ORIGINAL ARTICLE

Clinical features and antibiotic susceptibility of *Salmonella* gastroenteritis in children: A ten-year review

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ABSTRACT

Introduction: *Salmonella* is a common organism, causing intestinal and extraintestinal infections among Thai children, especially infants, and leading to overwhelming antibiotic use.

Materials and Methods: In this retrospective review, data collected during 2006-2015 from the medical charts of patients with evidence of infection, caused by any *Salmonella* serogroup or clinical form, were examined. We aimed to assess the clinical manifestations, antibiotic susceptibility, and antibiotic use in children with *Salmonella* gastroenteritis over the ten years' period.

Results: A total of 419 patients had non-typhoidal *Salmonella* infection. Four-hundred (95.5%) patients were diagnosed with acute gastroenteritis, which was common in children aged <12 months (72.3%). The clinical features of patients with gastroenteritis included fever (74.5%), diarrhoea with bloody mucus (60.5%), watery diarrhoea (39.5%), and vomiting (19.8%). Serogroup B was most commonly detected in the stool specimens. The susceptibility of non-typhoidal *Salmonella* to ampicillin, norfloxacin, and co-trimoxazole was 36.3%, 98.0%, and 80.5%, respectively. Serogroup B was the most resistant strain, which was sensitive to ampicillin in only 21.6% of specimens, while it showed high susceptibility to norfloxacin and co-trimoxazole (98.1 and 84.0%, respectively). Third-generation cephalosporin and fluoroquinolone were most commonly prescribed.

Conclusions: Acute gastroenteritis is the most common form of *Salmonella* infection. Gastroenteritis caused by serogroup B is still the most common infection, which mostly occurs among infants under one year of age. The majority of stool specimens were still susceptible to antimicrobial agents, especially fluoroquinolone and co-trimoxazole; however, there was an overuse of antibiotics without proper indications.

KEYWORDS:
Salmonella infections, Gastroenteritis, Children

INTRODUCTION

Salmonella infection is one of the most common foodborne diseases, which commonly causes gastroenteritis among children. It is a disease with a high burden in developing countries, including Thailand, leading to the unnecessary use of antibiotics and inducing antimicrobial resistance. *Salmonella* is a Gram-negative bacillus, belonging to the Enterobacteriaceae family. In two species of *S.bongori* and *S.enterica*, over 2,500 different serotypes or serovars have been identified so far. However, only two types are categorized with respect to clinical manifestations, that is, non-typhoidal and typhoidal *Salmonella* (enteric fever).[1,2]

According to the Centers for Disease Control and Prevention (CDC), there were more than ten million patients with Salmonella infection (4,847,000 Disability Adjusted Live Years (DALYs) lost) and 1.2 deaths per 100,000 population in 2010.[3-6] The Bureau of Epidemiology in Thailand reported that non-typhoidal *Salmonella* infection was more common than typhoidal and paratyphoidal *Salmonella*. Evidence shows that the incidence of enteric fever in Thailand is decreasing. In 2015, the prevalence of enteric fever was 2.3 patients per 100,000 population versus 20.74 patients per 100,000 population in 1998. Non-typhoidal Salmonella is still a major public concern, and its actual burden is substantial and underreported. Infants younger than three months, immunocompromised patients, and patients with HIV infection, malaria infection, and malnutrition are at risk of *Salmonella* infection.[3,6]

We aimed to assess the clinical manifestations and treatment outcomes of patients with *Salmonella* gastroenteritis and to evaluate the antibiotic susceptibility pattern and antibiotic use over a ten years period.

MATERIALS AND METHODS

This retrospective chart review of *Salmonella* infection was conducted at the HRH Princess Maha Chakri Sirindhorn Medical Center, Thailand, during 2006-2015. From the 469 cases with positive culture for *Salmonella*, only 419 patients were younger than 15 years and were diagnosed with a clinical form of *Salmonella* infection, including gastroenteritis, bacteremia, localized infection, disseminated infection, and enteric fever. Demographic data, including age, gender, underlying disease, duration of hospitalization, ICU admission, and clinical manifestations, were recorded. The results of antibiotic susceptibility tests of specimens and treatment information were also collected in the case record forms. The exclusion criterion was having incomplete data.

