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Original Article

The epidemiology of non-typhoidal *Salmonella* gastroenteritis and *Campylobacter* gastroenteritis in pediatric inpatients in northern Taiwan



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Abstract *Background:* *Campylobacter* and Non-typhoidal *Salmonella* (NTS) are the two most common bacterial pathogens associated with acute gastroenteritis in children. This study aims to elucidate the epidemiology of *Campylobacter* and NTS gastroenteritis and develop a scoring system to differentiate them.

Materials and methods: This retrospective study enrolled 886 children ≤ 18 years of age, hospitalized due to acute gastroenteritis with stool culture-proven *Campylobacter* or NTS infection from July 2012 to December 2015. Pearson's chi-square test and multivariate logistic regression were used to compare clinical manifestations and laboratory data. Receiver operating characteristic curves were plotted to evaluate the scoring system.

Results: Seasonality was found in NTS gastroenteritis from May to September, but no seasonality in *Campylobacter* gastroenteritis. *Campylobacter jejuni* and *Salmonella* serogroup B were the most common pathogens. The median ages were 68.2 and 18.5 months and the incidence rates of bacteremia were 0.6% and 7.1% in the *Campylobacter* and NTS groups, respectively. *Salmonella* serogroup C2 infection had the highest risk of bacteremia (OR: 5.9, 95% CI: 2.8–12.7, $p < 0.001$). Multivariate analysis showed significant differences in sex, age, fever, dehydration, immature WBC, CRP and Na between the two groups. A score of ≥ 2 points indicated *Campylobacter* gastroenteritis, with sensitivity 75%, specificity 77%. The positive and negative predictive values were of 73.3% and 93.9% after validation.

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Conclusion: *Campylobacter* gastroenteritis is associated with older age and male sex, while NTS gastroenteritis is associated with moderate to severe dehydration and bacteremia. *Salmonella* serogroup C2 infection has the highest risk of bacteremia.

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Introduction

Campylobacter and Non-typhoidal *Salmonella* (NTS) are the two common bacterial pathogens associated with acute gastroenteritis in children.^{1–3} *Campylobacter jejuni* is one of the most common causes of bacterial diarrhea in humans.⁴ *Campylobacter* gastroenteritis is usually sporadic, occurring in the summer months and early fall in many countries and usually following the ingestion of improperly handled poultry.⁴ A typical case is characterized by diarrhea, fever, and abdominal cramps.⁴ In the United States, the incidence of campylobacteriosis often exceeds that of salmonellosis and shigellosis in several studies.^{5,6} NTS remains the leading cause of childhood bacterial enterocolitis requiring hospitalization in Taiwan.⁷ The clinical manifestations of NTS gastroenteritis are more severe in younger children <2 years of age than older children.⁸ NTS gastroenteritis may predispose pediatric patients to NTS bacteremia or to focal suppurative complications such as osteomyelitis or meningitis.^{9–11}

The invasive cases of *Campylobacter* infection are relative rare.^{12–14} Most *Campylobacter* infections are self-limited, and treatment is usually supportive and an antibiotic could be withheld even when C-reactive protein is high and before stool culture results are known.¹⁵

Antimicrobial therapy has a role in severe and prolonged gastrointestinal illness caused by NTS and *Campylobacter*. In patients to whom antibiotic treatment is considered, obtaining cultures of the organism from stool samples remains the best way to confirm the etiology. Due to a formal culture result is deferred, a scoring system to differentiate *Campylobacter* from NTS gastroenteritis by history, early symptoms and signs and laboratory data is warranted. The scoring system can help clinicians to decide the use of antibiotic or not, and which antibiotic to use. Although there have been studies on the clinical manifestations of *Campylobacter* gastroenteritis in children,^{12,16} we aim to compare the epidemiology of *Campylobacter* and NTS gastroenteritis in pediatric patients in a medical center in northern Taiwan.

Materials and methods

Study population

This retrospective study was conducted at MacKay Children's Hospital, a tertiary referral hospital in northern Taiwan, from July 2012 to December 2015, and enrolled children aged 0–18 years of age, hospitalized due to stool culture-proven *Campylobacter* gastroenteritis or NTS gastroenteritis. Patients with underlying diseases including

cancer, leukemia, diffuse disease of connective tissue, cerebral palsy, biliary atresia and Hirschsprung disease were excluded. This study was approved by the Institutional Review Board of Mackay Memorial Hospital (IRB number: 15MMHIS215e).

