

Nontyphoidal *Salmonella* Bacteremia in Children in Northern Thailand

Virat Sirisanthana, M.D.*

Aurmporn Sreshthaputra, M.D.*

Orawan Boonpala B.Sc.*

Abstract

Since the outbreak of pediatric AIDS in Northern Thailand, the number of patients with nontyphoidal *Salmonella* bacteremia has increased markedly. To evaluate the characteristics and the effectiveness of treatment of this infection, we prospectively followed children with nontyphoidal *Salmonella* bacteremia. All patients with nontyphoidal *Salmonella* bacteremia who were admitted to Chiang Mai University Hospital from January 1995 to December 1996 were included. The antimicrobial susceptibility test of the organism was performed by the standard disk diffusion method. During the study period, there were 44 patients (51 episodes) of nontyphoidal *Salmonella* bacteremia in children. Underlying conditions were present in 36 (84%) patients, including HIV infection in 30 patients, hematological diseases, cirrhosis and third degree malnutrition in 6 patients. The susceptibility of nontyphoidal *Salmonella* to ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol had decreased in the previous years to 45, 62 and 63 percent respectively in 1996. The tested strains were all susceptible to cefotaxime or ceftriaxone, norfloxacin, and imipenem. Antimicrobial treatment in 11 episodes (10 patients). Treatment with antimicrobial agents was successful in 47 episodes (40 patients). Four patients died. During the follow-up of at least 7 months, 9 patients (22.5%) had relapses. In conclusion there has been an increasing number of patients with nontyphoidal *Salmonella* bacteremia since the AIDS epidemic began in Thailand. The isolated strains were resistant to several commonly used antimicrobial agents, as proven by clinical failure. In this study, the efficacy of the third-generation cephalosporins (cefotaxime or ceftriaxone) was demonstrated. (*J Infect Dis Antimicrob Agents* 1998;15:59-63.)

INTRODUCTION

Nontyphoidal *Salmonella* species are widely disseminated in nature and are intimately associated with animals. Food products derived from animals, such as eggs and milk are main sources of *Salmonella* species for human infection. Symptomatic infection includes gastroenteritis, enteric fever, bacteremia, and localized infections. It is well recognized that patients with human immunodeficiency virus (HIV) infection are at increased risk for nontyphoidal *Salmonella* bacteremia. With the HIV epidemic, there are increasing numbers of reported cases of nontyphoidal *Salmonella*

bacteremia (1-3).

Recently there has been a significant increase in ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol resistance among nontyphoidal *Salmonella* isolated from humans (4-7).

Thailand has been severely affected by the HIV epidemic. Increased numbers of patients of nontyphoidal *Salmonella* bacteremia in HIV-infected children, together with the difficulty in managing these patients, led us to study the antimicrobial susceptibility of the infecting organisms and the outcome of treatment in these patients.

* Section of Infectious Disease, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand.

Received for publication: September 1, 1997.

Reprint request: Virat Sirisanthana, M.D., Section of Infectious Disease, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

Keywords : Nontyphoidal *Salmonella*, bacteremia, children.

METHODS

In 1995 and 1996, all patients with proven nontyphoidal *Salmonella* bacteremia were followed prospectively by one of the authors (VS or AS). The initial antimicrobial agents were chosen by the attending pediatricians. Hemocultures were repeated in all patients that did not improve after 48-72 hours of antimicrobial treatment, prior to the change of the antimicrobial regimen. Patients with positive hemoculture after 48-72 hours of antimicrobial treatment were counted as treatment failures. All isolates of nontyphoidal *Salmonella* obtained from clinical specimens were classified as described in the Manual of Clinical Microbiology (8). The laboratory used commercially available polyvalent antisera (Difco Laboratories, Detroit, Michigan, U.S.A.) to determine the O-antigen groups. The serogroup C₁ strain was further identified by its biochemical characteristics for serotype *choleraesuis*. Other serogroups were not further classified for serotype. These serogroups, as well as the non-*choleraesuis* strains of serogroup C1 were reported as *Salmonella enteritidis*. All isolates were tested for antimicrobial susceptibility by the disk diffusion method to the following antimicrobial agents: ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, gentamicin, cefotaxime, ceftriaxone, norfloxacin, ciprofloxacin and imipenem (9).