SPSS version 22 was used to evaluate categorical and continuous data, presented as percentage, mean, median, interquartile range (IQR), and standard deviation (SD). The

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Table I: Demographic characteristics of patients with Salmonella infection

Characteristics	Number (%)
Gender	
Male	217 (51.8)
Female	202 (48.1)
Age (years)	
0-1	303 (72.3)
>1-15	116 (27.7)
Median (IQR)	1.12 (0.01-15.94)
Underlying disease	34 (8.1)
Anemia	11 (32.3)
Hepatoblastoma	1 (2.9)
Congenital heart disease	8 (23.5)
Cow's milk protein allergy	2 (5.8)
Neurological diseases	4 (11.7)
Others	8 (23.5)
Clinical forms	
Gastroenteritis	400 (95.9)
Bacteremia	16 (3.8)
Meningitis	2 (0.5)
Septic arthritis	1 (0.2)

Table II: Clinical characteristics of Salmonella gastroenteritis

Clinical manifestations	Number (%)	Mean±SD of duration (days)
Fever	298 (74.5)	1.89±1.52
Vomiting	79 (19.8)	2.47±3.17
Diarrhea	400 (100)	1.51±0.93
Stool appearance		
Watery	158 (39.5)	-
Bloody mucous	242 (60.5)	-

Table III: Antibiotic prescriptions in patients with Salmonella gastroenteritis

Antibiotic prescription	Total N (%)	2006-2008 N (%)	2009-2011 N (%)	2012-2015 N (%)	P-value[b]
Overall	297/400 (74.2)	54/70 (71.1)	92/115 (80)	151/215 (70.2)	0.546
With indication[a]	43/297 (14.5)	9/54 (16.7)	10/92 (10.9)	24/151 (15.9)	0.491

[a]Infants <3 months and immunocompromised hosts, including patients with HIV infection and hemoglobinopathies.
[b]Significant at p<0.05.

Table IV: Antibiotic susceptibilities of different Salmonella serogroups in patients with Salmonella gastroenteritis

Antibiotic susceptibility	Total	Serogroup B	Serogroup C	Serogroup D	Other serogroups	P-value[a]
Number (%)	400 (100)	213 (53.3)	104 (26)	43 (8.5)	49 (12.3)	
Ampicillin (%)	145 (36.3)	46 (21.6)	55 (52.9)	11 (32.4)	33 (67.3)	<0.001
Norfloxacin (%)	392 (98)	209 (98.1)	100 (96.2)	34 (100)	49 (100)	0.62
Co-trimoxazole (%)	322 (80.5)	179 (84)	77 (74)	24 (70.6)	42 (85.7)	0.14

