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ORIGINAL ARTICLE

Time to positivity in blood cultures of adults with nontyphoidal *Salmonella* bacteremia

Hui-Wen Lin [a], Hsin-Sui Hsu [a], Yu-Tsung Huang [a], Chia-Jui Yang [a], Meng-Shiuan Hsu [a], Chun-Hsing Liao [a,b,*]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[b] *School of Medicine, National Yang Ming University, Taipei, Taiwan*

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Background: Nontyphoidal *Salmonella* (NTS) is an important bacterial etiology of diarrheal disease, and it causes invasive diseases in immunocompromised hosts. For bacteremia from some species, blood culture with a rapid time to positivity (TTP) is associated with greater mortality. This study investigated TTP of NTS bacteremia and its relationship to clinical parameters and prognosis.
Methods: Adult patients with NTS bacteremia who were admitted to a tertiary care facility in northern Taiwan from January 2010 to December 2012 were enrolled. Demographics, clinical and microbiological characteristics, and treatment response were reviewed. The TTP for each patient was retrieved from the automated machine.
Results: Sixty-six adult patients (mean age, 66.1 years; range, 27–96 years) with NTS bacteremia were identified by the following serogroup distributions: serogroup B (23.4%), serogroup C1 (1.6%), serogroup C2 (6.3%), and serogroup D (68.8%). The in-hospital mortality, 14-day mortality, and 30-day mortality were 15.2%, 7.6%, and 12.1%, respectively. The TTP ranged 6.5–41.7 hours (median: 11.5 hours). Patients with rapid TTP (less than 10 hours), compared to patients without rapid TTP, were more likely to have liver cirrhosis (31.6% vs. 6.4%, $p = 0.013$), endovascular lesions (21.1% vs. 4.3%, $p = 0.05$), higher bacteremia score, intensive care unit admission (57.9% vs. 25.5%, $p = 0.021$), and septic shock (63.2% vs. 12.8%, $p < 0.001$). There were no significant differences in the in-hospital mortality and 14-day mortality between patients with TTP <10 hours and patients with TTP ≥ 10 hours.
Conclusion: The TTP of blood cultures, interpreted with a cut-off point of <10 hours, in patients with NTS bacteremia may provide useful diagnostic and prognostic information.

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Far Eastern Memorial Hospital, Number 21, Section 2, Nan-Ya South Road, Pan-Chiao District, New Taipei City 220, Taiwan.
E-mail address: liaochunhsing@gmail.com (C.-H. Liao).

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Introduction

Nontyphoidal *Salmonella* (NTS), a cause of food-borne infections, is an important bacterial etiology of diarrheal disease. Most patients with NTS infections have self-limited gastroenteritis, although invasive disease with bacteremia occurs in 3—8% of patients.[1] A nontyphoidal *Salmonella* infection may also manifest as an extraintestinal infection such as endovascular infection, meningitis, pneumonia, septic arthritis, or osteomyelitis, either as a primary infectious focus or secondary to primary bacteremia.[2,3]

Numerous factors affect the incidence of bacteremia such as *Salmonella* serotype, geographic location, season, and patient characteristics. Previous studies report that several patient characteristics increase the risk of salmonellosis such as extreme age of being in a chronic or immunosuppressed state due to malignancy, rheumatological disease, tumor necrosis factor (TNF) blockade, human immunodeficiency virus (HIV) infection, or congenital immune defects.[4—8] A study in Taiwan reported that solid organ malignancy, age, and extraintestinal infection were independent predictors for in-hospital death among patients with NTS bacteremia.[9]

A previous study suggested that the severity of Gram-negative bacilli bacteremia, as determined by quantitative blood culture, may be correlated with mortality.[10] However, quantitative blood cultures are not performed routinely in clinical practice. Time to positivity (TTP) for a given microorganism, as assessed by automated blood culture processing devices, depends on the bacterial inoculum,[11] which may be influenced by the source of infection, the presence of antimicrobial agents,[12] and the patient's clinical characteristics.

Previous studies have shown that a rapid TTP is associated with a significantly greater mortality risk in patients infected with *Staphylococcus aureus*[13,14] and *Klebsiella pneumoniae* bacteremia.[15] Rapid TTP is also an independent predictor of fatal outcome in patients with diverse-source *Escherichia coli* bacteremia,[16] and it is a marker of severe sepsis or shock and meningitis in individuals with bacteremia caused by *Streptococcus pneumoniae*.[17] However, TTP and the variables associated with it have only been evaluated for a limited number of bacterial species. There is little information regarding the association of TTP with clinical parameters in patients with *Salmonella* bacteremia.[18,19] The present study accordingly investigated the TTP in patients with NTS bacteremia and the relationship of TTP with clinical parameters and prognosis.

