



Duration of antimicrobial therapy for non-typhoid *Salmonella* bacteremia in healthy children

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Medical records of patients less than 17 years of age with positive blood culture for non-typhoid *Salmonella* from June 1996 through December 1998 at the Chang Gung Children's Hospital were collected. Patients were categorized into 3 groups according to the duration of effective antibiotic therapy they received. Group 1 received effective antibiotic therapy for less than 7 days; Group 2 for 7 to 9 days; and Group 3 for 10 days or more. Information on clinical presentations, laboratory data, and outcome were collected and analyzed. A total of 59 children were eligible, with 21 in Group 1, 17 in Group 2, and 21 in Group 3. Demographic data were similar among the 3 groups. No significant difference was found in the clinical symptoms and laboratory data among these groups, including white blood cell count, immature to total ratio of white blood cell, and serum C-reactive protein level. *Salmonella* group B (n = 37) were the most common isolates, followed by group D (n = 9), group C2 (n = 8), *choleraesuis* (n = 4), and C1 (n = 2). Third-generation cephalosporins were the final antibiotic therapy in most (90%) patients, and no isolates showed resistance to these agents in this study. No focal suppurative complications were noted at the initial evaluation and in the 1-year period after treatment. No clinical recurrent diseases were noted during a follow-up period of at least 1 year. Results suggest that for otherwise healthy children with non-typhoid *Salmonella* bacteremia, less than 10 days of antibiotics therapy could be adequate if they are more than 1 year old and no focal extra-intestinal infection is noted in the initial evaluation.

Key words: Focal suppurative complication, non-typhoid *Salmonella* bacteremia, third-generation cephalosporins

Non-typhoid *Salmonella* (NTS) infection is an important public health issue worldwide. Intestinal infection (salmonellosis) is the most common mode of clinical presentation of NTS infections. Non-typhoid *Salmonella* bacteremia is usually seen in high-risk populations, including young infants, children with hemolytic anemia or other hematological diseases, and people with immunosuppression. However, NTS bacteremia can also occur in otherwise healthy children. Unlike *Salmonella typhi*, which predominates among older children and adults, NTS bacteremia is usually seen in young children less than 2 years of age [1]. Although there have been many studies on the clinical characteristics and treatment of NTS bacteremia, very few reports have focused on the optimal duration of antibiotic treatment, and the approaches used in these studies differed with each other [2,3]. The recommended therapy for NTS bacteremia at present is appropriate antibiotics for 10 to 14 days, depending on the condition and response of the patient [4]. However, not all bacteremic patients receive the recommend therapy in

Taiwan because of a number of reasons. First is the wide variation of clinical presentation; bacteremic children may be clinically well and have only mild symptoms. Their symptoms may resolve gradually under oral antibiotics or supportive care only. Second is the variation among attitudes of clinicians. Due to the possibility of transient bacteremia, some clinicians may not give antibiotics and just take a second blood sample for culture if the symptoms are mild and the patient is not sick. Whether a full course of 10- to 14-day antibiotic therapy is critical for all bacteremic children is questionable. Hospitalization duration for these children may be shortened if a shorter course of antibiotic therapy suffices. This retrospective study was conducted to evaluate whether a shorter course of antibiotic therapy is appropriate for otherwise healthy children with NTS bacteremia by comparing the clinical presentations and outcomes between cases with different durations of antibiotic treatment.

Materials and Methods

Study design and patient enrollment

Children under 17 years of age with blood culture positive for NTS identified from the microbiological

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laboratory at Chang Gung Children's Hospital between June 1996 and December 1998 were included in this retrospective study. Data on demographic characteristics, clinical presentations, laboratory results, microbiological results, antimicrobial sensitivity, antimicrobial treatment, and clinical outcome were collected. Data on the recurrence of positive blood culture, fever, and other focal signs such as arthralgia or meningismus during follow up were collected. If patients were lost to follow up after discharge, their family members were contacted by telephone to obtain information. Patients were classified into 3 groups according to the duration of effective antibiotics usage. Group 1 received effective antibiotic therapy for less than 7 days, Group 2 for 7 to 9 days, and Group 3 for 10 days or more. Clinical presentations and laboratory data including complete blood cell count/differential count (CBC/DC) and C-reactive protein (CRP) among the 3 groups were compared to determine the difference in the disease severity before treatment. We also compared the difference of these parameters between children younger and older than 1 year. The incidence of bacteremia relapse or focal suppurative complication was compared among these 3 groups, and also between the 2 different age groups.

Statistical analysis

The data were analyzed by using analysis of variance or independent *t* test for continuous data and by using chi-square test for categorical data. A *p* value less than 0.05 was considered statistically significant.

