Pediatrics and Neonatology (2012) 53, 193–198

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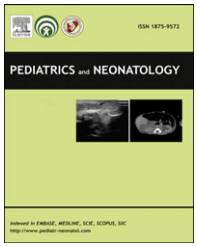

ORIGINAL ARTICLE

Clinical Manifestations of Nontyphoid Salmonellosis in Children Younger than 2 Years Old—Experiences of a Tertiary Hospital in Southern Taiwan

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Received May 16, 2011; received in revised form Aug 24, 2011; accepted Sep 26, 2011

Key Words
antibiotic resistance;
clinical manifestation;
nontyphoid salmonellosis;
young children

Background: Few published studies have explored the clinical manifestations of nontyphoid salmonellosis in children <2 years of age. The aim of this study was to investigate the clinical manifestations, microbiological features, complications, fecal excretion time, and responses to treatment in children <2 years of age with nontyphoid salmonellosis.
Methods: Between January 2005 and December 2009, pediatric patients who were admitted to Kaohsiung Veterans General Hospital with positive cultures for nontyphoid *Salmonella* were enrolled. The following data were recorded: demographic, clinical, and microbiological features, underlying diseases, treatment regimen, complications, responses to treatment, and fecal excretion time. The clinical manifestations were compared between patients <2 years of age and patients >2 years of age.
Results: Of a total 279 enrolled patients, 179 were >2 years of age. Compared with the patients who were ≥2 years of age, patients <2 years of age demonstrated a significantly higher incidence of bloody stool, mixed infection, extraintestinal infection, longer course of antibiotics, longer course of diarrhea after admission, and more days spent in the hospital. The rates of insusceptibility of nontyphoid *Salmonella* to ampicillin, chloramphenicol, trimethoprim/sulfamethoxazole, ceftriaxone, and ciprofloxacin in patients <2 years of age were 37.87%, 29.09%, 23.73%, 3.26%, and 2.25%, respectively. Younger patients were generally more

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doi:10.1016/j.pedneo.2012.04.007

susceptible to antibiotics than patients ≥2 years of age, although this result was not statistically significant.
Conclusion: The clinical manifestations of nontyphoid salmonellosis are more severe in younger children <2 years of age than older children. Local susceptibility patterns could serve as a guide for the prescription of antibiotics by clinicians.

1. Introduction

Nontyphoid *Salmonella* is widely spread throughout nature and is the cause of an ongoing worldwide pandemic of foodborne infections.[1] Nontyphoid *Salmonella* can survive in a wide range of hosts and is strongly associated with agricultural products.[2] In Taiwan, nontyphoid *Salmonella* infection is also rampant.[3] Although most cases of gastroenteritis that are caused by nontyphoid *Salmonella* infection are self-limiting. Up to 8% of patients with nontyphoid *Salmonella* gastroenteritis develop bacteremia, and of these 5–10% develop localized infections.[4,5] The risk of developing a nontyphoid *Salmonella* infection and suffering from complications is higher in patients at the extremes of age and those who are immunocompromised, such as HIV-positive patients or those with pathogens that block the reticuloendothelial system. Shimoni et al postulated that there are major differences in the predispositions, clinical presentations, and clinical outcomes of children and adults who are infected with *Salmonella*; nontyphoid *Salmonella* bacteremia is usually secondary to gastroenteritis in children, but it frequently presents as primary bacteremia in adults.[6] The incidence of extraintestinal nontyphoid *Salmonella* infection in Israel demonstrates a U-shaped age-related pattern, with increased risk at the extremes of age, especially in patients <2 years of age or >80 years of age.[7,8] Chiu et al found that being <3 years of age is one of the characteristics of pediatric patients at high risk of having an extraintestinal infection.[9] Chao et al found that being >1 year of age is one of the risk factors associated with intestinal perforation in pediatric patients with nontyphoid *Salmonella* toxic megacolon.[10] Chiu et al further indicated that such complications are regulated through immune-mediated responses, hence young infants are often spared.[11] Based on the aforementioned studies, we hypothesized that there might be different clinical manifestations in children with nontyphoid salmonellosis depending on age. Cross-talk between T and B cells is of fundamental importance for the establishment of a solid acquired immunity to salmonellosis.[12] Children <2 years of age are incapable of mounting a T cell-dependent immune response to polysaccharide macromolecules.[13] However, with the exception of extraintestinal infection, very few published studies have focused on the clinical manifestations in children <2 years of age with nontyphoid salmonellosis.

The aim of this study was to investigate the clinical manifestations, microbiological features, complications, fecal excretion time, and response to treatment in young children <2 years of age with nontyphoid salmonellosis.