Materials and methods

Setting and patients

This study was conducted at the Far Eastern Memorial Hospital, a 1040-bed tertiary care facility in northern Taiwan (New Taipei City). The methodology of the study followed the previous work of the corresponding author as a model.[15] From January 2010 to December 2012, patients with NTS bacteremia were identified by central laboratory personnel. Enrolled patients were diagnosed as having NTS bacteremia. The TTP for each patient was retrieved from the hospital's automated blood culture instrument (see the "TTP of blood cultures" section later). Each patient was included only once, at the time of the first bacteremia. Patients younger than 20 years, patients with polymicrobial bacteremia, and patients who were not admitted to the hospital were excluded. The following data were recorded for each patient: age, sex, underlying illness and associated Charlson Comorbidity Index,[20] location of care in the hospital, and severity of bacteremia, as determined by the Pittsburgh bacteremia score.[21] The primary outcome measure was the association of TTP with in-hospital mortality. Secondary analyses determined the associations between TTP with age, underlying diseases, severity of illness, source of infection, intensive care unit (ICU) admission, and 14-day and 30-day mortality.

TTP of blood cultures

Two sets of blood samples (10 mL each) were generally taken from separate locations, inoculated into aerobic and anaerobic culture flasks, and then incubated using the BACTEC 9240 automated detection blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). All bottles were loaded when they were received in the central laboratory. The BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems) continuously monitors carbon dioxide (CO_2) production every 10 minutes, and indicates positivity by a fluorescent signal. All positive blood samples were subcultured and bacterial isolates were identified, according to the BD Phoenix automated microbiology system and conventional biochemical methods.[22] Serogroups of *Salmonella* isolates were examined with O antisera using the slide agglutination method. Antimicrobial susceptibilities were determined using the disk-diffusion method. The interpretation of susceptibility data followed the criteria of the Clinical Laboratory Standard Institute (CLSI).[23] Isolates in the "intermediate" category were considered resistant.

The TTP, defined as the time from the start of incubation to the start of an alert signal (documented by the BACTEC 9240 system), was recorded for each blood culture. When multiple cultures were positive, the shortest TTP was used for analysis.

Definitions

The clinical course and primary site of infection were determined from information supplied by primary care physicians and medical records. The infection focus of bacteremia was determined clinically by the presence of an active infection site concomitant with NTS bacteremia, or by isolation of an identical organism from clinical specimens other than blood. A urinary tract infection (UTI) was defined as a positive urine culture and pyuria. Enteritis was defined as a positive stool culture and diarrhea. Intra-abdominal infection included all infections within the abdomen, except enteritis. If no infection focus could be identified, the bacteremia was classified as primary. Septic shock is identified in accordance with the Surviving Sepsis Campaign criteria.[24] The study population was divided into two groups: (1) patients with rapid TTP (less than10 hours) and (2) patients with slow TTP (10 hours or greater), based on the results of univariate analyses, which showed that a TTP cut-off

point of <10 hours had the highest odds ratio (OR) (TTP cut-off point = 9, OR = 1.78; cut-off point = 10, OR = 1.82; cut-off point = 11, OR = 1.63; cut-off point = 12, OR = 0.97).

Statistical analysis

The demographic and clinical characteristics of patients in the two groups were initially compared using univariate analysis. Continuous variables are expressed as the means ± the standard deviations and were compared using the Mann–Whitney test. Categorical variables are expressed as the number and percentage and were compared using the Chi-square test or the Fisher's exact test. Univariate analysis was used to assess the associations between risk factors and in-hospital mortality. Variables that were significant in the univariate analysis ($p < 0.1$) were then entered into a multivariate model. The ORs and corresponding 95% confidence intervals (CIs) were calculated. Cumulative survival after the day of blood sample collection until day 30 was calculated by the Kaplan–Meier method and the mortality rates of the two groups are shown. A value of $p < 0.05$ was significant. In addition, the potential factors associated with the 30-day mortality of patients with NTS bacteremia were examined by the Cox proportional hazards regression analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software for Windows (version 17.0; SPSS, Chicago, IL, USA).

