

## Experience of *Campylobacter* gastroenteritis in Korean children: Single-center study

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**Objectives:** Although *Campylobacter* is the main cause for bacterial acute gastroenteritis (AGE), there has been no notable clinical research into it, especially for Korean children. In this study, we share our experience of clinical, laboratory and image findings with *Campylobacter* AGE.

**Methods:** Between May 2013 and June 2016, children diagnosed as having *Campylobacter* AGE were retrospectively enrolled in our study. *Campylobacter* AGE was considered diagnosed when a patient had symptoms of bacterial AGE and a positive *Campylobacter* result in stool using multiplex PCR.

**Results:** Among 539 patients with suspected bacterial AGE, 31 (5.8%) patients had a positive result for *Campylobacter*. The average age of the 31 patients was  $10.2 \pm 5.0$  years with a range between 1.1 and 16.9 years. Eighteen (58%) of the total patients were hospitalized between June and August. Diarrhea (93.5%), abdominal pain (83%) and fever (83%) were common symptoms. For 20 patients (65%), diarrhea lasted for less than three days, and fever lasted for 2.1 days on average. Among the 20 patients subjected to imaging studies, 12 patients (60%) showed bowel wall thickening on the right side of colon. In blood tests of 30 patients, 22 (73%) and 29 (97%) patients exhibited leukocytosis and elevated C-reactive protein, respectively. During treatment for *Campylobacter* AGE, prediagnostic empirical antibiotics were used for 6 (19%) patients. All patients recovered without complications.

**Conclusions:** Among the children with suspected bacterial AGE, 5.8% had a positive result on *Campylobacter* in stool using multiplex PCR. Therefore, we observe that *Campylobacter* AGE should be considered in school-age children who have diarrhea, fever, and abdominal pain.

**Key Words:** Acute gastroenteritis, *Campylobacter*, Child

*Campylobacter* is known as the main cause of bacterial gastroenteritis, and is reported to be found in 7.5% of gastroenteritis patients who were subjected to multiplex PCR testing by Korean researchers.<sup>1,2</sup> While some Korean researchers have studied the mechanism of bacterial gastroenteritis,<sup>3,4</sup> *Campylobacter* was not the bacteria

generally identified in the stool analysis for gastroenteritis and there are not many reports available on gastroenteritis caused by *Campylobacter* in Korea. Moreover, because many young patients tend to show non-specific tendency of diseases, they may present differently from adult patients, but in Korea, there is no report of studies of clin-

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ical characteristics of *Campylobacter* gastroenteritis in children.

Therefore, the authors of this study report clinical and laboratory findings and prognoses of *Campylobacter* AGE experienced in the single-center study.

## MATERIALS AND METHODS

Patients 19 years old and under with suspected bacterial AGE and who were subjected to analysis with Seeplex® Diarrhea ACE Detection kit (Seegene, Seoul, Korea) in the Busan Children's Hospital of Busan National University between May 2013 and June 2016 were retrospectively examined. Bacterial AGE was suspected in cases where the patients had symptoms of diarrhea, fever, abdominal pain, vomiting, bloody stool, tenesmus, etc. at least three times a day, separately or in combination thereof after they suddenly got ill. *Campylobacter* AGE was diagnosed if the patients had a positive result for *Campylobacter* spp. Items of examination included the patient's age, gender, in- or out-patient, hospitalization duration, history of hospitalization in intensive care units, the number of in-patients by seasons, infection, underlying diseases, and presence of symptoms during overseas travel. Potential infection by other causes was also examined. The examination included digestive symptoms of nausea, vomiting, diarrhea, abdominal pain and tenesmus, and clinical symptoms of fever (38°C or

higher), feeling chill, headache, dizziness, muscle pain, and weight loss. The duration of fever and diarrhea was examined, and diarrhea was characterized as to whether it was mucus, bloody, or watery. Moreover, the examination also examined the use of antibiotics, recovery after treatment and possible complications. A blood test was performed to check levels of total white cells, neutrophils, the level of C-reactive protein, ESR (Erythrocyte Sedimentation Rate), albumin, aspartate aminotransferase, alanine aminotransferase, total bilirubin levels, and creatinine.

