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Non-Typhoidal *Salmonella* Gastroenteritis Outcomes in Immunocompetent Children

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Abstract:

Objective: To compare the clinical outcomes in children older than 3 months with non-typhoidal *Salmonella* (NTS) gastroenteritis treated with or without empirical antibiotics.

Material and Methods: Medical records of all patients aged 3 months to 15 years having experienced their first episode of NTS and treated at Songklanagarind Hospital from January 2007 until December 2021 were reviewed.

Results: NTS infections occurred in 18 (8.0%) of 224 patients, with NTS gastroenteritis. Antibiotics were empirically prescribed to 159 (70.9%) patients. The antibiotics group included a significantly higher proportion of patients with a general sick appearance (20.1% vs. 6.3%), bloody diarrhea (56.6% vs. 33.3%), and abdominal pain (12.9% vs. 1.9%) than that in the no-antibiotics group. The antibiotics group seemed to have a shorter median (interquartile range [IQR]) duration of bloody diarrhea (3.0 [1.3–4.8] vs. 4.5 (3.0–6.5) days, p-value=0.051), but similar duration for fever (3.0 [1.0–4.0] vs. 3.0 [1.3–5.0] days, p-value=0.566) compared to that for the no-antibiotics group. In multivariate analysis, children with underlying diseases (extravascular hemolytic anemia and/or abnormal kidney and urinary bladder system), fever duration ≥5 days by the first visit, and white blood cell (WBC) count >15,000 cells/mm^3 were at risk of iNTS infections, with an odds ratios (95% confidence intervals) of 7.96 (1.70, 37.30), 7.75 (1.74, 34.46), and 8.69 (2.39, 31.55), respectively.

Conclusion: Patients aged 3-36 months with NTS gastroenteritis having an underlying disease, fever duration ≥5 days, and/or WBC count >15,000 cells/mm^3 should be treated with empirical antibiotics while waiting for hemoculture.

Keywords: antibiotics, invasive NTS, non-typhoidal *Salmonella* infection, NTS, Immunocompetent children, risk factor

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Introduction

Non-typhoidal *Salmonella* (NTS) is a common cause of diarrhea in children worldwide, especially in many developing countries, such as Africa and Asia[1]. Common symptoms of NTS infection include fever and gastrointestinal symptoms, such as vomiting, dysentery and diarrhea, which are usually self-limited. Nonetheless, in some cases, invasive

NTS (iNTS) infections, including septicemia, meningitis, and urinary tract infections, may develop not only in immunocompromised hosts and children aged less than three months but also in immunocompetent children[2-5]. If timely administration of appropriate antibiotics is not commenced, morbidity and mortality rates can be high.

A previous systematic review and meta-analysis of 12 randomized controlled trials, comparing any antibiotic treatment for diarrhea caused by NTS species with placebo or no antibiotic treatment, found no difference in outcomes, including duration of diarrhea, duration of fever, and clinical failure, between the groups in all age groups[6]. However, there are few studies comparing the clinical outcomes of infants receiving or not receiving antibiotics[4,5].

Expert opinion often suggests that infants aged less than 3 months should receive empirical antibiotic treatment for NTS gastroenteritis, whereas it is generally not recommended for older and otherwise healthy children[7]. Antibiotic treatment for NTS gastroenteritis is only indicated if there are risk factors for invasive disease because NTS excretion in the stool can be prolonged and its resistant strains can be increased. However, the duration of gastrointestinal symptoms is not shortened by antibiotic treatment[8-10].

Antibiotic treatment of NTS gastroenteritis is recommended for patients aged over 3 months who are unwell, based on the physician's experience. A previous study found that clinical symptoms could not be used to differentiate between patients with or without NTS bacteremia[11].

Hence, this study aimed to compare the clinical outcomes of NTS gastroenteritis in immunocompetent children older than 3 months treated with and without empirical antibiotics, and to determine the prevalence and risk factors of iNTS infections.

Material and Methods

Study design and population

The medical records of all pediatric patients aged 3 months to 15 years having experienced their first episode of culture-positive NTS, and treated at Songklanagarind Hospital, from January 2007 until December 2021, were reviewed in this retrospective study. Patients younger than 3 months and those with an immunocompromised status or without clinical gastroenteritis were excluded.

Demographic data; such as age: gender, underlying diseases, clinical presentation; including general appearance, body temperature, stool characteristics, dehydration status, laboratory investigations; including complete blood counts (CBCs), stool examination, site of culture positive for NTS, antibiotic susceptibility, antibiotic use, and clinical outcomes; including fever duration, diarrhea duration and admission duration, were reviewed.