Study method

We retrospectively reviewed the charts of the enrolled children. The study period was divided into two phases. In the first three years, we analyzed variables including fever, diarrhea, vomiting, bloody stool, abdominal cramping, dehydration, total duration of fever, duration of fever before admission, total duration of diarrhea, duration of diarrhea before admission, initial serum WBC count, differential count, CRP level, Na level, whether or not the patient was complicated with bacteremia, and the patient's age. Fever was defined as ear temperature $\geq 38^\circ\text{C}$. Diarrhea was defined as watery stool more than 3 times a day. Abdominal cramping was defined according to the chart record or irritable crying under the age of one. Dehydration was defined according to medical history and physical signs that showed more than 5% of dehydration. After comparing the clinical manifestations and laboratory data between the patients with *Campylobacter* and NTS gastroenteritis, we used factors that were statistically significant in multivariate analysis to design a simple scoring system to predict the result of stool cultures. We graded the factor according to the odds ratio. If the odds ratio was >1 , then we give a positive point, and vice versa. We then validated the sensitivity and specificity of the scoring system by using data from the final six months.

Statistical analysis

All of the statistical analyses were performed using SPSS software, version 20 (IBM Corp., Armonk, NY, USA). Pearson's chi-square test and multivariate logistic regression were used to compare the clinical manifestations and laboratory results between the patients with stool culture-proven NTS and *Campylobacter* gastroenteritis. A *P* value <0.05 was considered to be statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the magnitude of association, and receiver operating characteristic curves were plotted to evaluate the scoring system.

Results

Of the 886 inpatients enrolled in this study, 724 were included in the first phase and 162 in the second phase. The

first phase included 164 cases of *Campylobacter* gastroenteritis and 560 cases of NTS gastroenteritis. The demographic data of these 724 cases are shown in Table 1. The median ages of the NTS and *Campylobacter* gastroenteritis groups were 18.5 (interquartile range [IQR]: 12.0–30.7) and 68.2 months (IQR: 28.2–132.1), respectively, and the mean durations of hospitalization were 5.4 ± 2.8 days and 3.7 ± 1.5 days. Among the *Campylobacter* gastroenteritis group, *C. jejuni* was the most commonly identified pathogen (60.3%), followed by *Campylobacter species* (33.5%) and *Campylobacter coli* (6.1%). *Salmonella* serogroup B was the most common pathogen in the NTS gastroenteritis (46.1%) group, followed by serogroup D (34%), serogroup C2 (8.4%), serogroup C1 (8.2%), and *Salmonella species* (2.9%). Multivariate analysis showed significant differences in sex, age, fever, dehydration, immature WBC, CRP and Na between the *Campylobacter* and NTS gastroenteritis groups (Table 1). The monthly distribution of cases of *Campylobacter* and NTS gastroenteritis are shown in Fig. 1(a and b), respectively. A seasonal pattern was observed for cases of NTS gastroenteritis, with an increase in cases during May, then peaking in July, August and September. However, no seasonal trend was observed for *Campylobacter* gastroenteritis ($P < 0.001$). The age distributions of the patients with

Campylobacter and NTS gastroenteritis are shown in Fig. 2(a and b), respectively.

Thirty-nine of the cases with NTS gastroenteritis were complicated with bacteremia, compared to only one case in the *Campylobacter* gastroenteritis group. Of the 39 cases with bacteremia caused by NTS, serogroup C2 accounted for 31%, serogroup B 23%, serogroup D 21%, and serogroup C1 15% (Table 2). We used multivariate analysis and adjusted by age and gender, serogroup C2 has the highest risk of bacteremia (OR: 5.9, 95% CI: 2.8–12.6, $p < 0.001$). Serogroup B has the lowest risk of bacteremia (OR: 0.3, 95% CI: 0.1–0.7, $p = 0.003$). We then developed the scoring system according to ORs to predict the results of stool cultures (Table 3). Receiver operating characteristic curves showed that a score of ≥ 2 points indicated *Campylobacter* infection, with an acceptable sensitivity (75%) and specificity (77%) (Fig. 3).

We enrolled 162 patients in the second phase of the study, of whom 30 had stool culture-proven *Campylobacter* gastroenteritis and 132 had NTS gastroenteritis. The median age of these patients were 6.6 (IQR: 2.8–15.0) and 1.6 years (IQR: 1.1–2.4), respectively. We analyzed these patients using our scoring system, and the sensitivity, specificity, positive predictive value and negative predictive value were 73.3%, 93.9%, 73.3% and 93.9%, respectively (Table 4).