The results of the imaging study were looked at for the patients subject to medical imaging, for example, abdominal ultrasound or abdominal CT scan. In cases where the bowel wall thickness was observed to be at least 3mm, the intestines were considered to be invaded. Furthermore, the intestines were divided into an ileum, cecum, the right side and the left side of colon depending on the invaded sites of intestines.

In addition, patients were divided into patient groups that were treated and not treated with antibiotics to find the differences between hospitalization duration, fever, duration of diarrhea, white blood cell counts, and C-reactive protein on the average by using the Mann-Whitney U test. For possible fever and hypotension, the Fisher's exact test was performed for their comparative analysis. For statistical analysis, IBM SPSS Statistics ver. 21.1 (IBM Co., Armonk, NY, US) was used, and it was considered statistically significant if *P* was smaller than 0.05.

## RESULTS

Multiplex PCR was performed for 539 patients with suspected bacterial AGE during the period of study and whose average age was  $6.2 \pm 5.0$  years. Thirty-one (5.8%) among 539 patients had a positive result on *Campylobacter* spp. The average age of 31 patients composed of 18 male children (58%) and 13 female children was  $10.2 \pm 5.0$  years (ranging from 1 to 16 years old). In The C positive patients group, two outpatients and 29 inpatients had an average hospitalization duration of  $4.4 \pm 2.3$  days, ranging from one day to 11 days. One patient suffered hypovolemic shock and was treated in the ICU. The number of patients observed by seasons was: 5 patients (16%) between March and May, 18 (58%) between June and August, 7 (31%) between September and November, and 1 (3%) between December and February. With regards to underlying diseases, one patient had acute lymphoblastic leukemia and another patient had Burkitt's lymphoma. In the history of overseas travel, one patient traveled to the Philippines, and another patient traveled India, and they got ill because of the disease on the third day and the sixteenth day of their travel, respectively. The findings in the multiplex CPR testing were one case of *Shigella* infection, and no infection was found in the stool, urine and blood tests.

Diarrhea (29 patients, 93.5%) was the most common symptom, followed by fever and abdominal pain (26 patients, respectively, 83.9%) and other

major symptoms (Table 1). The fever persisted for an average of  $2.1 \pm 0.9$  days with a maximum of 4 days. Twenty patients (65%) has persistent diarrhea for a duration not longer than 3 days; 8 patients (26%) for 4 to 7 days; and 3 (9%) for at least 7 days. Seventeen patients (55%) suffered watery diarrhea; one (3%) mucus diarrhea; and 11 (35%) bloody diarrhea.

While the patients had *Campylobacter* AGE, antibiotics were used for 6 patients. Empirical antibiotics were used for 4 patients, and antibiotics after diagnosis were used for 2 patients. The empirical antibiotics were used for 2 patients who were taking anticancer drugs to treat acute lymphoblastic leukemia and Burkitt's lymphoma, respectively, and 2 patients with suspected sepsis. Two patients were treated with both ampicillin/sulbactam and amikacin; one patient each with cefotaxime, nafcillin, cefotaxime and metronidazole, respectively; and one patient with ceftriaxone. One patient was treated with azithromycin after diagnosis of *Campylobacter* and the patient who travelled India was treated with ceftriaxone because the patient got *Shigella*. All patients recovered without complications.

When thirty patients were analyzed by blood test, 22 (73%) showed high white blood cell counts, and 29 (97%) showed high CRP levels. Most patients showed normal levels of albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, and creatinine (Table 2). Twenty patients (64%) were subject to some type of imaging study. Fifteen patients (48%) were subject to abdominal

**Table 1. Clinical manifestations of 31 children with *Campylobacter* acute gastroenteritis**

Symptom	Number of patients (%)	
Diarrhea	29 (93.5%)	
Abdominal pain	26 (83.9%)	
Fever	26 (83.9%)	
Vomiting	13 (42.0%)	
Headache	11 (35.5%)	
Nausea	10 (32.3%)	
Tenesmus	6 (19.4%)	
Dizziness	4 (12.9%)	
Generalache	2 (6.5%)	
Hypotension	2 (6.5%)	
Consistency of diarrhea	watery	17 (54.8%)
	mucus	1 (3.2%)
	bloody	11 (35.5%)
Duration of diarrhea (days)	≤ 3	18 (58.1%)
	4-7	8 (25.8%)
	≥ 8	3 (9.7%)