Patients were classified into two groups according to whether they received empirical antibiotics within 48 hours of the first visit. A general well appearance was considered if a patient was described as active, alert, looking well, or playful. On the other hand, a general sick appearance was considered if the patient was described as having fatigue, irritability, looking sick, toxic, or lethargic. iNTS infection was based on a confirmed NTS culture from sterile sites, including blood, cerebrospinal fluid, joint fluid, and urine.

Statistical analysis

Categorical variables are described using frequencies and percentiles and analyzed using Pearson's chi-square and Fisher's exact tests. Nonparametric continuous data were analyzed using the Mann–Whitney U test and are presented as the median and interquartile range (IQR). All results were considered statistically significant at p-value<0.05. Risk factors for extraintestinal NST infection were analyzed using logistic regression analysis, and significant variables from the univariate analysis were included in the initial multivariate logistic regression model to assess the independent risk factors.

Ethical approval

This study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC. 65-275-1-1).

Results

During the 15-year study period, 355 medical records of pediatric patients with cultures positive for NTS were reviewed. Patients having had no gastrointestinal symptoms, were immunocompromised, or were younger than 3 months of age, were excluded. Finally, 224 patients were enrolled.

Clinical characteristics

The median age of the included 224 patients diagnosed with NTS gastroenteritis was 9.6 (6.0–13.2) months, and 208 (92.9%) were aged less than 36 months. Overall, 77.7% of patients presented with fever and 41.5% had a body temperature ≥39 °C. The median (IQR) fever duration until first visit was 1.0 (0–2.5) days, and nearly half (49.6%) of the patients had bloody diarrhea.

Of the 159 patients that were empirically treated with antibiotics within 48 hr after the first visit, the commonly prescribed empirical antibiotics included ceftriaxone (40.2%), oral third-generation cephalosporin (25.2%) and oral fluoroquinolone (23.3%).

Comparison of the clinical characteristics and laboratory findings between the groups treated with and without antibiotics.

Although the median (IQR) age in the antibiotics group was lower (8.4 [6.0–13.2] vs. 10.8 [7.2–14.4] months, p-value=0.019), the proportion of patients aged 3–12 months was not significantly different between the two groups.

The empirical antibiotics group had a higher proportion of patients with body temperatures over 39 °C (62.9% vs. 48.8%) than the no-antibiotics group; however, the difference was not significant (p-value=0.113). The antibiotics group had a significantly higher proportion of patients with bloody diarrhea (56.6% vs. 33.3%), general sick appearance (20.1% vs. 6.3%), abdominal pain (12.9% vs. 1.9%), and hospitalization (57.9% vs. 38.5%) than that in the no-antibiotics group (Table 1).

The median (IQR) of white blood cell (WBC) count and mean (standard deviation [S.D.]) percentages of neutrophils, platelet counts, and hemoglobin levels in the CBC test were not significantly different between the two groups. The antibiotics group had a significantly higher median (IQR) band count (4.0% vs. 1.0%, p-value=0.02) than that of the no-antibiotic group (Table 2).

The antibiotics group also had a significantly higher proportion of patients with WBCs (83.0% vs. 53.8%, p-value<0.01) and red blood cells (RBCs) (45.1% vs. 11.8%, p-value<0.01) in their stool samples than that in the no-antibiotics group (Table 2).

Comparison of the outcomes between the groups treated with and without antibiotics

Although the median (IQR) duration of bloody

Table 1 Comparison of the clinical characteristics between groups treated with and without empirical antibiotics

Clinical characteristic	Empirical antibiotics (N=159)	No empirical antibiotics (N=65)	p-value
Age, months, median (IQR)	8.4 (6.0–13.2)	10.8 (7.2–14.4)	0.019
Age 3–12 months, n (%)	115 (72.3)	39 (60.0)	0.164
Age >12–36 months, n (%)	33 (20.8)	21 (32.3)	
Age >36 months, n (%)	11 (6.9)	5 (7.7)	
Male, n, (%)	93 (58.5)	35 (53.8)	0.524
Underlying disease, n, (%)	16 (10.1)	3 (4.6)	0.290
Fever, n, (%)	127 (79.9)	47 (72.3)	0.217
Highest BT, °C, mean (S.D.)	39.3 (0.9) (n=116)	39.1 (1.1) (n=41)	0.440
BT ≥39 °C, n, (%)	73 (62.9)	20 (48.8)	0.113
Duration of fever until first visit, days median (IQR)	1.0 (0.5–2.0) (n=121)	1.0 (0–3.0) (n=46)	0.445
Diarrhea, n, (%)	156 (8.1)	63 (96.9)	0.623
Bloody diarrhea, n, (%)	90 (56.6)	21 (33.3)	<0.001
Mucous diarrhea, n, (%)	117 (73.6)	46 (70.8)	0.667
Vomiting, n, (%)	55 (35.3) (n=156)	23 (37.1) (n=62)	0.798
Abdominal pain, n, (%)	15 (12.9) (n=116)	1 (1.9) (n=52)	0.024
General appearance	(n=154)	(n=64)	0.014
Well, n, (%)	123 (79.9)	60 (93.8)	
Sick, n, (%)	31 (20.1)	4 (6.3)	
Hospitalization, n, (%)	92 (57.9)	25 (38.5)	0.008
Invasive NTS infection, n, (%)	16 (10.1)	2 (3.1)	0.105
Bacteremia, n, (%)	12 (7.5)	2 (3.1)	0.361
Meningitis, n, (%)	2 (1.3)	0 (0)	>0.999
Urinary tract infection, n, (%)	2 (1.3)	0 (0)	>0.999