Results

From June 1996 through December 1998, a total of 60 children treated at the Chang Gung Children's Hospital met the diagnostic criteria for NTS bacteremia. A 15-year-old boy was excluded from the analysis due to refractory Hodgkin's disease. The demographic and laboratory data of the patients are shown in Table 1. All patients resided in Taoyuan, Taipei, Hsinchu counties, or Taipei City. There were 30 boys and 29 girls with age ranging from 14 days to 4 years 9 months (mean, 1 year 4 months) (Table 1). The mean age was 1 year 6 months, 1 year 5 months, and 1 year 3 months for Groups 1, 2, and 3, respectively ($p > 0.1$). Thirty-one (53%) patients were less than 1 year old, and 28 (47%) were over 1 year of age. One-way analysis of variance revealed no significant difference among the 3 groups in the white blood cell count, hemoglobin level, platelet count, and serum CRP level (Table 1). Serum aspartate aminotransferase (AST) level was between 19 and 229 U/L, and the mean level was 57 U/L.

Table 1. Demographic characteristics of 59 children with non-typhoid *Salmonella* bacteremia grouped by duration of antimicrobial therapy

Characteristic	Total n = 59	Duration of appropriate antibiotic use			<i>p</i>
		Group 1 n = 21	Group 2 n = 17	Group 3 n = 21	
Age					
mean (range)	1y4m (14d-4y5m)	1y6m (6m-4y5m)	1y5m (14d-4y9m)	1y3m (2m-4y)	0.905
0-3m	3	0	1	2	
>3m-1y	28	11	7	10	
>1y	28	10	9	9	
Sex (M/F)	30/29	14/7	5/12	11/10	
WBC (/mm ³)					
Mean ± SD	11618 ± 4340	10695 ± 3964	10776 ± 3450	13223 ± 6204	0.278
I/T > 10%	14	4	5	5	
No. of cases measured	59	21	17	21	
Hemoglobin (g/dL)					
Mean (range)	11.2 (8.9-13.2)	11.4 (9.8-13.2)	11.3 (10.1-12.5)	10.9 (8.9-12.9)	0.174
Platelet (x1000 /mm ³)					
Mean (range)	334 (141-714)	343 (170-714)	292 (198-409)	361 (141-621)	0.406
CRP (mg/L)					
Mean (range)	74 (4.2-403)	59 (11-358)	70.4 (5-403)	94 (4.2-312)	0.120
No. of cases measured	55	20	16	19	
AST (U/L)					
Mean (range)	57 (20-239)	36 (23-57)	82 (30-239)	40 (20-63)	0.014
No. of cases measured	29	8	12	9	

Abbreviations: WBC = white blood cell count; I/T = immature to total ratio^a; CRP = C-reactive protein; AST = aspartate aminotransferase
^aCalculated by (band + myelocyte)/(segment + band + myelocyte).

Table 2. Clinical manifestations in 95 children with non-typhoid *Salmonella* bacteremia grouped by duration of antibiotic use

Symptom/sign	Appropriate antibiotic treatment				p
	Total n = 59	<6 days n = 21	7-9 days n = 17	≥10 days n = 21	
Fever	57	21	16	20	NS
Days lapsed before admission (mean)	5.3	4.8	7.0	4.7	NS
Diarrhea (positive stool culture)	47 (25)	19 (7)	13 (7)	15 (11)	NS
Bloody or mucoid diarrhea (positive stool culture)	26 (13)	13 (6)	8 (4)	5 (3)	NS
Nausea / vomiting	11	3	2	6	NS
Definitive antibiotics therapy					
Third-generation cephalosporin	46	19	17	21	
Ampicillin	5	2	0	3	

L. Patients in Group 2 had a higher AST level than the other 2 groups, but AST level were measured in only 50% of cases, and only 2 patients had serum AST level above 100 U/L. Hepatosplenomegaly was not noted clinically in this review.

All but 2 patients had fever before admission, with a mean duration of 5.38 days (range, 1-30 days) (Table 2). Associated gastrointestinal symptoms were noted in 50 (85%) patients (diarrhea in 47 and nausea/vomiting in 11). The character of stool was bloody or mucoid in 55% of patients with diarrhea. Stool culture was done in 47 patients, among which 25 (53%) specimens were positive for *Salmonella*. Among the patients with bloody or mucoid diarrhea, the positive culture rate was similar (13/26, 50%). About 41% of patients also had respiratory symptoms including cough (either dry or productive) and runny nose. The mean days of fever before admission, rate of diarrhea, and rate of nausea or vomiting were not different among these 3 groups (Table 2). Group 2 had a higher rate of respiratory symptoms than the other 2 groups. All but 5 cases were hospitalized for treatment; 4 patients visited the emergency department and were then discharged due to mild clinical symptoms after blood culture was taken, and one patient was discharged from the outpatient clinic after blood culture was taken. Clinical manifestations did not differ between children younger and older than 1 year (Table 3). However,

children less than 1 year of age tended to receive a longer course of antibiotic therapy than older children did, but this difference was not significant (mean, 9 vs 6.6 days, $p=0.06$).