Results

Study population and patient characteristics

There were 66 adult patients with clinically significant episodes of NTS bacteremia who were admitted to the Far Eastern Memorial Hospital during a 3-year study period. The mean age was 66.1 ± 15.9 years (age range, 27–96 years) and most patients were male (43/66, 65.1%). Diabetes mellitus was the most common underlying disease (21/66, 27.3%). The most frequent manifestation of NTS blood stream infection was primary bacteremia (45/66, 68.2%), followed by enteritis (11/66, 16.7%), and mycotic aneurysm (6/66, 9.1%). The distribution of serogroups of NTS isolates was (in descending order) as follows: serogroup D (68.8%), serogroup B (23.4%), serogroup C2 (6.3%), and serogroup C1 (1.6%). All NTS isolates were sensitive to third-generation cephalosporins, and only one isolate was resistant to ciprofloxacin. The in-hospital mortality rate was 15.2%, the 14-day mortality rate was 7.6%, and the 30-day mortality rate was 12.1%.

TTP of blood cultures

The median TTP was 11.5 hours (range, 6.5–41.7 hours; mean, 13.7 hours; standard deviation, 7.0 hours). The analysis of the different cut-off values indicated that a TTP cut-off of 10 hours yielded the best sensitivity and specificity for predicting the source and outcome of infection. The demographic information and associated clinical factors of the two TTP groups are summarized in Table 1 and Table 2, respectively. The rapid-TTP group (i.e., TTP < 10 hours) had significantly more severe illness, but the two groups had no significant differences in age, sex, type of infection, and NTS serogroups. Patients in the rapid-TTP group, compared to patients in the slow-TTP group, had greater Pittsburgh bacteremia scores, probability of ICU admission (57.9% vs. 25.5%, $p = 0.021$), and risk of septic shock (57.9% vs. 12.8%, $p < 0.001$). There were no significant differences in the proportion of patients with diabetes mellitus, chronic

Table 1 The demographic characteristics of the two time to positivity (TTP) groups (<10 hours or ≥ 10 hours) in nontyphoidal *Salmonella* bacteremia.

Variables	TTP <10 (n = 19)		TTP ≥10 (n = 47)		OR	95%CI	p
	No.	%	No.	%			
Age (y)	67.58 ± 13.2		65.53 ± 16.9		1.01	0.98–1.04	0.723
Sex (male)	12	63.2	31	66.0	0.89	0.29–2.69	>0.99
Location of patients							
Emergency department	13	68.4	31	66.0	1.12	0.34–3.50	>0.99
General ward	4	21.1	13	27.7	0.70	0.20–2.50	0.759
Intensive care unit	2	10.5	3	6.4	1.73	0.27–11.25	0.621
Underlying illness							
Charlson Comorbidity Index	3.84 ± 2.9	—	3.34 ± 2.3	—	1.08	0.88–1.33	0.552
Heart disease	2	10.5	5	10.6	0.99	0.18–5.60	>0.99
Stroke	2	10.5	10	21.3	0.44	0.09–2.21	0.484
Diabetes mellitus	8	42.1	12	25.5	2.12	0.69–6.52	0.239
Chronic kidney disease (GFR < 60)	3	15.8	14	29.8	0.44	0.11–1.76	0.354
Liver cirrhosis	6	31.6	3	6.4	6.77	1.49–30.88	0.013
Malignancy	6	31.6	10	21.3	1.71	0.52–5.63	0.526
Solid organ tumor	4	21.1	8	17.0	1.30	0.34–4.97	0.732
Hematological malignancy	2	10.5	2	4.3	2.65	0.35–20.31	0.573
HIV infection[a]	0	0.0%	3	6.4	—	—	0.550

[a] Only 16 patients received a HIV test.

CI = confidence interval; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; OR = odds ratio.

Table 2 Clinical factors and outcomes associated with time to positivity (<10 hours or ≥10 hours) in nontyphoidal *Salmonella* bacteremia.