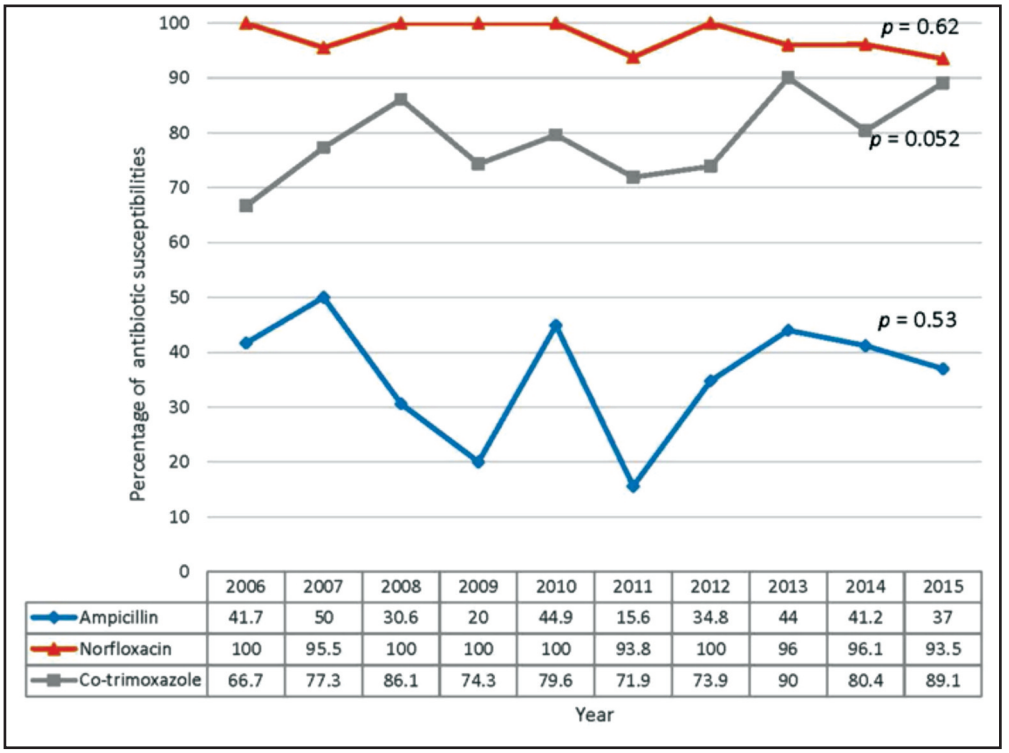
[a]Significant at P<0.05.

level of significance was set at P<0.05. This study was approved by the Institutional Review Board (IRB) of Srinakharinwirot University.

RESULTS

All the 419 patients were infected with non-typhoidal *Salmonella*. Overall, 217 (51.8%) patients were males. The mean age of the subjects was 1.12 years (IQR: 0.01-15.94), and the study sample mostly included children younger than one year (72.3%). Approximately 8% of patients had underlying diseases. Four-hundred (95.9%) patients were diagnosed with gastroenteritis. Other clinical forms included bacteremia (3.8%), meningitis (0.5%), and septic arthritis (0.2%), as shown in Table I. All patients with gastroenteritis had diarrhoea. Diarrhoea with bloody mucus was reported in 242 (60.5%) patients. Other clinical manifestations of patients with gastroenteritis included fever (74.5%) and vomiting (19.8%), as shown in Table II. Nearly 51% (204 patients) with *Salmonella* gastroenteritis were hospitalized. The mean duration of hospitalization was 5.55±3.71 days.

Antibiotics were prescribed empirically before the results of stool cultures were available for 297 (74.2%) patients, while only 43 (14.5%) patients were prescribed antibiotics with proper indications (i.e., infants <3 months and immunocompromised hosts, including patients with HIV infection and haemoglobinopathies). Almost all of the



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Ampicillin	41.7	50	30.6	20	44.9	15.6	34.8	44	41.2	37
Norfloxacin	100	95.5	100	100	100	93.8	100	96	96.1	93.5
Co-trimoxazole	66.7	77.3	86.1	74.3	79.6	71.9	73.9	90	80.4	89.1

Fig. 1: Antibiotic susceptibility trend of non-typhoidal *Salmonella* isolates from stool cultures. Susceptibility to norfloxacin, co-trimoxazole, and ampicillin did not change significantly during 2006-2015 (P=0.62, 0.052, and 0.53, respectively).

patients (97.6%) who received antibiotic improperly were not discontinued their antibiotics after *Salmonella* was reported in stool specimens. There was no improvement in antibiotic prescriptions, based on the indications over the ten years period (p=0.496), as shown in Table III. Third-generation cephalosporin was the most commonly used antibiotic, which was prescribed in 206 (69.4%) patients, whereas norfloxacin, co-trimoxazole, and other antibiotics were prescribed in only 25.9%, 2.7%, and 2% of patients, respectively. The mean duration of antibiotic use was 5.37±2.468 days. There was a significant difference regarding the length of hospital stay between the prescribed and non-prescribed groups of patients (5.22 vs. 3.76 days; p<0.001).