**Table 2. Laboratory finding of patients in 30 patients with *Campylobacter* gastroenteritis**

	Mean ± standard deviation
White blood cell (WBC) (/uL)	12,800 ± 4,800
Absolute neutrophil count (ANC) (/uL)	9,600 ± 50,00
Albumin (mg/dL)	4.3 ± 0.3
Creatinine (mg/dL)	0.59 ± 0.23
Aspartate aminotransferase (AST) (IU/L)	30 ± 14
Alanine aminotransferase (ALT) (IU/L)	21 ± 16
Bilirubin (mg/dL)	0.58 ± 0.47
Erythrocyte sedimentation rate (ESR) (mm/hr)	23.5 ± 14.6
C-reactive protein (mg/dL) (normal: < 0.5mg/dL)	8.08 ± 6.74

ultrasound, 3 patients (10%) were subject to abdominal CT scan, and two patients (6%) were subject to both tests. Sixteen cases (80%) showed an invaded distal end of the ileum and right large intestine, among which 4 patients (20%) suffered invasion on all parts of the large intestine. A case of invasion just on the left large intestine was not found, and it was impossible to see lesions of invasion in the imaging study in 4 cases (20%) (Table 3).

With respect to the use of antibiotics, the duration of hospitalization was  $6.0 \pm 1.1$  days for the patients treated with antibiotics and  $3.8 \pm 2.4$  days for those not treated with antibiotics ( $P = 0.009$ ). The durations of fever between the groups treated and not treated with antibiotics were  $4.5 \pm 3.8$  days and  $3.0 \pm 2.2$  days ( $P = 0.679$ ), respectively. Hypotension was found in two patients treated with antibiotics. The white blood cell counts of the groups treated and not treated with antibiotics were 16,200/dL and 12,000/dL ( $P$

$= 0.143$ ), respectively. C-reactive protein levels were 11.9 mg/dL and 7.1 mg/dL ( $P = 0.402$ ), respectively (Table 4).

## DISCUSSION

In this study the authors found *Campylobacter* in 5.8% of young patients with bacterial AGE which has a relatively small number of available reports, and most patients with the disease were school-age children. Major symptoms included diarrhea, fever and abdominal pain.

In this study of patients with clinical symptoms of infectious AGE, patients having a positive result for *Campylobacter spp.* in multiplex PCR testing were considered as *Campylobacter* gastroenteritis patients. Dey SK, et al. analyzed the usage of multiplex PCR for identifying *Campylobacter* in stool analysis, and reported 90.5% and 100% of sensi-

**Table 3. Distributions of involved segment in 20 patients with *Campylobacter* gastroenteritis on imaging study**

Lesion			Number of patients (%)
Ileum and/or cecum	Right-side colon	Left-side colon	
+	+	+	4 (20%)
+	+	-	3 (15%)
+	-	+	2 (10%)
+	-	-	2 (10%)
-	+	+	4 (20%)
-	+	-	1 (5%)
-	-	+	0 (0%)
-	-	-	4 (20%)

**Table 4. Comparisons of 31 *Campylobacter* gastroenteritis patients treated with or without antibiotics**

	Treated with antibiotics	Treated without antibiotics	<i>P</i> -value
Number of patients	6	25	
Duration of hospitalization (days)	6.0 ± 1.1	3.8 ± 2.4	0.009
Fever	5(83%)	21(84%)	0.687
Duration of fever (days)	1.3 ± 1.0	2.0 ± 1.1	0.291
Duration of diarrhea (days)	4.5 ± 3.8	3.0 ± 2.2	0.679
Hypotension	2(33%)	0(0%)	0.032
C reactive protein (mg/dL)	11.95 ± 11.30	7.11 ± 4.96	0.402
Total White blood cell (/μL)	16,200	12,000	0.143