BT=body temperature, S.D.=standard deviation, NTS=non-typhoidal *Salmonella*, IQR=interquartile range

Table 2 Comparison of the laboratory results between groups treated with and without empirical antibiotics

Laboratory result	Empirical antibiotics (N=159)	No empirical antibiotics (N=65)	p-value
WBC $\times 10^3$, cells/mm^3, mean (S.D.)	13.9 (6.4) (n=94)	12.2 (3.8) (n=28)	0.170
WBC >15,000 cells/mm^3, n, (%)	31 (32.0)	4 (13.8)	0.062
Neutrophil, %, mean (S.D.)	46.1 (16.0) (n=94)	46.7 (19.1) (n=28)	0.853
Neutrophil >10,000 cells/mm^3, n, (%)	16 (16.5)	2 (6.9) (n=29)	0.241
Band, %, median (IQR)	4.0 (1.0–9.0) (n=84)	1.0 (0–4.5) (n=25)	0.031
Band >1500 cells/mm^3, n, (%)	14 (16.1)	2 (8.0)	0.517
Hemoglobin, g/dL, mean (S.D.)	11.6 (3.0) (n=100)	10.9 (1.4) (n=29)	0.180
Platelet $\times 10^3$, cells/mm^3, mean (S.D.)	359.5 (133.1) (n=99)	368.4 (121.7) (n=28)	0.750
Mucus positive in stool, n, (%)	91 (88.3) (n=103)	27 (71.1) (n=38)	0.020
WBC in stool, n, (%)			0.001
No and few/WBC 0–5	19 (17.0) (n=112)	18 (46.2) (n=39)	
Moderate and numerous/WBC >5	93 (83.0) (n=112)	21 (53.8) (n=39)	
Stool exam: RBC			0.001
No and few/RBC 0–5, n, (%)	56 (54.9) (n=102)	30 (88.2) (n=34)	
Moderate and numerous/RBC >5, n, (%)	46 (45.1) (n=102)	4 (11.8) (n=34)	

WBC=white blood cell, S.D.=standard deviation, IQR=interquartile range, RBC=red blood cell

diarrhea in the antibiotics group seemed shorter (3.0 [1.3–4.8] vs. 4.5 [3.0–6.5] days, p-value=0.051), that of fever (3.0 [1.0–4.0] vs. 3.0 (1.3–5.0) days, p-value=0.556), diarrhea (5.0 [3.0–7.0] vs. 6.0 [4.0–7.5] days, p-value=0.213), and hospitalization (4.0 [3.0–7.0] vs. 4.0 [2.5–6.5] days, p=0.896) were similar when compared to those of the no-antibiotics group (Table 3).

Of the 65 patients who were not initially treated with antibiotics within 48 hr, 21 (32.3%) subsequently received antibiotics. This was due to bacteremia in two patients, persistent high fever ≥39 °C and/or duration of fever >5 days in 12 patients, and bloody diarrhea in 7 patients. None of the 65 patients developed serious complications.

Clinical characteristics of patients with iNTS infections

Of the 18 patients with iNTS infections, 16 were empirically treated with antibiotics. Bacteremia, meningitis, and urinary tract infections developed in 14, 2, and 2 patients, respectively (Table 1). A long-term complication developed in one patient with NTS meningitis, and magnetic resonance imaging of the brain showed ventriculitis with temporal lobe bleeding.

Two patients with NTS bacteremia who were not initially treated with antibiotics were administered antibiotics on days 6 and 7, respectively. Both patients were under 1 year of age and exhibited both fever and bloody diarrhea.