The most common serogroup of *Salmonella* infection was serogroup B, which was detected in the stool specimens of 213 (53.3%) patients. Serogroup C, serogroup D, and others were detected in 104 (26%), 34 (8.5%), and 49 (12.3%) patients, respectively. Overall, non-typhoidal *Salmonella*, isolated from the stool cultures, was sensitive to ampicillin, norfloxacin, and co-trimoxazole (36.3%, 98%, and 80.5%, respectively). Serogroup B was the most resistant serogroup, which was susceptible to ampicillin in only 46 (21.6%) specimens. However, it still showed high sensitivity to norfloxacin in 209 (98.1%) specimens and to co-trimoxazole in 179 (84%) specimens, as shown in Table IV. Also, there were significant differences in ampicillin susceptibility between different serogroups (p<0.001). The trend of antibiotic susceptibility was also compared during 2006-2015, and there was no significant change over this period (Figure 1).

DISCUSSION

In this retrospective, descriptive review, patients living in rural areas of Thailand, who were diagnosed with different forms of *Salmonella* infection, including typhoidal, paratyphoidal and non-typhoidal *Salmonella*, were evaluated. During 2006-2015, there was no typhoidal or paratyphoidal *Salmonella* detected. This finding is consistent with the latest data from the Thai Bureau of Epidemiology, which reported a decreasing incidence of typhoid fever or enteric fever.

The southern and northern areas of Thailand are still endemic areas of enteric fever.[7] In this regard, Techasaensiri C. reviewed the incidence of enteric fever in Thailand. The peak incidence was 8.6 cases per 100,000 person-years in 2003, which gradually decreased to three cases per 100,000 person-years in 2014.[8] In contrast, a previous study from Cambodia reported an increasing trend of enteric fever. *Salmonella paratyphi* A isolates were recovered from blood cultures, representing a 44-fold increase from 2007 to 2010. Moreover, infections with *S.typhi* showed a two-fold increase within the same period.[9]

Gastroenteritis and bacteremia were the most common forms of *Salmonella* infection in this review and were commonly found in infants under one year of age. There was no outbreak of *Salmonella* gastroenteritis during this ten-year period. These findings are consistent with two previous studies during 2006-2010, which found gastroenteritis and bacteremia as the most common forms of *Salmonella* infection.[10,11] In these studies, the most common age group was <1 year (59.7% in children <1 year vs. 49.3% in children

>1 year). We reviewed the clinical presentations of patients with gastroenteritis and found that most of them (60.5%) had diarrhoea with bloody mucus. This result contradicts the previous studies, which only reported an incidence rate of 17.1%.[12] However, there is a possibility of over-reporting, because in general practice, physicians typically collect stool cultures only from patients with a history of bloody diarrhoea.

In our cases, the susceptibility of non-typhoidal *Salmonella*, isolated from stool cultures, to ampicillin, norfloxacin, and co-trimoxazole was 36.3%, 98%, and 80.5%, respectively. Based on the findings, antibiotic susceptibility has not changed significantly over the ten years period. There was an increasing trend of co-trimoxazole susceptibility from 66.7% to 80.4% (P=0.052); this finding may be related to the less frequent use of co-trimoxazole today. On the contrary, ampicillin susceptibility showed a decreasing trend because of inappropriate penicillin and cephalosporin use. These findings are consistent with a previous study from China, which reported the high susceptibility of non-typhoidal *Salmonella* to fluoroquinolones and co-trimoxazole (81.1% and 73.9%, respectively), whereas it showed very poor susceptibility to ampicillin (38.7%).[13] Antibiotic use might cause some selective pressure which allow antibiotic resistant strains to survive and finally develop more antibiotic resistances.[14] During this decade, the third-generation cephalosporins were predominantly prescribed. It could explain why the majority of the stool specimens were resistant to penicillin and appeared to sensitive to cotrimoxazole and fluoroquinolone during most recent years.