2. Material and Methods

2.1. Study population and case definition

Between January 2005 and December 2009, all of the pediatric patients who were admitted to Kaohsiung Veterans General Hospital with positive cultures for nontyphoid *Salmonella* were enrolled in the study. The following data were retrospectively collected and recorded using a standard case report form for each episode of nontyphoid salmonellosis: demographic, clinical, and microbiological features, underlying diseases, treatment regimen, complications, and responses to treatment. The decision to administer antibiotic treatment was at the discretion of the attending physician, with no input from the authors. The criteria for admission and discharge were customary. Patients were admitted if they presented with fever and diarrhea with any symptoms/signs of dehydration or bloody stool. Fever was defined as >37.5°C, as measured by an ear thermometer. Diarrhea was defined as a decrease in consistency (i.e., soft or liquid) and an increase in the frequency of bowel movements to three stools per day, and bloody stool was defined as any stool reported by the parent or guardian as containing blood in one 24-hour period. Patients were discharged when afebrile for >24 hours and when the symptoms/signs of dehydration had resolved. Furthermore, examination of the fecal excretion time was prospectively designed. After thorough explanation to and agreement from the patients' families, repeated stool cultures were collected from some patients on the day of discharge. Then, additional stool cultures were collected every 5–7 days until two consecutive stool cultures were negative. Fecal excretion time was defined as the time from the first positive stool culture through the first of two consecutive negative results.

2.2. Microbiological features

All isolates were cultured and identified according to standard methods, with no major changes regarding the policy for the identification of *Salmonella*. All isolates were serotyped using the Wellcolex color *Salmonella* test (Murex, Dartford, United Kingdom), then confirmed by slide agglutination test using the O antiserum to detect the O antigen (Bacto, Liverpool, NSW, Australia). The antimicrobial susceptibility of the *Salmonella* isolates was examined using the standard disc diffusion method. Resistance to specific antimicrobials was based on reference interpretive standards of the zone diameter.[14]

2.3. Nontyphoid salmonellosis in children < 2 years of age

Patients were further divided into two subgroups: patients <2 years of age and patients >2 years of age. The following data were collected: sex, fever, days with diarrhea before admission, days with bloody stool and dehydration, laboratory data, underlying diseases, mixed infection, complications, extraintestinal infection, use of antibiotics, response to treatment including days with fever and diarrhea after admission, days spent in the hospital, and fecal excretion time. All data were compared between the two groups. Mixed infection was defined as the simultaneous detection of a pathogen other than nontyphoid *Salmonella* in the stool. Complications included toxic megacolon, bowel perforation, septic arthritis, and upper gastrointestinal (UGI) bleeding. Toxic megacolon was defined as the clinical presentation of a toxic appearance with a high spiking fever (>39°C), dehydration, and marked colon dilatation (colon diameter >1.5 times the width of the vertebral body of the first lumbar spine [L1-VB]) on plain abdominal X-ray films.

2.4. Statistical analysis

Clinical and laboratory data were entered into a computer data base for analysis (SPSS 16.0 for Windows). Categorical data were analyzed using the Chi-square or Fisher exact test. Continuous variables were compared by using the *t* test or the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical features

Two hundred and ninety-seven consecutive patients were enrolled in the study. The characteristics and clinical manifestations of these patients are shown in Table 1. The age distribution is shown in Figure 1, and the median age was 19 months (range: 2–193 months old). Of all of the patients, 58.9% (175 of 297) were male. Twenty-two patients (7.4%) presented with underlying diseases. Diarrhea and fever were the most common clinical manifestations of nontyphoid salmonellosis. Mixed infection was identified in 44 patients (14.8%). In the patients with mixed infections, *Aeromonas sobria* (11 of 297) was the most common pathogen, followed by *A hydrophila* (10 of 297) and rotavirus (9 of 297). Twenty-nine patients (9.8%) experienced extraintestinal infection. In 27 of these patients, isolates were obtained from blood samples; in addition, isolates were obtained from the urine of one patient and from the joint fluid of one patient. Eight patients had both positive blood and stool cultures. Eight patients developed complications: five patients developed toxic megacolon, one experienced colon perforation, one developed septic arthritis, and one developed UGI bleeding. Forty-five patients agreed to be followed until two consecutive stool cultures demonstrated a negative result, and the mean fecal excretion time was 16.2 days. Of these patients, 23 patients were <2 years of age.

Table 1 Demographics, underlying conditions, and clinical features of 297 patients with nontyphoid salmonella enterocolitis.