RESULTS

There were 44 patients (51 episodes) with nontyphoidal *Salmonella* bacteremia during this 2-year

period. The clinical characteristics of these patients are shown in Table 1. All presented with fever, the duration of which ranged from 5 to 14 days. Twelve patients also had diarrhea, which stool cultures were positive for respective *Salmonella* spp. in 6 patients. Six other sites of *Salmonella* infection were also found. The patient with osteomyelitis was an 8-year-old thalassemic boy, who had acquired HIV through blood transfusion. The 3 cases of meningitis patients were infants, two 1-month and one 3-month-old. Two of these infants were born on the same day and were infected with the same nontypable strain of *Salmonella*, suggestive of a nosocomial infection. *Salmonella* bacteremia was the first presenting symptom of HIV infection in 15 patients, 50 percent of HIV-infected patients.

Nine (22.5%) patients had relapses during the follow-up of at least 7 months, including one relapse in 7 patients, 2 relapses in one patient and 3 relapses in one patient. The duration between the completion of treatment and relapse ranged from 9-710 days (median 63 days). All relapses were in HIV-infected patients and with strains of the same serotype or serogroup and similar patterns of antimicrobial susceptibility as the original episodes. Of the 44 original episodes, 14 organisms were identified as *Salmonella* serogroup C₁ serotype *choleraesuis*, 17 were *Salmonella* serogroup B, 11 were *Salmonella* serogroup D and 2 were non-typable *Salmonella*. The antimicrobial susceptibility of 44 original nontyphoidal *Salmonella* are shown in Table 2. The susceptibility to ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol

Table 1. Clinical characteristics of children with nontyphoidal *Salmonella* bacteremia.

Underlying Diseases	Number of cases	Age or range of age (median)	Other sites of <i>Salmonella</i> infection			
			gastroenteritis	meningitis	osteomyelitis	UTI
HIV-infected children	30					
perinatally acquired	27	5-66 months (23 months)	6			1*
transfusion acquired**	3	8 years, 9 years, 11 years			1	
Normal hosts	8	1-48 months (5 months)		3		
Hematologic diseases***	4	1 year, 2 years, 2 years, 12 years				1
Cirrhosis	1	18 months				
Third degree malnutrition	1	32 months				
Total	44					

* also had *Salmonella* gastroenteritis

** Beta-thalassemia, 2; hemophilia, 1.

*** Leukemia, 2; autoimmune hemolytic anemia (on prednisolone), 1; thalassemia, 1.

was less than 63 percent. The tested strains were all susceptible to cefotaxime and/or ceftriaxone, norfloxacin and/or ciprofloxacin, and imipenem.

Since the relapses were not always treated with the same antimicrobial regimens, the results of treatment were evaluated using all 51 episodes. There were 11 episodes of treatment failure (Table 3). The failures occurred in both groups (with and without underlying immunocompromised condition). The failure of two episodes with trimethoprim-sulfamethoxazole and one with amoxicillin were in patients infected with strains resistant to the respective antimicrobial agent (episodes 1, 10 and 11). Treatment with ampicillin failed in both groups, with ampicillin-susceptible and ampicillin-resistant strains. Although the infecting strains were susceptible to gentamicin, this alone or gentamicin combined with ampicillin were not successful in 7 episodes (episode 3-9).

Antimicrobial therapy was successful in 47 episodes (Table 4). In 37 episodes, intravenous cefotaxime 100 mg/kg/day or intravenous ceftriaxone 50 mg/kg/day were given for 7 days or more, followed by oral

antimicrobial agents to which the respective organisms were susceptible, to complete 14 days of antimicrobial therapy. Other regimens included 4 episodes of intravenous cefotaxime 200 mg/kg/day for 21-56 days (in three cases of meningitis and one case of osteomyelitis), 4 episodes of intravenous ampicillin 100 mg/kg/day for 7 days, followed by oral amoxicillin 50 mg/kg/day for 7 days, 1 episode of intravenous trimethoprim-sulfamethoxazole 10 mg-trimethoprim/kg/day for 3 days, followed by oral trimethoprim-sulfamethoxazole 10 mg-trimethoprim/kg/day for 11 days, and 1 episode of oral amoxicillin 75 mg/kg/day for 14 days. The organisms in all episodes were susceptible to the antimicrobial agents given. Although antimicrobial therapy were successful in all 3 patients with meningitis, the patients recovered with severe complications. These included cortical blindness, hydrocephalus and bilateral hearing loss. Four patients died, giving a mortality rate of 9 percent (4/44).

DISCUSSION

Human immunodeficiency virus infection is the

Table 2. Percent of nontyphoidal *Salmonella* susceptible to antimicrobial agents.