Table 1 Demographic data of the pediatric inpatients with *Campylobacter* gastroenteritis and *Salmonella* gastroenteritis.

	<i>Campylobacter</i> (<i>N</i> = 164) no. (%)	<i>Salmonella</i> (<i>N</i> = 560) no. (%)	Univariate			Multivariate		
			OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Sex, Male	112 (68.2)	318 (56.8)	1.571	1.055–2.337	0.026	2.325	1.276–4.236	0.006
Fever	136 (82.9)	529 (94.5)	0.264	0.147–0.477	<0.001	0.324	0.131–0.797	0.014
Diarrhea	161 (98.2)	556 (99.3)	0.269	0.03–2.439	0.243			
Vomiting	52 (31.7)	187 (33.4)	0.685	0.452–1.037	0.074			
Abdominal cramping	103 (62.8)	167 (29.9)	3.963	2.752–5.708	<0.001			
Bloody stool	80 (48.8)	309 (55.2)	0.89	0.596–1.328	0.568			
Dehydration	40 (24.4)	192 (34.3)	0.64	0.417–0.981	0.041	0.488	0.255–0.936	0.031
Bacteremia	1 (0.6)	40 (7.1)	0.067	0.008–0.563	0.013			
Age (years)						1.479	1.336–1.637	<0.001
<2	33 (20.1)	361 (64.5)	0.139	0.091–0.211	<0.001			
≤2 ~ <5	43 (26.2)	159 (28.4)	0.902	0.608–1.337	0.607			
≤5 ~ <10	44 (26.8)	27 (4.8)	7.238	4.31–12.156	<0.001			
≥10	44 (26.8)	13 (2.3)	15.428	8.058–29.538	<0.001			
Immature WBC (%)	2.43 ± 4.81	4.36 ± 6.93				0.930	0.873–0.991	0.026
<2	112 (68.7)	293 (52.7)	1.971	1.361–2.855	<0.001			
≤2 ~ <4	18 (11.0)	76 (13.7)	0.784	0.454–1.354	0.382			
≥4	33 (20.2)	187 (33.6)	0.501	0.329–0.763	0.001			
CRP (mg/dl)	6.86 ± 7.02	6.33 ± 6.25				0.942	0.888–1.000	0.049
<1	17 (11.3)	85 (15.8)	0.678	0.389–1.181	0.167			
≤1 ~ <5	54 (35.8)	223 (41.4)	0.789	0.543–1.147	0.214			
≤5 ~ <10	36 (23.8)	114 (21.2)	1.167	0.761–1.790	0.479			
≤10 ~ <15	29 (19.2)	66 (12.2)	1.704	1.054–2.753	0.028			
≥15	15 (9.9)	51 (9.5)	1.055	0.576–1.935	0.862			
Na (mEq/L)	137.3 ± 2.68	135.63 ± 2.51				1.263	1.121–1.424	<0.001
<136	22 (19.3)	173 (46.9)	0.271	0.163–0.450	<0.001			
≥136	92 (80.7)	196 (53.1)	3.691	2.221–6.135	<0.001			