Variables	TTP <10 (n = 19)		TTP ≥10 (n = 47)		OR	95% CI	p
	No.	%	No.	%			
Serogroup							
Group B	5	26.3	10	21.3	1.39	0.40—4.82	0.744
Group C	2	10.5	3	6.4	1.79	0.27—11.73	0.615
Group D	11	57.9	33	70.2	0.62	0.20—1.94	0.550
Unspecified	1	5.3	1	2.1	—	—	—
Origin of infection							
Urinary tract infection	0	0.0	2	4.3	—	—	1.000
Respiratory tract infection	1	5.3	0	0.0	—	—	0.288
Enteritis	4	21.1	7	14.9	1.52	0.39—5.96	0.716
Primary bacteremia	10	52.6	35	74.5	0.38	0.13—1.16	0.143
Mycotic aneurysm[a]	4	21.1	2	4.3	6.00	1.00—36.12	0.052
Severity of illness							
Pittsburgh score	2.47 ± 1.57	—	1.64 ± 2.13	—	1.21	0.93—1.58	0.019
Septic shock	11	57.9	6	12.8	9.40	2.69—32.81	<0.001
ICU transfer	11	57.9	12	25.5	4.01	1.3—12.32	0.021
Antibiotic sensitivity							
Ampicillin	11	57.9	24	51.1	1.32	0.45—3.86	0.786
Ceftriazone	19	100.0	47	100.0	—	—	—
Ciprofloxacin	19	100.0	46	97.9	—	—	—
Sulfamethoxazle/trimethoprim	16	84.2	31	66.0	0.36	0.29—1.43	0.229
Effective antibiotics within 48 hours[b]	17	89.5	33	70.2	3.61	0.73—17.74	0.311
In-hospital mortality	4	21.1	6	12.8	1.82	0.45—7.36	0.456
14 days mortality	2	10.5	3	6.4	1.73	0.27—11.25	0.621
30 days mortality	2	10.5	6	12.8	0.80	0.15—4.39	0.801

[a] Forty-six patients overall had an imaging study and six patients had mycotic aneurysm. In the rapid-TTP group, 15 patients had an imaging study and four (26.7%) patients had a mycotic aneurysm. In the slow-TTP group, 31 patients had an imaging study and only two (6.5%) patients had a mycotic aneurysm (p = 0.076).
[b] Effective antibiotics include ampicillin/sulbactam, piperacillin/tazobactam, 3rd and 4th generation cephalosporin, quinolones, and carbapenems.
CI = confidence interval; ICU = intensive care unit; OR = odds ratio; TTP = time to positivity.

kidney disease, heart disease, or malignancy. However, patients in the rapid-TTP group were more likely to have liver cirrhosis (31.6% vs. 6.4%, p = 0.013). Mycotic aneurysm was also more common in the rapid-TTP group than in the slow-TTP group (21.1% vs. 4.3%, p = 0.05).

Clinical outcomes

Univariate analysis indicated that a high Pittsburgh bacteremia score (i.e., 3 or greater) was significantly associated with greater in-hospital mortality. The relationship of septic shock at bacteremia onset with in-hospital mortality had borderline significance. After adjusting for age, sex, and Charlson Comorbidity Index by logistic regression analysis, both a high Pittsburgh bacteremia score of 3 or greater (OR = 5.46; 95%CI, 1.18—25.24; p = 0.030) and septic shock at bacteremia onset (OR = 4.47; 95%CI, 1.01—19.81; p = 0.048) were independent predictors of in-hospital mortality (Table 3). As for 30-day mortality, the Kaplan—Meier analysis indicated no significant difference between the rapid-TTP and slow-TTP groups (Fig. 1). The Cox regression model showed that septic shock at bacteremia onset remained a potential risk factor for 30-day mortality (Table 4).

Discussion

The association of the TTP of blood cultures with the outcome in patients with bacteremia has only been established for a limited number of pathogens. Initial investigations aimed to determine the utility of TTP for bacteremia caused by specific Gram-positive organisms, such as *Staphylococcus aureus* and *Streptococcus pneumoniae*.[13,14,17] These studies indicated that a rapid TTP was correlated with disease severity, source of infection, and poor patient outcome. Additional studies of *E. coli* and *K. pneumoniae*,[15,16,25] Gram-negative bacilli bacteremia,[19] and another study of Gram-positive and Gram-negative bacteria together,[18] indicated similar associations with rapid TTP. Numerous studies evaluated the association of TTP for Gram-negative bacteremia; however, the present study is the first to investigate the association of clinical outcome and TTP of blood cultures in patients with NTS bacteremia. Nearly 30% of our patients with NTS bacteremia had rapid TTP (i.e., less than 10 hours), and we determined that a TTP less than 10 hours was an important predictor of severe illness. Patients with more rapid TTP were more likely to have underlying liver cirrhosis and a mycotic aneurysm as the infection focus. This association

Table 3 Risk factors for in-hospital mortality in patients with non-typhoidal *Salmonella* bacteremia.