	% (*n*/total)
Sex (male/total)	58.9 (175/297)
Age (mo) (median; range)	19; 2–193
Underlying diseases	7.4 (22/297)
Congenital heart diseases	7/297
Prematurity	5/297
Kawasaki disease	4/297
Genitourinary anomaly	3/297
Neurological deficit	2/297
Others (Down syndrome, Prader-Willi syndrome)	2/297
Clinical features	
Fever	95.3 (283/297)
Diarrhea	96.3 (286/297)
Bloody stool	38.4 (114/297)
Dehydration	76.8 (228/297)
Seizure	3.0 (9/297)
Mixed infection	14.8 (44/297)
Aeromonas spp.	24/297
Staphylococcus aureus	10/297
Rotavirus	9/297
Adenovirus	3/297
Others (*Bacillus cereus*, *Plesiomonas shigellosis*)	4/297
Extraintestinal infection	9.8 (29/297)
Blood	27/297
Urine	1/297
Joint fluid	1/297
Complications	8/297
Fecal excretion time (d)*	16.2

* Forty-five patients agreed to be followed until two consecutive stool cultures demonstrated negative results.

3.2. Microbiological features

Salmonella enteritidis B caused 56.2% (167 of 297) of the episodes reported here, followed by *S enteritidis* D (21.9%; 65 of 297), C1 (10.1%; 30 of 297), C2 (8.1%; 24 of 297), E (1.4%; 4 of 297) and *S choleraesuis* (1.0%; 3 of 297). The results of the isolates obtained from the different age groups and different sites are shown in Figure 2. Of these isolates, 39.1% (108 of 276) were resistant to ampicillin, 34.5% (30 of 87) were resistant to chloramphenicol, and 24.1% (71 of 295) were resistant to trimethoprim/sulfamethoxazole (TMP/SMX). Seven isolates were intermediately resistant to ceftriaxone, and six were resistant to ciprofloxacin. The antibiotic susceptibility of nontyphoid *Salmonella* in the different age groups is shown in Table 2. Nineteen isolates were resistant to more than three antibiotics.

3.3. Nontyphoid salmonellosis in children < 2 years of age

Of the total of 297 patients admitted with nontyphoid salmonellosis, 179 patients were <2 years of age. When

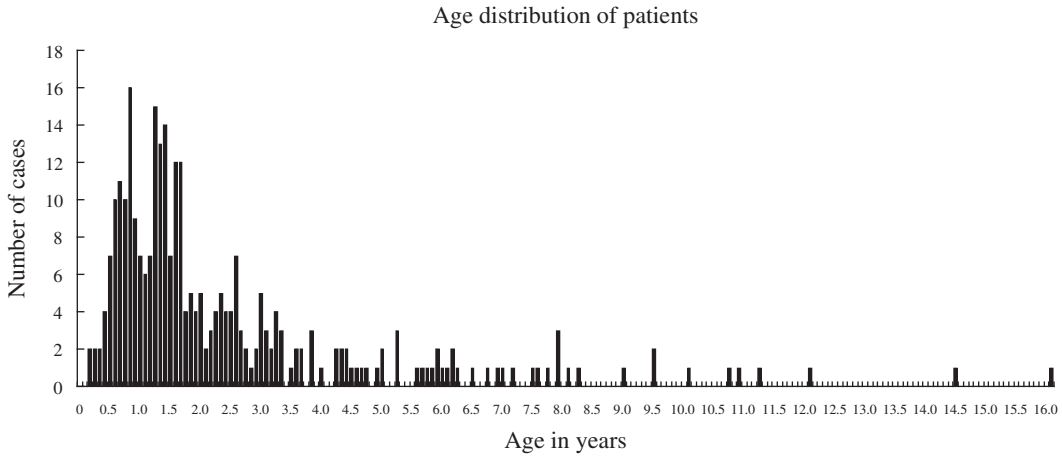

Figure 1 Number of cases and age distribution of nontyphoid salmonellosis in southern Taiwan.

compared with patients >2 years of age, significantly more patients <2 years had bloody stool (46.9% vs. 25.4%, $p < 0.001$), mixed infection (18.4% vs. 9.3%, $p = 0.031$), extraintestinal infection (16.9% vs. 2.8%, $p < 0.001$), experienced diarrhea for more days after admission (4.5 vs. 3.3 days, $p < 0.001$), received antibiotics treatment (62.0% vs. 47.5%, $p = 0.017$), and required longer stays in the hospital (8.6 vs. 6.8 days, $p < 0.001$). Furthermore, although it was not statistically significant, a longer fecal excretion time was also noted in the group that was <2 years of age (19.9 vs. 12.3 days, $p = 0.227$; Table 3). The nontyphoid *Salmonella* isolates from the patients <2 years of age were generally more susceptible to antibiotics than those from the patients >2 years of age; however, this finding was not statistically significant (Table 2).