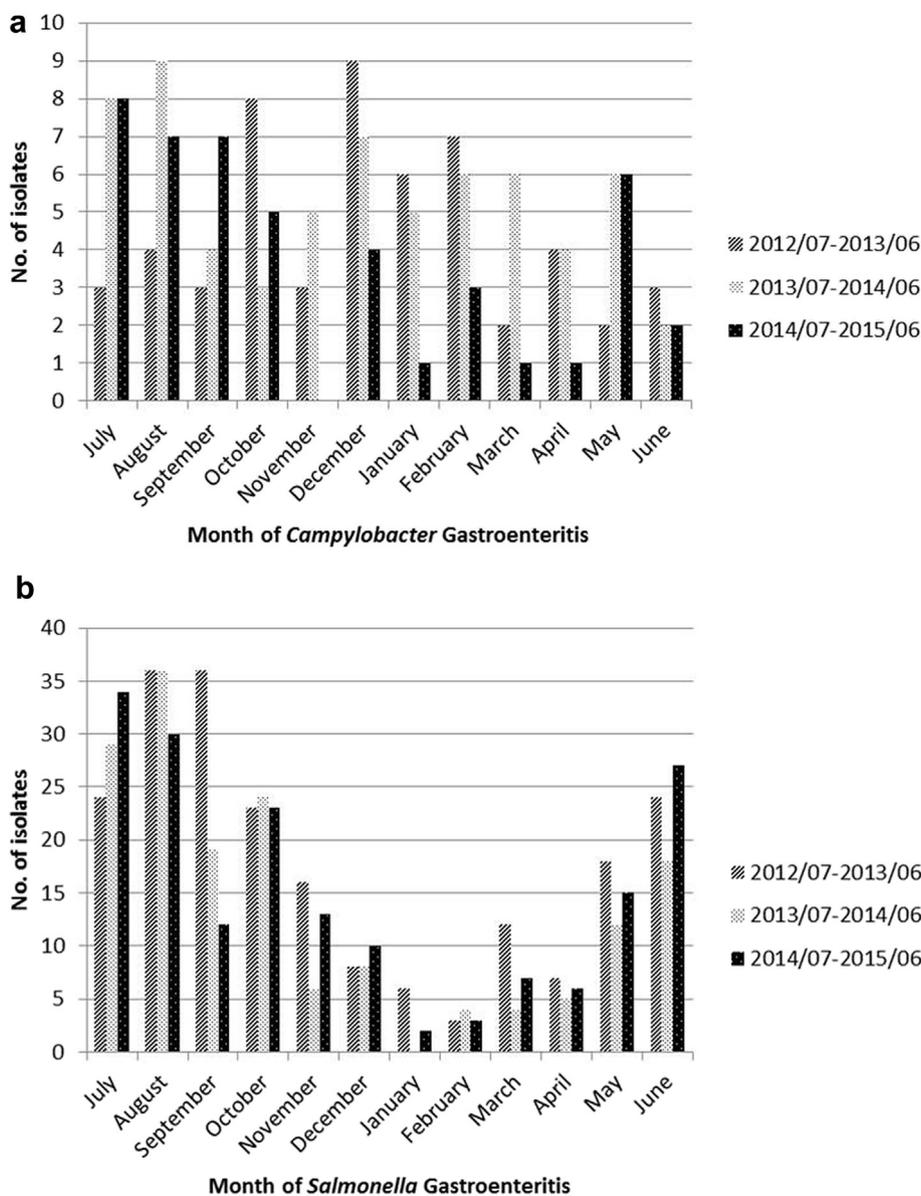


Figure 1. Hospitalized cases of stool culture-proven *Campylobacter* gastroenteritis (1a) and non-typhoidal *Salmonella* gastroenteritis (1b) from July 2012 to June 2015.

Discussion

Our results showed that the inpatients with *Campylobacter* gastroenteritis were older than NTS gastroenteritis, and were predominantly male. In addition, NTS gastroenteritis was associated with higher rates of moderate to severe dehydration and bacteremia than *Campylobacter* gastroenteritis. One previous study conducted in Southern Taiwan also compared patients with *Campylobacter* and NTS gastroenteritis. They found *Campylobacter* infection was associated with older age, abdominal pain, watery diarrhea and higher WBC count.¹⁵ We didn't observe seasonality in cases of *Campylobacter* gastroenteritis, which is consistent with a previous study in Taiwan.¹² In comparison, a seasonal trend was observed for NTS gastroenteritis, with an increase in the number of cases from May to September each year. Another retrospective study in Taiwan also revealed a

peak in the number of cases of NTS gastroenteritis during July and August.¹⁷

In our study, the patients aged 5–10 years had the highest rate of *Campylobacter* gastroenteritis, followed by those aged 2–5 years. One study about sporadic *Campylobacter* infections in the United States reported a bimodal distribution of incidence by age, with the highest incidence among children aged <4 years followed by those aged 20–29 years.¹³ In this study, children >10 years old accounted for more than 25% of all hospitalized cases of *Campylobacter* gastroenteritis, whereas most of the children hospitalized due to NTS gastroenteritis were under the age of five.