In the current review of cases, Group B *Salmonella* was the most common serogroup in patients with gastroenteritis, which is consistent with several previous studies.[12,15-18] Serogroup B also showed the lowest susceptibility to ampicillin, compared to other serogroups (p<0.001). Moreover, Vithayasai N. found that group B *Salmonella* had the lowest susceptibility to ampicillin (21%), whereas it showed higher susceptibility to fluoroquinolone and co-trimoxazole (98.4% and 83.9%, respectively); other serogroups showed better susceptibility to ampicillin (p<0.001).[12] Another study from Thailand demonstrated that serogroup B was the most common cause of *Salmonella* gastroenteritis, which was susceptible to ampicillin, co-trimoxazole, chloramphenicol, third-generation cephalosporin, and ciprofloxacin (10.7%, 75.3%, 63.3%, 77.3%, and 98.8% susceptibilities, respectively).[11]

Most patients with acute diarrhoea recovered without antibiotics. The World Health Organization (WHO) recommends prescribing antibiotics only for patients with severe cholera and *Shigella* infections, but not *Salmonella*.[2] Although improper antibiotic therapy may affect the stool culture results within the first week, it has no clinical significance. It also results in prolonged Salmonella excretion after three weeks.[19,20] In our cases, the mean duration of hospitalisation was 5.5±3.5 days in gastroenteritis patients. This finding is similar to a study by Lan WT et al., which reported a mean hospital stay of 6.6±3.5 days.[21] Patients who received antibiotics had significantly longer hospital stays. We found significant correlation between antibiotic prescription and hospitalisation. The physicians tended to give antibiotics to patients who had more severe symptoms and needed hospitalization (p<0.001). Therefore, these patients might need longer duration in hospital admission to complete course of antibiotics. Thus, previous studies have also shown that antibiotic prescription results in a significantly longer duration of diarrhoea, but does not affect the duration of fever.[12,20]

The Infectious Diseases Society of America (IDSA) recommends antibiotics only for patients at risk of invasive infection, including neonates (up to three months old), individuals over the age of 50 years with suspected atherosclerosis, and patients with immunosuppression, cardiac disease, or a major joint disease.[22] Treatment options include ciprofloxacin and ceftriaxone. However, in children <3 months, third-generation cephalosporin is preferred, considering the side effects of fluoroquinolone. In our cases, third-generation cephalosporin was the most frequently prescribed antibiotic, used generally without proper indications (85.5%). The reason which could explain why the rates of antibiotic prescription have been very high because general physicians sometimes concerned and could not distinguish the clinical symptoms of *Shigella* from *Salmonella* infection. Therefore, most patients in our review were given antibiotic empirically to the patients with mucous bloody diarrhoea before the results of stool culture were reported. Almost all physicians (97.6%) who prescribed antibiotic improperly did not discontinue their antibiotic prescriptions after final results of stool specimens were reported. Overall, if the proper use of antibiotics is enforced, the likelihood of drug resistance will reduce in the future.

There were some limitations in this review. Firstly, the incidence of *Salmonella* gastroenteritis might have been underestimated. Secondly, physicians normally collect stool samples for culture studies only if the patient has bloody mucous diarrhoea or when the stool leukocytes are positive.

CONCLUSION

There was no typhoidal or paratyphoidal *Salmonella* infection over the ten years' period of review. Gastroenteritis caused by serogroup B was still the most common form of *Salmonella* infection, which mostly occurred in infants <1 year of age. The majority of stool specimens were still susceptible to antimicrobials, especially fluoroquinolone and co-trimoxazole, whereas the overuse of antibiotics without proper indications was observed. These findings can guide us and promote more appropriate antibiotic stewardship programmes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board (IRB) of Srinakharinwirot University (SWUEC 107/60).

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