Variables	Death (n = 10)		Recovery (n = 56)		Univariate analysis			Multivariate analysis		
	No.	%	No.	%	OR	95% CI	p	OR	95% CI	p
Age ≥60 y	5	50.0	40	71.4	0.40	0.10–1.57	0.19	—	—	—
Sex (male)	8	80.0	35	62.5	2.40	0.47–12.39	0.30	—	—	—
Charlson Comorbidity Index ≥ 3	6	60.0	32	57.1	1.13	0.29–4.43	0.87	—	—	—
Malignancy	4	40.0	12	21.4	2.44	0.59–10.08	0.22	—	—	—
HIV infection[a]	0	0.0	3	5.4	—	—	—	—	—	—
Origin of infection										
Enteritis	0	0.0	11	19.6	—	—	—	—	—	—
Primary bacteremia	8	80.0	37	66.1	2.05	0.40–10.65	0.39	—	—	—
Mycotic aneurysm	1	10.0	5	8.9	1.13	0.12–10.87	0.91	—	—	—
Serogroup D	6	60.0	38	67.9	0.63	0.16–2.55	0.52	—	—	—
Pittsburgh score ≥ 3	7	70.0	17	30.4	5.35	1.23–23.22	0.03	5.46	1.18–25.24	0.030
Septic shock at BSI onset	5	50.0	12	21.4	3.67	0.91–14.78	0.07	4.47	1.01–19.81	0.048
ICU transfer	5	50.0	18	32.1	2.11	0.54–8.23	0.28	—	—	—
Effective antibiotics within 48 hours[b]	9	90.0	41	73.2	3.29	0.38–28.23	0.28	—	—	—
Time to positivity < 10 hours	4	40.0	15	26.8	1.82	0.38–28.24	0.40	—	—	—

[a] Only 16 patients received a HIV test.
[b] Effective antibiotics include ampicillin/sulbactam, piperacillin/tazobactam, 3rd and 4th cephalosporin, quinolones, and carbapenems.
BSI = blood stream infection; CI = confidence interval; HIV = human immunodeficiency virus; ICU = intensive care unit; OR = odds ratio.

may have resulted from greater endovascular bacterial burden of these patients. However, there was no significant difference in the mortality rates of the rapid-TTP and slow-TTP groups.

Approximately 5% of individuals with gastrointestinal illnesses due to NTS develop bacteremia. Bacteremia is more likely to occur in immunologically compromised patients such as patients who are extremely aged, or who have diabetes mellitus, HIV infection, or malignancy.[2] One Taiwanese study[8] demonstrated that malignancy was associated with elevated in-hospital mortality rate in patients with NTS bacteremia. In that study, patients with malignancy had a worse prognosis than patients without malignancy (40.5% vs. 17.7%, $p < 0.001$). As for our study, malignancy still carried a trend for mortality, but it did not reach statistical significance because of the limited case number. In addition, our univariate analysis indicated that a high Pittsburg bacteremia score (i.e., 3 or greater) was associated with greater in-hospital mortality. Disease severity at bacteremia onset determined a patient's outcome.

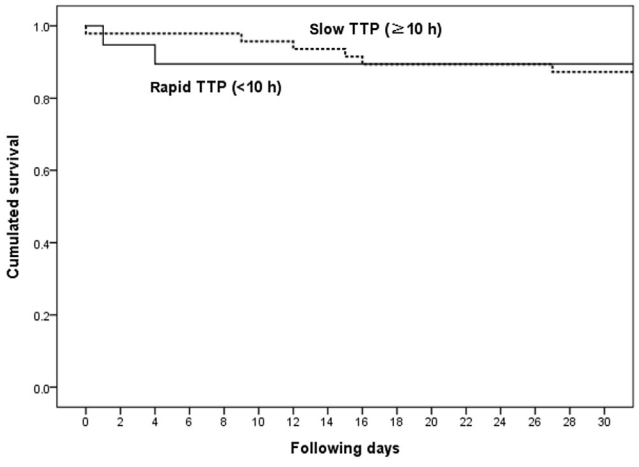

Figure 1. The Kaplan–Meier survival curve of patients with rapid or slow TTP (log rank test, $p = 0.841$). TTP = time to positivity.

Table 4 Cox regression analysis of risk factors associated with 30-day mortality in patients with nontyphoidal *Salmonella* bacteremia.