Risk factors of iNTS infections in febrile children with NTS gastroenteritis

The iNTS infection group had a significantly higher proportion of patients with underlying diseases (33.3% vs. 7.1%), fever duration until first visit ≥5 days (38.9% vs. 8.4%), fever duration prior to antibiotic administration ≥5 days (44.4% vs. 16.3%), WBC count >15,000 cells/mm^3 (66.7% vs. 20.4%), and polymorphonuclear cell count >10,000 cells/mm^3 (33.3% vs. 11.1%) than that in the no-iNTS infection group. The iNTS infection group did not have a significantly higher proportion of patients with a general sick appearance (38.9% vs. 17.4%, p-value=0.053) than that in the no-iNTS infection group (Table 4).

Out of the 4 patients that had bacteremia, Southeast Asia ovalocytosis (SAO), hemoglobin H disease, and hydronephrosis were identified in 2, 1, and 1 patient, respectively.

Two patients with urinary tract infection each had neurogenic bladder and duplex kidney with grade 1 vesicoureteral reflux.

The underlying diseases in 13 individuals without iNTS infections included: cardiovascular diseases in five patients; allergic diseases in two patients; and hydronephrosis, SAO, infantile spasm, congenital adrenal hyperplasia, glucose 6 phosphate dehydrogenase deficiency, and thalassemia trait with mild anemia in one patient each.

Table 3 Comparision of outcomes compared between the groups treated with and without antibiotics

Outcomes	Antibiotics (N=159)	No antibiotics (N=65)	p-value
Duration of fever, days, median (IQR)	3.0 (1.0–4.0) (n=94)	3.0 (1.3–5.0) (n=28)	0.566
Duration of diarrhea, days, median (IQR)	5.0 (3.0–7.0), (n=93)	6.0 (4.0–7.5), (n=29)	0.213
Mucous diarrhea	4.0 (2.0–7.0), (n=61)	5.0 (3.5–8.0) (n=21)	0.129
Bloody diarrhea	3.0 (1.3–4.8), (n=56)	4.5 (3.0–6.5) (n=10)	0.051
Duration of hospitalization, days, median (IQR)	4.0 (3.0–7.0) (n=92)	4.0 (2.5–6.5) (n=25)	0.896

IQR=interquartile range

Of the 162 available stool examination results, the proportion of patients with WBCs (69.8% vs. 76.9%, p-value=0.760) and RBCs (30.5% vs. 36.4%, p-value=0.740) in the stool samples were not significantly different between the iNTS infection and no-iNTS infection groups.

In multivariate analysis, febrile patients with acute gastroenteritis who had underlying diseases, a fever lasting more than five days until the first visit, and a WBC count of more than 15,000 cells/mm3 were more likely to develop iNTS infections, with odds ratios of 7.96 (1.70, 37.30), 7.75 (1.74, 34.46), and 8.69 (2.39, 31.55), respectively (Table 5).

Discussion

In this study, we compared the clinical outcomes in children older than 3 months with NTS gastroenteritis treated with or without empirical antibiotics and determined the risk factors for iNTS infections. Antibiotics were empirically prescribed to 159 (70.9%) out of 224 immunocompetent children with NTS gastroenteritis who were aged >3 months.

Table 4 Clinical characteristics of febrile patients with and without iNTS infections

Clinical characteristic	iNTS (N=18)	No iNTS (N=155)	p-value
Age, years, median (IQR)	0.9 (0.5–1.0)	0.8 (0.6–1.2)	0.709
Male, n, (%)	11 (61.1)	88 (56.8)	0.920
Underlying disease, n, (%)	6 (33.3)	11 (7.1)	0.003
BT ≥39 °C, n, (%)	13 (72.2)	80 (58.0)	0.366
Bloody diarrhea, n, (%)	6 (33.3)	74 (47.7)	0.362
Fever duration prior to first visit, days, median (IQR)	3.0 (1.0-7.3)	1.0 (1.0-2.0)	0.002
Fever duration at first visit ≥5 days	7 (38.9)	13 (8.4)	0.001
Fever duration prior to antibiotics, days, median (IQR)	3.5 (2.0–7.0)	1.0 (1.0–3.5), (n=123)	0.005
Fever duration prior to antibiotics ≥5 days	8 (44.4)	20 (16.3)	0.010
General appearance			0.053
Well, n, (%)	11 (61.1)	128 (82.6)	
Sick, n, (%)	7 (38.9)	27 (17.4)	
WBC >15,000 cells/mm^3, n, (%)	12 (66.7)	21 (20.4), (n=103)	<0.001
PMN >10,000 cells/mm^3, n, (%)	6 (33.3)	12 (11.1), (n=13)	0.028
Band >1,500 cells/mm^3, n, (%)	3 (18.8), (n=16)	13 (14.1), (n=92)	0.703

iNTS=invasive non-typhoidal *Salmonella*, IQR=interquartile range, WBC=white blood cell, PMN=polymorphonuclear cell, BT= body temperature

