6%), cholecystitis (one, 1·6%), and infective endocarditis (one, 1·6%). Interestingly, most bone and joint infections were spinal osteomyelitis (10/11 patients), with the other infection being septic hip arthritis. Overall, four of these patients died despite adequate antibiotic treatment with or without surgical therapy. Of 11 patients with pleuropulmonary infections, two with underlying malignancy and recent immunosuppressive therapy died of pulmonary empyema. Three out of seven patients with intra-abdominal infections died (two SBP, one liver abscess).

Clinical features of the elderly patients with NTS bacteraemia

Most elderly patients (152/162, 93·8%) aged ⩾55 years had at least one underlying disease. Compared to young adults, the percentages of diabetes mellitus, hypertension, ischaemic stroke, coronary arterial disease, chronic lung diseases, congestive heart failure, and renal insufficiency were significantly higher in elderly patients, while those of HIV infection, autoimmune diseases and those receiving immunosuppressive therapy were lower (Table 2). The elderly were often complicated with mycotic aneurysm, less likely to have fever but more likely to develop shock or leukocytosis at initial presentation, have a longer duration of hospitalization, and a higher 30-day mortality rate.

Variables associated with 30-day mortality in elderly patients

A total of 162 patients aged ⩾55 years were included for analysis of the factors associated with 30-day outcome (one missing follow-up due to transfer to another hospital). Underlying diseases with congestive heart failure or malignant solid tumour and the development of shock status, acute renal failure, or mycotic aneurysm, were significantly associated with 30-day mortality in elderly patients with NTS bacteraemia according to univariate analysis. In multiple-logistic regression analysis, malignant solid tumour, the presence of mycotic aneurysm or shock was independently associated with 30-day mortality in the ⩾55 years age group (Table 3).

Antimicrobial susceptibility of NTS blood isolates

In NTS strains from elderly patients aged ⩾55 years, the susceptibility rate to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole was 50%, 50·6%, and 75·7%, respectively. More than 90% (145/160) of isolates were susceptible to ciprofloxacin, while 65·9% (85/129) were susceptible to nalidixic acid, the prototype of fluoroquinolones. Very few isolates were resistant to ceftriaxone or cefotaxime and cefepime, accounting for <1% of all isolates tested. All tested isolates were susceptible to imipenem or meropenem. Overall, the resistance profiles of NTS isolates from young adults or the elderly were similar.

DISCUSSION

In the present study, EFIs were observed in 38·3% of elderly patients (aged ⩾55 years) with NTS bacteraemia. Half of EFIs were mycotic aneurysms, which were regarded as one of the lethal complications of *Salmonella* bacteraemia. The probability of developing an EFI, especially mycotic aneurysm, increases with age. Such a trend has been seen in previous reports. Fernandez Guerrero *et al.* reported that the risk of endovascular infections in patients aged >60 years with NTS bacteraemia was 23% [12]. Other studies have shown that 10–17% of patients with NTS bacteraemia had mycotic aneurysm and most affected patients were aged >50 years [9, 13]. Another population-based study of NTS bacteraemia within a decade in Denmark also reported that 9% of patients aged >50 years had mycotic aneurysm [14]. Ageing has been well known to be associated with atherosclerosis, which is an important risk factor of developing aortic aneurysm [15, 16]. In addition, the most common Gram-negative pathogen causing aortic aneurysms was NTS, which accounted for 35% of cases [17], and ranked second to *Staphylococcus aureus* among the causative pathogens [18].