Salmonella serogroup B was the most common pathogen among our cases with NTS gastroenteritis, accounting for 46.1% of the cases. Two previous studies conducted in Taiwan also reported that serogroup B was the predominant

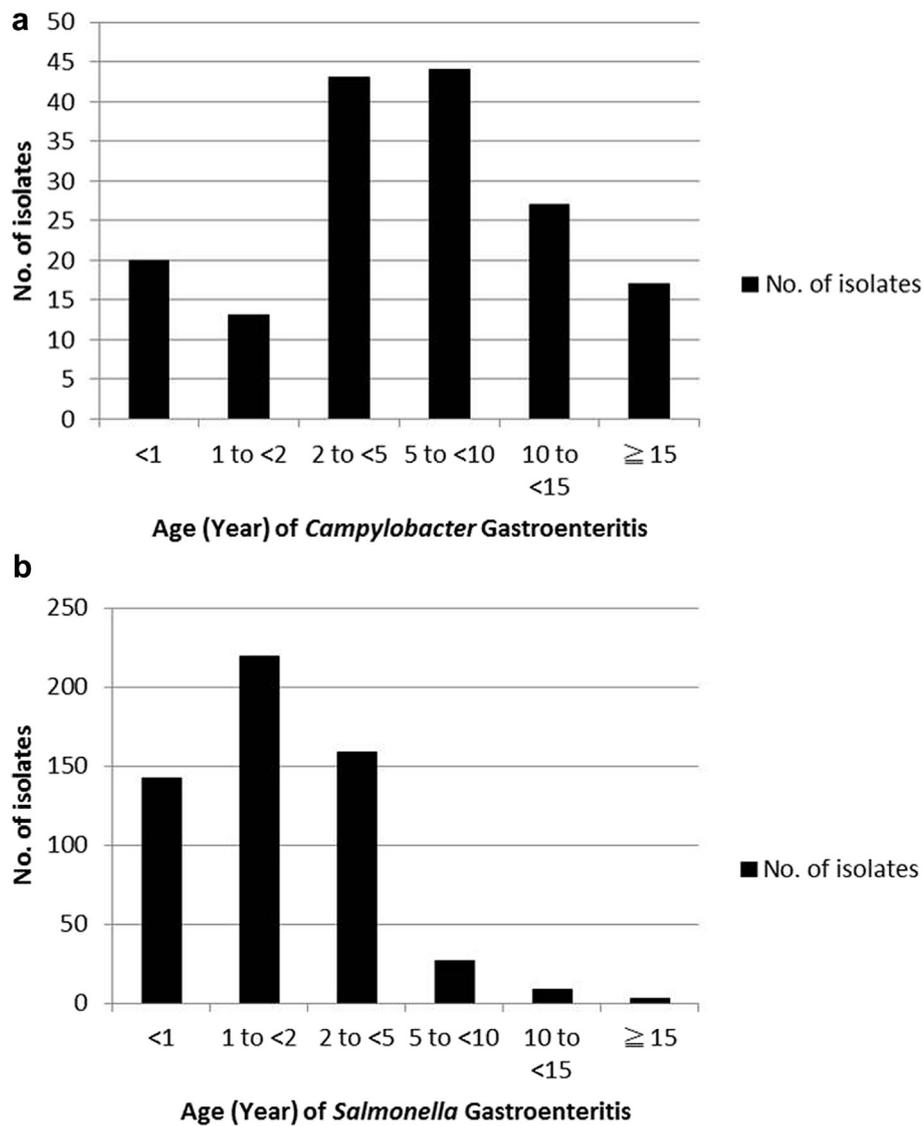


Figure 2. Age distribution of *Campylobacter* (2a) and non-typhoidal *Salmonella* (2b) gastroenteritis from July 2012 to June 2015.

Table 2 Number of patients with concurrent bacteremia of *Campylobacter* gastroenteritis and non-typhoidal *Salmonella* gastroenteritis.

	Total	With bacteremia	Without bacteremia	OR	95% CI	P value
<i>Campylobacter</i>						
<i>C. coli</i>	10	0	10	0.994	0.981–1.006	0.798
<i>C. jejuni</i>	99	1	98	1.011	0.99–1.031	0.416
Species	55	0	55	0.991	0.973–1.009	0.476
<i>Salmonella</i>						
Serogroup B	258	9	249	0.316	0.148–0.677	0.002
C1	46	6	40	2.118	0.839–5.345	0.105
C2	47	12	35	5.939	2.782–12.677	<0.001
D	192	8	184	0.457	0.206–1.011	0.048
Species	16	4	12	4.704	1.444–15.323	0.005