Table 5 Multivariate analysis predicting extraintestinal NST infection

Clinical presentation	Crude OR (95% CI)	Adjusted OR (95% CI)	p (Wald's test)	p (LR-test)
Had underlying disease	5.22 (1.39, 17.51)	7.96 (1.70, 37.3)	0.009	0.009
Fever duration ≥5 days by the first visit	10.29 (2.93, 36.13)	7.75 (1.74, 34.46)	0.007	0.007
Appearing sick	2.09 (0.73,6)	3.2 (0.84,12.12)	0.088	0.09
WBCs >15,000 cells/mm^3	7.81 (2.62, 23.25)	8.69 (2.39, 31.55)	0.001	<0.001

NST=non-typhoidal *Salmonella*, OR=odds ratio, CI=confidence interval, WBC=white blood cell

iNTS infections were observed in 18 (8.0%) patients. Patients with an underlying disease, fever duration ≥5 days until first visit, and WBC count >15,000 cells/mm^3 were more likely to develop iNTS infections.

Similar to previous studies, it was found that NTS gastroenteritis was common in children aged less than 12 months, and more than 70% of them were prescribed antibiotics. Fever, bloody diarrhea with mucus, and/or a general unwell appearance were common indications for antibiotic prescription[12,13]. However, this study found that antibiotic treatment in healthy children with NTS gastroenteritis did not affect the duration of fever or diarrhea, consistent with previous reports[6,11].

Nevertheless, this study found that the median (IQR) duration of bloody diarrhea in the antibiotics group seemed to be shorter (3.0 vs. 4.5 days) than that in the no-antibiotics group. Therefore, we are in agreement with the current guidelines on antibiotic use in acute gastroenteritis, which indicates that antibiotics should be administered to patients with bloody diarrhea[14].

In this study, the prevalence of iNTS infections in immunocompetent patients aged >3 months having presented with NTS gastroenteritis was 8.0%; which is comparable to that reported in previous studies (6.6–12.4%)[3,13,15]. In addition, it was found that iNTS infections were common in children aged less than 12 months, and less than half of them presented with bloody diarrhea, similar to the findings of a previous study[13]. It was also found, as in previous studies, that patients with iNTS infections visited the hospital with a longer duration of symptoms[15-17], and the risk factor for iNTS infections was fever duration until the first visit ≥5 days[15].

The delayed presentation of iNTS infections could be explained by the mild and gradual clinical presentation of NTS bacteremia, with associated gastroenteritis and dehydration being less pronounced than when the initial diagnosis's were viral infections[16,17]. However, most patients with acute viral infection had a fever duration of less than 5 days[18]. Altogether, we suggest that patients that are initially diagnosed with viral gastroenteritis should be reevaluated for bacterial infections if they have persistent fever lasting ≥5 days. This should also be in combination with performing CBC and blood culture tests; additionally, if the WBC count is >15,000 cells/mm^3 close follow-up and/or empirical antibiotics should be prescribed while waiting for hemoculture results.

In this study, it was found that underlying diseases were a risk factor for iNTS infections. In our cohort four out of 14 patients with NTS bacteremia had hemolytic diseases that might impair the reticuloendothelial system, which plays an important role in preventing iNTS infections[2]. Urinary tract infections caused by NTS is uncommon; however, this study found that two patients with neurogenic bladder disease and vesicoureteral reflux had urinary tract infections during NTS gastroenteritis. In a previous study, pneumonia was observed in 20 (47%) children with iNTS infections[19]. However, in this study, only 1/18 (5.5%) of patients with NTS bacteremia was found.

The first limitation of this study was its retrospective design; moreover, the patient management and antibiotic prescriptions depended on individual physician experience and clinical judgment. Hence, future studies designed to overcome the limitations of the present study may be proposed.

Conclusion

Febrile children with NTS gastroenteritis having an underlying disease, fever lasting ≥5 days, and/or WBC count >15,000 cells/mm^3, should be empirically treated with antibiotics while awaiting hemoculture results. In addition, antibiotics shortened the duration of bloody diarrhea by 1.5 days. Empirical antibiotics should not be prescribed to

healthy children aged more than 3 months who present with non-bloody diarrhea with a fever duration of less than 5 days.

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Conflict of interest

The authors have no conflicts of interest or funding to disclose. This manuscript has not been previously published, and is not presently being submitted to any other journal. All authors have made a significant contribution and have read and approved the final draft.

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