Table 2. *Comparisons of clinical characteristics between elderly (aged ⩾55 years) and young patients with non-typhoidal* Salmonella *bacteraemia*

Clinical characteristics	Case number (%)		
	Young patients (n = 110)	Elderly (n = 162)	P value
Age (median, IQR)	42 (30–50)	70·5 (65–75)	<0·0001
Sex, male	69 (62·7)	90 (55·6)	0·24
Extraintestinal focal infections (EFIs)	21 (19·1)	62 (38·3)	<0·0001
EFI other than mycotic aneurysm	19 (17·3)	32 (19·8)	
Mycotic aneurysm	3 (2·7)	30 (18·5)	
Appropriate antimicrobial therapy	64 (58·2)	107 (66·0)	0·23
Underlying diseases			
Immunosuppressive therapy	51 (46·4)	41 (25·3)	<0·0001
Diabetes mellitus	23 (20·9)	58 (35·8)	0·008
Hypertension	17 (15·5)	70 (43·2)	<0·0001
Atherosclerotic diseases	5 (4·5)	41 (25·3)	<0·0001
Ischaemic stroke	1 (0·9)	15 (9·3)	0·004
Coronary arterial disease	1 (0·9)	25 (15·4)	<0·0001
Peripheral arterial occlusive disease	3 (2·7)	3 (1·9)	0·688
Autoimmune disease	32 (29·1)	12 (7·4)	<0·0001
Renal insufficiency	25 (22·7)	59 (36·4)	0·02
HIV infection	17 (15·5)	0	<0·0001
Solid malignant tumour	15 (13·6)	44 (27·2)	0·008
Liver cirrhosis	12 (10·9)	22 (13·6)	0·51
Congestive heart failure	3 (2·7)	24 (14·8)	0·001
Chronic lung disease	1 (0·9)	24 (14·8)	<0·0001
Clinical presentations			
Fever	95 (86·4)	104 (64·2)	<0·0001
Leukocytosis	39 (35·5)	84 (51·9)	0·008
Thrombocytopenia	28 (25·5)	51 (31·5)	0·28
Leukopenia	25 (22·7)	14 (8·6)	0·001
Shock	19 (17·3)	53 (32·7)	0·005
Diarrhoea	16 (14·5)	36 (22·2)	0·11
Hospital days of survivors (median, IQR)	11 (6·3–22)	17 (10–29)	0·002
30-day mortality rate	12/106 (11·3)	39/161 (24·2)	0·009

IQR, Interquartile range.

In addition, NTS has a greater propensity to cause early aneurysm rupture than other species [19]. Six weeks of intravenous antimicrobials followed by prolonged oral therapy is recommended to treat documented or suspected NTS endovascular infections.

Although the prevalence of other non-mycotic aneurysm EFIs were steady over the various age groups, the disease spectrums of NTS EFIs in young and elderly adults were quite different. For example, spinal osteomyelitis occurred exclusively in older patients. There were some special features in our patients with NTS-related osteomyelitis. First, previous studies reported that *Salmonella* osteomyelitis usually occurred in young patients with sickle cell disease [20], but none of our patients had sickle cell disease. Second, *Salmonella* bone and joint infections in patients without sickle cell disease were uncommon, and spinal infection was rarely reported [21, 22]. A review on clinical features of *Salmonella* vertebral osteomyelitis found that the extreme of ages, male preponderance, lumbar involvement, and monomicrobial nature of infections are similar to those of pyogenic spinal infections caused by other pathogens

Table 3. *Multivariate analysis of host factors associated with 30-day mortality in 161 patients aged ⩾55 years with non-typhoidal* Salmonella *bacteraemia*

Host factors	Adjusted OR	95% CI	P value
Shock	12·1	4·9–29·6	<0·0001
Mycotic aneurysm	3·7	1·2–11·1	0·023
Malignant solid tumour	4·4	1·6–11·9	0·003
Congestive heart failure	1·6	0·5–5·2	0·424
Acute renal failure	1·1	0·4–2·8	0·882
Fever	0·9	0·4–2·4	0·899

OR, Odds ratio; CI, confidence interval.

[23]. Elderly patients usually had degenerated joint disc disease and haematogenous spread of *Salmonella* isolates may seed the injured sites [24]. Moreover, the elderly are at a high risk of suffering frequent falls, which may lead to trauma of spine and bacterial seeding.