Salmonella group B were the most common isolates ($n = 37$, 62%), followed by group D (9), group C2 (8), and *Salmonella choleraesuis* (4) (Table 4). None of the isolates were resistant to third-generation cephalosporins (ceftriaxone, cefotaxime, ceftizoxime, and cefixime). Rates of resistance of *Salmonella* isolates to ampicillin, chloramphenicol and trimethoprim/sulfamethoxazole (TMP/SMX) were 71%, 81%, and 52%, respectively. For each serogroup of *Salmonella* isolates the distribution and antibiotic resistance were similar between different treatment groups. The rate of resistance to ampicillin was more than 80% in *Salmonella* group B and *S. choleraesuis*, and more than 50% in Group D isolates. About 46% of *Salmonella* isolates were resistant to more than 2 of these 3 antibiotics. Ciprofloxacin was effective against most isolates; however, resistance was noted in 2 *Salmonella* group B isolates.

The clinical course was uneventful in 58 patients despite the use of different regimens and duration of antibiotic therapy. A 1-year-old boy with group B infection developed cecal perforation 7 days after the onset of loose diarrhea and fever. He was treated with laparotomy and cecostomy on admission, and then

Table 3. Clinical manifestations in children with non-typhoid *Salmonella* bacteremia grouped by age

Symptom/sign	All n = 59	Group A, ≤1 y/o n = 29	Group B, >1 y/o n = 30	p
	Fever	57	28	
Diarrhea (positive stool culture)	47 (25)	24 (13)	23 (12)	NS
Bloody or mucoid (positive stool culture)	26 (13)	12 (7)	14 (6)	NS
Nausea or vomiting	11	3	8	NS
Duration of antibiotic use (days)	7.8 ± 4.9	9 ± 5.3	6.6 ± 4.1	0.06
Third-generation cephalosporin	46	26	28	
Ampicillin	5	3	2	

Table 4. Antimicrobial resistance of *Salmonella* isolated from blood by serogrouping

Antimicrobial	Serogroup					Resistance n = 57 (%)
	Group B n = 37 (%)	Group C2 n = 8	<i>S. Choleraesuis</i> n = 4	Group D n = 9	Unspecified n = 1	
Ampicillin	31/36 (86)	1/8	4/4	5/9	0/1	41/58 (71)
Chloramphenicol	19/21 (90)	2/2	2/2	3/5	0/1	25/31 (81)
TMP/SMX	9/21 (43)	3/3	2/2	3/6	0/1	17/33 (52)
Ciprofloxacin	2/19 (11)	0/6	0/2	0/5	0/1	2/33 (6)

Abbreviation: TMP/SMX = trimethoprim/sulfamethoxazole

ceftriaxone and metronidazole were used for a total of 17 days. A 1-year-old girl with group B bacteremia had received a 5-day course of ceftriaxone therapy in another hospital 2 months before admission to the Chang Gung Children's Hospital. *S. choleraesuis* bacteremia was found on admission and she received ceftizoxime for 12 days. Stool culture grew both groups B and C2 *Salmonella*. She was the only patient in this series who had multiple episodes of *Salmonella* infection during a short period of time, but nitroblue tetrazolium test done later showed normal phagocytic function.

Initial empiric antibiotics used included ampicillin and/or gentamicin in 22 (37%) cases, ceftriaxone in 12 (20%), ceftizoxime in 16 (27%), cefotaxime in 2 (3%), and cephalothin with gentamicin in 2 (3%). Among the 24 children receiving ampicillin/gentamicin or cephalothin/gentamicin as empiric therapy, antibiotics were later shifted to third-generation cephalosporins in 16 (67%) cases due to isolations of resistant strains of *Salmonella*. Third-generation cephalosporins (ceftriaxone, ceftizoxime, or cefotaxime) were given intravenously as definitive therapy in 46 children, and ampicillin in 5 cases (3 and 2 in children younger and older than 1 year, respectively). Sixteen children received oral medication later as sequential therapy, including cefixime (10 cases), amoxicillin (3), ciprofloxacin (1), and cefaclor (2). No clinically significant side-effect was noted in any of the cases. The decision of when to shift to oral antibiotics depended on the physician's judgment and the patient's clinical condition, with a median of 7 days (range, 6.85 ± 3 days). Eight patients did not receive appropriate antibiotics. Four of them visited the emergency department, one visited the outpatient department, and all returned home without antibiotics. Three of them did not receive antibiotics at subsequent outpatient department follow-up due to improved condition, and the other 2 cases also improved without appropriate antibiotics (information obtained by telephone interview). The other 3 hospitalized patients improved under supportive care; 2 of them did not receive any antibiotics though *Salmonella* bacteremia was found later during hospitalization. The