Year	No. tested	amp	tms	chlo	gen	cefo/ceft	norf/cipr	imp
1995	22	50	55	58	86	100	100	100
1996	22	45	62	63	73	100	100	100

amp: ampicillin, tms: trimethoprim-sulfamethoxazole, chlo: chloramphenicol, gen: gentamicin, cefo/ceft: cefotaxime and/or ceftriaxone, norf/cipr: norfloxacin and/or ciprofloxacin, imp: imipenem.

Table 3. Failure of antimicrobial therapy.

Episode	Age	Underlying condition	Serotype	Susceptibility*			Antimicrobial therapy**	Duration of treatment (day)
				amp	tms	gen		
1	5 months	HIV	enteritidis B	R	R	R	amp100MKD + tms20MKD	2
2	4 months	none	choleraesuis	S	S	S	amp100MKD	2
3	10 months	HIV	choleraesuis	S	R	S	amp100MKD + gen7.5MKD	3
4	4 years	HIV	choleraesuis	S	R	S	amp100MKD + gen7.5MKD	3
5	11 months	none	enteritidis B	R	S	S	amp100MKD + gen7.5MKD	3
6	2 years	HIV	enteritidis B	R	R	S	amp200MKD + gen7.5MKD	2
7	2 years	HIV	enteritidis B	R	R	S	amp200MKD + gen7.5MKD	2
8	14 months	HIV	enteritidis D	R	S	S	amp100MKD + gen7.5MKD	7
9	6 months	none	choleraesuis	S	S	S	gen3MKD	4
10	10 months	HIV	choleraesuis	S	R	S	tms10MKD (orally)	4
11	11 months	HIV	choleraesuis	R	S	S	amox75MKD (orally)	7

* amp: ampicillin, tms: trimethoprim-sulfamethoxazole, gen: gentamicin, amox: amoxicillin,

** all antimicrobial agents, except in episodes 10 and 11 were given intravenously, MKD: mg/kg/day

Table 4. Successful antimicrobial therapy.

Antimicrobial agents*	Duration of treatment (day)	Number of episodes
Cefotaxime or ceftriaxone	14	37
Cefotaxime	21-56	4**
Ampicillin-IV \geq amoxicillin PO	14	4
Tms-IV \geq tms-PO	14	1
Amoxicillin-PO	14	1

* Tms: Trimethoprim-sulfamethoxazole, IV: intravenously, PO: per oral

** Septicemia with meningitis 3 cases, septicemia with osteomyelitis 1 case.

major underlying disease in this study. With rather stable numbers of yearly childhood admissions at the hospital, the number of nontyphoidal *Salmonella* bacteremia increased from less than 10 patients per year before 1990 to 22 patients per year during this studied period. This rise coincided with an increased number of symptomatic HIV-infected children admitted to this hospital (10).

In this study there was no seasonal variation in the incidence of nontyphoidal *Salmonella* bacteremia. This contrasts with one study from China which reported higher incidence from June through October (11).

Many of the isolated organisms were resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, which were routinely recommended drugs for *Salmonella* bacteremia. Similar findings have been reported from studies from other Asian countries (4,5,11), as well as countries in Europe and America (6,7).

The failure of ampicillin in 3 episodes of infection with ampicillin susceptible isolates (episode 2,3 and 4) demonstrated that an other mechanism is needed to eradicate the organism. These three episodes were in HIV-infected patients and in an infant who could have had impaired cellular immunity. This study also demonstrated that patients infected with ampicillin-resistant organisms failed to respond to very high doses of the drug (ampicillin 200 mg/kg/day intravenously). Gentamicin had better bactericidal *in vitro* activity than ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, but had no *in vivo* effect. Thus gentamicin should not be used for systemic *Salmonella* infection despite its *in vitro* activity. The experience with chloramphenicol is limited in this study. With 40 percent resistance to chloramphenicol, the drug should not be chosen as the first drug of choice for

nontyphoidal *Salmonella* bacteremia in this region.

There was no failure in treatment of nontyphoidal *Salmonella* bacteremia with cefotaxime or ceftriaxone in this study. This has been the experience of other physicians since the late 1980s (12,13). At present these third-generation cephalosporins are one of the recommended treatment regimens for nontyphoidal *Salmonella* bacteremia and/or meningitis. We did not find cefotaxime or ciprofloxacin resistance in this study, but reports of cefotaxime-resistant and ciprofloxacin-resistant strains have been published (14-17).