4. Discussion

Our study confirms the widely held assumption that nontyphoid salmonellosis patients <2 years of age demonstrate severe clinical manifestations, including a higher incidence of bloody stool, mixed infection, extraintestinal infection, and diarrhea after admission. Children <2 years also demonstrated higher rates of complications (3.9% vs. 0.8%); however, this result was not statistically significant, which may be due to the small numbers of patients with complications. Early childhood is characterized by an increased susceptibility to infectious diseases, and this has been attributed to both the immaturity of the immune system at birth and to the sluggish development of immunocompetence during the postnatal and early childhood years. This vulnerability to infections appears to be particularly pronounced in relation to intracellular pathogens, reflecting the functional immaturity of cell-mediated immunity.[15] Furthermore, gastric hypoacidity, the home environment, and intrafamiliar transmission also play roles the development of nontyphoid salmonellosis in younger children.[16–18]

Antibiotics were prescribed more often to patients <2 years of age, which may also have resulted in the longer hospital stays. Previous studies have revealed that the antibiotic treatment of patients with nontyphoid

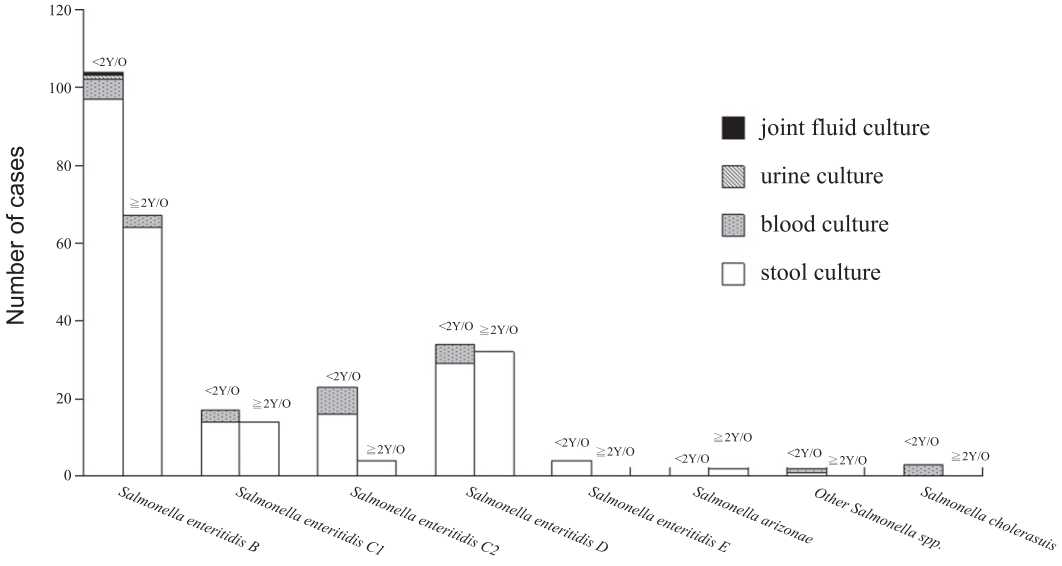

Figure 2 Isolates obtained from different age groups and different sites.

Table 2 Antibiotic susceptibility of nontyphoid Salmonella isolates obtained from different age groups.

	<2 y/o		≥2 y/o		p	Total	
	Resistant	Intermediate	Resistant	Intermediate		Resistant	Intermediate
Ampicillin	37.9% (64/169)		41.1% (44/107)		0.614	39.1% (108/276)	
Chloramphenicol	29.1% (16/55)		43.8% (14/32)		0.242	34.5% (30/87)	
Trimethoprim/ sulfamethoxazole	23.7% (42/177)		24.6% (29/118)		0.890	24.1% (71/295)	
Ceftriaxone		3.3% (3/92)		6.8% (4/59)	0.433		4.6% (7/151)
Ciprofloxacin	2.3% (4/178)		1.7 (2/118)		1.000	2.0% (6/296)	