tivity and specificity, respectively, in comparison with the culture test for patients with AGE.<sup>5</sup> An advantage is that it enables subtypes of strains to be quickly identified depending on the method and the type of primers.<sup>6</sup> Multiplex PCR used in stool analysis of patients with AGE is a popular kit available in the market. Because multiplex PCR for *Campylobacter* is considered to have higher specificity than the culture test, the patient is considered infected when the patient has a positive result in the stool analysis. Another available method for detecting *Campylobacter* is immunochromatography specific to *Campylobacter* in addition to multiplex PCR. It is reported that its sensitivity and specificity is 86% and 100%<sup>5</sup> compared to the stool culture test, and 98.5% and 98.2%<sup>7</sup> compared to the multiplex PCR method, respectively. It is considered that both tests can detect causes quickly in comparison with the stool culture test for bacterial AGE. Although the above methods do not identify *Campylobacter* which is

a common cause of bacterial AGE in stool culture test, it is possible to diagnose *Campylobacter* infection quickly to avoid the unnecessary use of antibiotics and be prepared for possible complications.

Regarding time of year, in this study, 58% of AGE patients with *Campylobacter* were enrolled between June and August, and 3% of the AGE patients between December and February. VTEC (Verotoxin-producing *Escherichia coli*), *Salmonella*, etc., which cause bacterial acute gastroenteritis were frequently found in summer like *Campylobacter*, but *Cryptosporidium* and *Giardia* were generally found in autumn and winter.<sup>8</sup> The average age of all the patients subject to tests in this study was 6.2 ± 5.0 years, and *Campylobacter* gastroenteritis patients averaged 10.2 ± 5.0 years, implying school-age children. Although studies of *Campylobacter* by Korean researchers are few, there are reports on middle school students in Incheon with *Campylobacter* gastroenteritis in-

ected through school meals.<sup>2</sup> Findings from a study in Denmark show age groups between 1 and 4, 15 and 24 had more *Campylobacter* gastroenteritis infection than other age groups.<sup>9</sup> While Park, et al., report acute *Salmonella* gastroenteritis patients averaging 4.4 years<sup>10</sup> old and Na, et al., report patients averaging 4.0 years old,<sup>4</sup> the patients in this study are older. However, because AGE cases caused by other bacteria were not analyzed, it is thus limited in terms of significance compared with slightly older patients.

While empirical antibiotics specific to *Campylobacter* were used before diagnosis of *Campylobacter* mainly for patients with underlying diseases, all patients recovered regardless of using antibiotics. Because it is hard clinically to tell AGE caused by *Shigella* from AGE caused by *Campylobacter*, empirical antibiotics can be used if patients are in critical condition.<sup>11</sup> Meta-analysis reports that using ciprofloxacin, norfloxacin or erythromycin in the initial stage of diagnosis contributes to reducing the gastrointestinal symptoms by 1.32 days in comparison with not using them.<sup>12</sup> However, it is known that patients with *Campylobacter* gastroenteritis recover generally by conservative treatment.<sup>11</sup> Bacteremia by *Campylobacter* is reported from 0.1-1% of *Campylobacter* patients with severe malnutrition or a low immune system.<sup>13,14</sup> Therefore, using empirical antibiotics can be considered for bacterial AGE patients with a normal immune system, provided that acute bloody diarrhea continues, sepsis is suspected or bacte-

rial migration to extraintestinal sites is also strongly suspected.

A typical complication after *Campylobacter* infection is Guillain-Barre syndrome (GBS), and a study conducted in the US reported it in 30.4 patients per 100,000 persons.<sup>15</sup> It also reported that *Campylobacter jejuni* was cultured in 8-50% of GBS patients' stool.<sup>16</sup> Moreover, possible complications after the infection include uveitis, hemolytic anemia, hemolytic uremic syndrome, pericarditis, toxic megacolon, etc.<sup>11</sup> In this study, 31 patients were consulted as an outpatient for surveillance and follow-up one month after being discharged, and no complication was found.

The limitations of this study are as follows: patients with a positive result using stool multiplex PCR were diagnosed as having *Campylobacter* gastroenteritis without application of culture test; subtypes of strains were not identified; the difference from other bacteria including *Salmonella* was not compared; data collection was limited due to retrospective analysis of medical records; and the number of patients was not great. However, while *Campylobacter* gastroenteritis is a common disease, this study is significant because the disease has not been fully studied in a clinical manifestation of a single strain in Korean children. On the basis of this study, it is essential that physicians consider *Campylobacter* as a cause of bacterial gastroenteritis that should be identified when they consult school-age patients with diarrhea, fever, abdominal pain in summer.

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