Risk factor	Hazard ratio (95% CI)	
	Univariate	Multivariate[a]
Age	1.00 (0.96–1.05)	—
Sex (male)	1.63 (0.33–8.08)	—
Charlson Comorbidity Index ≥ 3	2.36 (0.48–11.70)	—
Malignancy	3.44 (0.86–13.75)	
Serogroup D	1.31 (0.26–6.49)	—
Septic shock at BSI onset	5.68 (1.36–23.81)*	6.64 (1.47–29.96)*
Effective antibiotics within 48 hours[b]	2.24 (0.28–18.19)	—
Time to positivity < 10 hours	0.85 (0.17–4.21)	—

[a] After adjustment for age, sex, and Charlson Comorbidity Index.
[b] Effective antibiotics include ampicillin/sulbactam, piperacillin/tazobactam, 3rd and 4th cephalosporin, quinolones, and carbapenems.
* $0.01 < p < 0.05$.
BSI = blood stream infection ; CI = confidence interval.

A previous study showed that NTS was the most common etiology in bacteremic patients with advanced HIV infection in Taiwan (approximately 80%).[26] Other studies also showed a higher (20- to 100-fold greater) incidence of NTS bacteremia in HIV-infected patients than uninfected patients.[27,28] A study in Spain reported a mortality rate up to 50% among patients with HIV infection and nontyphoidal salmonellosis.[29] However, our study group had only three patients (3/66, 4.5%) with HIV infection. All of these patients had quite low CD4 count (46 cells/μL, 57 cells/μL, and 16 cells/μL), high HIV viral load (all had more than 200,000 copies/mL), and no antiretroviral therapy (i.e., they were treatment-naive). However, none of these patients died and they still had a relatively long TTP (19.65 hours, 22.52 hours, and 33.31 hours, respectively) and low disease severity, even though they were immunocompromised. Because of our small sample size, we suggest that more clinical experience is needed to understand the role of TTP of NTS bacteremia in HIV-infected patients.

The prevalence of NTS serotypes varies in different geographic areas. In Taiwan, a previous study reported a high prevalence of serogroups B and C in patients with NTS bacteremia.[30] However, another recent study in Taiwan showed an increasing proportion of serogroup D and a decreasing proportion of *S. choleraesuis* during a 10-year observation period.[8] *S. choleraesuis* has decreased in recent years, although it has been reported as a cause of invasive extraintestinal infections in the elderly, especially mycotic aneurysm.[31] In Taiwan, *S. choleraesuis* is also associated with greater antibiotic resistance, compared to serogroups B or D isolates.[31,32] Up to 56% of *S. choleraesuis* isolates were resistant to ciprofloxacin, but few (less than 5%) isolates were resistant to ceftriaxone.[31] In our study, there were five serogroup C isolates; only one patient had *S. choleraesuis* bacteremia. This patient did not have endovascular lesions or other extraintestinal infection, and the TTP was 21.97 hours. In addition, this *S. choleraesuis* was the only isolate of all isolates that was resistant to ciprofloxacin. All isolates in this study were susceptible to ceftriaxone.

A short TTP is correlated with mycotic aneurysm, which has been described in *S. aureus* bacteremia.[13] We reviewed all patients for the performance of image studies. Forty-six (69.7%) patients overall had received abdominal computed tomography and six patients had a mycotic aneurysm. Therefore, the corrected rate of mycotic aneurysm in this study was 13%, which was more close to the result (16.8%) of a previous study.[33] Compared to previous studies,[9,33] the percentage of group C *Salmonella* was lower in this study, which could partly explain the lower incidence of mycotic aneurysm. The correlation between a short TTP and liver cirrhosis, which has been described repeatedly,[15,18] could be related to the large bacterial burden among cirrhotic patients resulting from impaired hepatic clearance.

The present study had several limitations. First, we did not record the duration of illness before the blood samples were collected for culture. In addition, we failed to record the time between blood sample collection and loading into the processing device. We assumed that the variations in this process occurred randomly. Third, the small number of patients did not have sufficient power to detect the effects of TTP on mortality. However, a rapid TTP was still correlated with a higher probability of ICU admission and greater disease severity.

In conclusion, measurement of the TTP of blood samples in patients with NTS bacteremia may provide diagnostic and prognostic information. A rapid TTP (i.e., <10 hours) is correlated with liver cirrhosis and may identify patients with a higher likelihood of endovascular infections.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

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