Relapses after two weeks of appropriate antibiotics in bacteremic cases occurred exclusively in HIV-infected patients. More effective antimicrobial regimens (drug, duration) and/or long-term suppressives are needed to prevent relapses. The mortality rate (9%) in this study was similar to that found in other studies, in the range of 5-13 percent (18,19).

References

1. Tumbarello M, Tacconelli E, Caponera S, Cauda R, Ortona L. The impact of bacteraemia on HIV infection. Nine years experience in a large Italian University Hospital. *J Infect* 1995;31:123-31.
2. Levine WC, Buehler JW, Bean NH, Tauxe RV. Epidemiology of nontyphoidal *Salmonella* bacteremia during the human immunodeficiency virus epidemic. *J Infect Dis* 1991;164:81-7.
3. Sperber SJ, Schlepner CJ. Salmonellosis during infection with human immunodeficiency virus. *Rev Infect Dis* 1987;9: 925-34.
4. Kam KM. Serotype epidemiology and patterns of antibiotic susceptibilities of *Salmonellae* isolated in Hong Kong 1983-93. *Chin Med J (Engl)* 1996;109:276-81.
5. Yang MT, Chi CS. *Salmonella* infections in infants and children. *Chung Hua I Hsueh Tsa Chih (Taipei)* 1994;54:38-43.
6. Ramos JM, Ales JM, Cuenca-Estrella M, Fernandez-Roblas R, Soriano F. Changes in susceptibility of *Salmonella enteritidis*, *Salmonella typhimurium*, and *Salmonella virchow* to six antimicrobial agents in a Spanish Hospital, 1980-1994. *Eur J Clin Microbiol Infect Dis* 1996;15:85-8.

7. Lee LA, Puhf ND, Maloney EK, Bean NH, Tauxe RV. Increase in antimicrobial resistant *Salmonella* infections in the United States, 1989-1990. *J Infect Dis* 1994;170:128-34.
8. Gray LD. *Escherichia, Salmonella, Shigella, and Yersinia*. In: Tenover FC, Baron EJ, Tenover FC, Murray PR, eds. *Manual of Clinical Microbiology*. 6th ed. Washington DC: American Society for Microbiology, 1995:450-6.
9. Woods GL, Washington JA. Antibiotic susceptibility test: dilution and disk diffusion methods. In: Tenover FC, Baron EJ, Tenover FC, Murray PR, eds. *Manual of Clinical Microbiology*. 6th ed. Washington DC: American Society for Microbiology, 1995:1327-41.
10. Sirisanthana V. Demographic and clinical characteristic of symptomatic vertical HIV-infected children at Chiang Mai University Hospital. *J Infect Dis Antimicrob Agents* 1996;13: 89-93.
11. Huang TC, Leu HH. Clinical study of 78 cases of nontyphoid *Salmonella* bacteremia. *Chang Keng I Hsueh* 1993;16:251-6. (Chinese)
12. Soe GB, Overturf GD. Treatment of typhoid fever and other systemic salmonellosis with cefotaxime; ceftriaxone, cefoperazone, and other newer cephalosporins. *Rev Infect Dis* 1987;9: 719-36.
13. Kinsella TR, Yagev R, Shulman ST, Gilmore R, Chadwick EG. Treatment of *Salmonella* meningitis and brain abscess with the new cephalosporins: two case reports and a review of the literature. *Pediatr Infect Dis J* 1987;6:476-80.
14. Poupard MC, Chantal C, Sirot D, Labia R, Sirot J. Identification of CTX-2, a novel cefotaximase from a *Salmonella* mbandaka isolate. *Antimicrob Agents Chemother* 1991;35:1498-500.
15. Rossi A, Lopardo H, Woloj M, et al. Non-typhoid *Salmonella* spp. resistant to cefotaxime. *J Antimicrob Chemother* 1995; 36:697-702.
16. Piddock LJ, Whale K, Wise R. Quinolone resistance in *Salmonella*: clinical experience [letter]. *Lancet* 1990;335:1459.
17. Frost JA, Kelleher A, Rowe B. Increasing ciprofloxacin resistance in *Salmonellas* in England and Wales 1991-1994. *J Antimicrob Chemother* 1996;37:85-91.
18. Huang FY, Huang SH, Chen SH, Hsu YC, Lin CH. Bacteremia in infants with *Salmonella* enterocolitis. *Acta Paediatr Sin* 1991;32:358-64.
19. Ryu CB, Lee ML, Namgoong EK, et al. Bacteremia with nontyphi *Salmonella* and therapeutic implication. *Korean J Intern Med* 1995;10:146-9.