In our study, pulmonary infections are one of common EFIs in elderly patients. Of 11 patients with pulmonary infection two died of pulmonary empyema, both having underlying malignant diseases under immunosuppressive therapy. Pulmonary infection caused by *Salmonella* is rare and has been reported in patients with underlying pulmonary disease and immunosuppressed status, such as HIV infection, malignancy or with immunosuppressive therapy [25–27]. In a Spanish report of pulmonary NTS infection, most cases were aged >60 years, and had a grave prognosis with a mortality rate of 63% [26]. Therefore, NTS should be considered as a possible pathogen which could cause fatal pulmonary infection in elderly patients with immunosuppressed diseases.

Increased prevalence of comorbid diseases have been observed in elderly persons [6, 28]. However, the spectrum of underlying diseases was different from the young comparators in our study. The rates of atherosclerosis, congestive heart failure, renal disease, and solid malignancy increased significantly in elderly patients. On the contrary, autoimmune diseases, patients receiving immunosuppressants and HIV disease were more common in young patients. HIV-infected adults have an increased risk for acquiring NTS infection [29], and their ages of developing NTS bacteraemia are usually between 30 and 50 years [5]. Several studies indicate that HIV infection will induce early immune senescence [30, 31], which is similar in

the elderly, such as a decline of T-cell numbers and function, disruption of the gastroenteral barrier and persistent inflammatory status [32–35].

As mentioned in previous studies, malignancy has been one of the leading predisposing diseases in patients with NTS bacteraemia [9]. Solid-organ malignancy has been reported as an independent predictor for in-hospital death in patients with NTS bacteraemia in a previous Taiwanese study [36]. Patients with malignancy probably have unfavourable outcome resulting from therapies for neoplasm, or NTS septicaemia itself. As NTS infections could be a fatal disease in elderly patients with underlying malignancy, aggressive antimicrobial treatment should be undertaken once the diagnosis of NTS bacteraemia is suspected or proved.

Antimicrobial susceptibility of NTS isolates in our hospital decreased in ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, the so-called first-line antibiotics for *Salmonella* infection. Although the susceptible rate of ciprofloxacin was 90·6%, the resistance rate of nalidixic acid reached 34·1%. Previous studies have shown that infections due to salmonellae with reduced susceptibility to fluoroquinolones may not respond satisfactorily to therapy with ciprofloxacin [37]. Therefore, resistance to nalixidic acid precludes the use of fluoroquinolones for invasive NTS infection. Almost all the NTS strains were susceptible to ceftriaxone or cefotaxime, cefepime and carbapenems. In view of the high resistance, third-generation cephalosporins should be the empirical antimicrobials for invasive NTS infections, unless fluoroquinolones can be proven to be active *in vitro*.

There are several limitations to our study. First, the data analysed in this study were based on retrospective cohorts in a single medical centre, which is prone to certain degrees of selection bias. However, the present study delineated different views of NTS EFIs between young and elderly adults. Second, the prevalence of NTS EFIs might be underestimated since only 27·7% of adult patients with NTS bacteraemia had ever been examined by computed tomography to assess deep-seated abscess or vascular infections (Dr P. L. Chen, unpublished data). A large-scale study and examination to survey the NTS infections in Taiwan is warranted. Third, the long-term outcome of NTS infection on survival was not evaluated. Nevertheless, our study still provided the information that NTS infections would be fatal, at least during short-term (30-day) follow-up.

Aggressive antimicrobial treatment and long-term follow-up for these patients are necessary.

CONCLUSIONS

NTS bacteraemia in elderly patients was usually complicated with EFIs, especially mycotic aneurysm and osteomyelitis. Detailed evaluation of EFIs in elderly patients with NTS bacteraemia is necessary and will promote timely surgical and medical therapy for such a life-threatening complication.

ACKNOWLEDGEMENTS

DECLARATION OF INTEREST

None.

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