remaining patient received ineffective antibiotics and was discharged before the blood culture result was known. However, follow-up blood culture later at the outpatient department was negative. All of the other hospitalized patients had negative follow-up blood culture results before discharge. No metastatic lesions such as meningitis, brain abscess or empyema, or osteomyelitis were noted in any of the patients during hospitalization and 1 year after discharge. The patient with intestinal perforation recovered uneventfully and remained well in the following year.

Discussion

The standard therapy for NTS bacteremia in children is appropriate antibiotics for 10 to 14 days, depending on the condition and response of the patient [4]. However, the criteria for assessing the condition and response of the patient remain subjective, especially in children who were otherwise healthy. Though rarely reported in the literature, the use of a shorter course of antibiotic therapy for bacteremic children who were otherwise healthy had been noted. For example, in a round-table discussion of the management of *Salmonella* infection in the first year of life, Rodriguez [2] recommended that for a patient older than 3 months of age in whom bacteremia was discovered as an outpatient, repeated blood culture should be taken and antibiotics should not be used if the infant looks well and is afebrile. If the patient is ill-appearing or febrile, a course of antibiotics for 7 to 10 days is recommended.

Patients admitted to the Chang Gung Children's Hospital for common febrile illness were cared for by physicians of various specialties, and thus the management differed when NTS bacteremia was noted later. Antibiotics therapy was administered inconsistently in these patients, with the choice of regimens depending on the opinion of each physician. In this study, except for the rate of cough and serum AST level, no significant differences was found in the clinical presentations, laboratory data, and distribution of each serotype of *Salmonella* isolates between the 3 groups treated with different durations of antibiotic

therapy. These findings suggest that there was no significant difference in the severity of the illness among patients in these different groups. For these 59 otherwise healthy children, no focal suppurative complication was noted after treatment, regardless of the antibiotic regimen received.

Salmonella group B were the most common isolate in this series (37 cases, 62%), as has been reported in both northern [5,6] and southern Taiwan [7]. Most patients in this study were less than 2 years of age, which is in agreement with the findings of a review by Graham [8]. Young age is a risk factor for NTS bacteremia [1]. The overall rates of resistance to ampicillin, chloramphenicol, and TMP/SMX were very high in this series, compatible with previous reports from Taiwan [4,9]. In addition, resistance to ciprofloxacin was noted in 2 isolates of group B *Salmonella* in this series, indicating that ciprofloxacin resistance may be an emerging problem in Taiwan. *S. choleraesuis* was probably the most resistant strain identified in this study, with tested isolates resistant to ampicillin, chloramphenicol, and TMP/SMX. *Salmonella* group C2 remained susceptible to ampicillin. Due to the high rate of resistance, commonly used first-line antibiotics are no longer the drug of choice for empirical therapy, and third-generation cephalosporins or new quinolones, although the latter are not recommended for children, are more suitable for suspected NTS infection. Third-generation cephalosporins were used in 90% of children in this series.

Salmonella bacteremia is a major problem in immunocompromised patients. Focal complication usually occurs in patients with immunocompromised status or hemoglobinopathy, especially sickle cell disease [11,12]. However, the course of NTS bacteremia is usually benign in an otherwise healthy child and the incidence of focal suppurative complication in this population is rare [11]. In a study from Thailand, Sirinavin *et al* [13] showed that infants aged 0 to 6 months were at high risk for localized infection. Zaidi *et al* [12] found that for NTS bacteremic children, most focal infections are apparent at the initial evaluation. In this study, no child had focal suppurative complications before, during, or after treatment, regardless of the duration of antibiotic therapy. The necessity of more than 10 days of antibiotic therapy for an otherwise healthy child maybe questionable, when taking into consideration the benign nature and low incidence of focal complications in this population. A similar suggestion was also made in a review by Chen [5], although no follow-up data was considered in the article. These findings suggest that a shorter course of

appropriate antibiotic therapy may be adequate for children more than 1 year old if they have no underlying diseases, clinical signs of toxicity, or risk of focal complication at the initial evaluation, and if close outpatient clinic follow-up is feasible. Determination of whether oral antibiotics are appropriate need further investigation, but cefixime or ciprofloxacin may be the drug of choice if sequential therapy is necessary, based on the drug susceptibility for NTS isolates. Due to the low incidence of focal complication in children with *Salmonella* bacteremia, a prospective study with a large number of patients is needed.

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