salmonellosis may prolong, rather than limit, the fecal shedding of these organisms.[19,20] Fecal excretion time was demonstrated to be more prolonged in younger children.[16,21] Although it was not statistically significant, fecal excretion time was also longer in patients <2 years of age in our study. The combined effect of antibiotic prescription and age might have contributed to the longer fecal excretion time in patients <2 years of age. Furthermore, the mean fecal excretion time was 16 days in our study, which is shorter than that reported in a previous study, where the fecal excretion time was reported to be 7 weeks in children <5 years of age.[21] The factors that result in variations in the fecal excretion time include the criteria for negativity (e.g., consecutive, 2, 3, or more negative stool cultures), specimen collection, methods of bacteriological analysis, measurement of the duration of infection, etc.[21] Furthermore, it was difficult to differentiate reinfection from continuous fecal excretion because the stool cultures were not collected every day in the previous studies or in this study. The aforementioned study was performed 20–30 years ago. The standards for hygiene, sanitation, availability of safe water, and food preparation practices have all been significantly improved since then. All of these factors might have contributed to the shorter fecal excretion time measured in our study.

In our previous study, which was conducted at the same institute 10 years ago, the rates of resistance of nontyphoid *Salmonella* to ampicillin, chloramphenicol, and TMP-SMX were 60.5%, 66.0%, and 46.1%, respectively.[22] In the present study, the rates of resistance of nontyphoid *Salmonella* to ampicillin, chloramphenicol, and TMP-SMX were 39.1%, 34.5%, and 24.1%, respectively, which are all lower than those reported in our previous study. However, the insusceptibility rate to ceftriaxone was higher in the present study than that of the previous study (4.6% vs. 0.3%). A trend of increasing insusceptibility to ceftriaxone has also been observed in northern Taiwan.[23] However, the susceptibility rate to ciprofloxacin has not obviously changed in the past 10 years (2.0% vs. 2.0%) according to the results of our studies. Furthermore, the nontyphoid *Salmonella* isolates obtained from the patients <2 years of age were generally more susceptible to antibiotics than those obtained from the patients >2 years of age, although statistical significance was not obtained for this result. The prevalence of resistance among nontyphoid *Salmonella* isolates may be consistent with the level of the antibiotics used to treat humans and animals because nontyphoid *Salmonella* is a zoonotic pathogen. Furthermore, some resistance genes are located on the plasmids, and the majority of the resistant isolates are usually coresistant to

Table 3 Characteristics of the study patients according to ages.

	<2 y/o (n = 179; mean ± SEM*)	≥2 y/o (n = 118; mean ± SEM)	p
Sex (male/total)	101/179	74/118	0.335
Duration of fever before admission (d)	2.3 ± 0.2	2.5 ± 0.2	0.399
Duration of diarrhea before admission (d)	2.5 ± 0.2	2.3 ± 0.2	0.353
Bloody stool	84/179	30/118	<0.001
Dehydration	132/179	96/118	0.160
Absolute neutrophil count (/Cumm)	5081 ± 208	5591 ± 280	0.138
C-reactive protein (mg/dL)	6.7 ± 0.6	7.7 ± 0.7	0.302
Underlying diseases	13/179	9/118	1.000
Duration of fever after admission (d)	2.8 ± 0.2	2.4 ± 0.2	0.129
Duration of diarrhea after admission (d)	4.5 ± 0.2	3.3 ± 0.2	<0.001
Extraintestinal infection	26/154	3/109	<0.001
Complications	7/179, 3.9%	1/118, 0.8%	0.152
Mixed infection	33/179	11/118	0.031
Duration of hospital stay (d)	8.6 ± 0.4	6.8 ± 0.3	<0.001
With antibiotics	111/179	56/118	0.017
Fecal excretion time (d)	19.9 ± 5.8 (n = 23)	12.3 ± 1.9 (n = 22)	0.227

* SEM: standard error of the mean.

many other antibiotics. The ability of these mobile elements to transfer within or between bacterial species is associated with the rapid spread of antimicrobial resistance among *Enterobacteriaceae*, including *Salmonella*.[23–25] Younger children have less chance of being exposed to antibiotics and the products of animal husbandry compared with older children. The prevalence of resistance among nontyphoid *Salmonella* in our study may have been caused by the inappropriate use of antibiotics in medicine, veterinary medicine, and the food industry. Therefore, in addition to creating innovative methods to limit the inappropriate use of antibiotics in animal feed, the usage of extended-spectrum cephalosporins in children should also be weighed against the development of resistance. Continuous surveillance of antibiotic resistance may provide additional data that could be used to help refine recommendations for the treatment of nontyphoid salmonellosis.

In conclusion, the clinical manifestations of nontyphoid salmonellosis, including bloody stool, mixed infection, extraintestinal infection, and duration of hospital stay, are more severe in children <2 years of age than older children. Whether the more severe manifestations are an indication of antibiotic treatment remains undetermined. Local susceptibility patterns could serve as a guide for the prescription of antibiotics by clinicians.

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