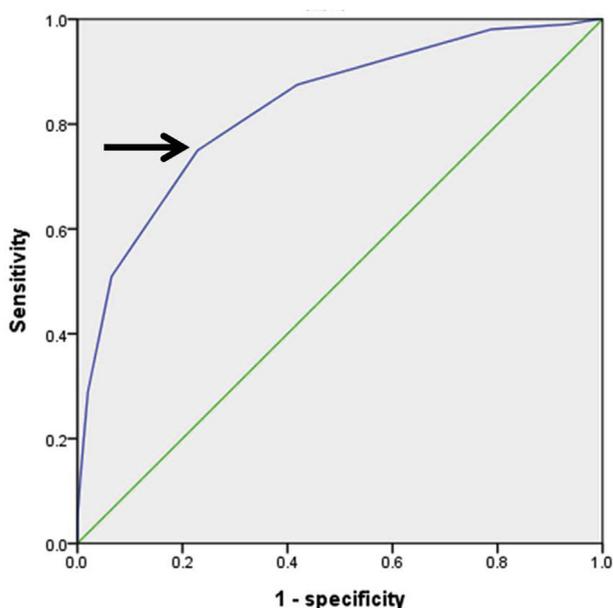
serogroup identified in salmonellosis.^{17,18} Between 2004 and 2012, one large study in Taiwan analyzed 18,280 human *Salmonella* isolates, and found that serogroup B accounted for 39%, serogroup D 29% and serogroup C 23%.¹⁹

Campylobacter gastroenteritis is rarely associated with systemic invasive disease, and the incidence of bacteremia caused by *Campylobacter* species has been reported to be <1%, which is compatible to our study (0.6%).^{12–14,20} The

Table 3 Predictive scoring system for *Campylobacter* and non-typhoidal *Salmonella* gastroenteritis.

Points	-1 point	1 point	2 points
Gender		male	
Age (year-old)	<2	5 ≤ Age < 10	≥10
Fever	Fever		
Dehydration	Dehydration		
Immature WBC (%)	≥4	<2	
CRP (mg/dl)		10 ≤ CRP < 15	
Na (mEq/L)			≥136

Total score: -4 ~ 7 points. A score ≥2 points suggested *Campylobacter* infection.

**Figure 3.** Receiver operating characteristic curves for the scoring system to predict the stool culture results.**Table 4** Validation of the scoring system in 162 patients.

	<i>Campylobacter</i> (Patient no.)	<i>Salmonella</i> (Patient no.)	Total (Patient no.)
Score ≥2	22	8	30
Score <2	8	124	132
Total	30	132	162

Sensitivity: 73.3%; Specificity: 93.9%; Positive predictive value: 73.3%; Negative predictive: 93.9%.

reported incidence of bacteremia in NTS gastroenteritis ranges from 3 to 45%,^{17,18,21–23} depending on geographic region, age and underlying disease. One study conducted in southern Taiwan reported that the incidence of NTS bacteremia in children was 15%.¹⁸ In our study, the incidence of bacteremia caused by NTS was 7.1%.

Differences in the severity of salmonellosis among different serotypes are substantial.²⁴ According to a large study of culture-confirmed *Salmonella* infections, some serovars are more likely to become invasive than others.

Salmonella enterica serotype choleraesuis, which belongs to serogroup C1, and *S. enterica* serotype Dublin, which belongs to serogroup D, are the two most invasive NTS serovars.²⁴ In our study, the most common serogroup complicating with bacteremia was serogroup C2. The difference between our findings and previous reports may be due to our study population was focused on children, difference of geographic area and difference of data collection periods. Hung YT et al. also reported 3 cases had blood cultures that tested positive for NTS, all of which were classified as belonging to serogroup C2.¹⁷

Our scoring system is easy to use and had an acceptable validity. As a result, the scoring system can be a simple tool, especially in patients to whom antibiotic treatment is considered and in hospitals where medical resource is limited. It also provides clinicians a tentative diagnosis before the culture results are confirmed.

There are two limitations to this study. First, we only enrolled hospitalized patients from one medical center in northern Taiwan. Future studies should include patients from outpatient department to represent the whole picture of *Campylobacter* and NTS gastroenteritis. Second, since this is a retrospective study, we could not trace back the dietary history or environmental contact history. Thus, we need a prospective study to investigate how dietary content and environmental contact influence *Campylobacter* and NTS gastroenteritis.

This study presents the epidemiology of *Campylobacter* and NTS gastroenteritis in children in northern Taiwan. Our scoring system can provide more information to clinicians who practice in places where medical resource is limited.

Disclosure

The authors declare no conflicts of interest or sources of funding.

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