Community-acquired Escherichia coli Enteritis in Korean Children: The Clinical Application of a Stool Polymerase Chain Reaction Assay

Youie Kim¹, Hyo-Jin Kim¹, Sooyeon Lim¹, Kil-Seong Bae¹,², Seung Beom Han¹,², Dae Chul Jeong¹,², Jin Han Kang¹,², Gook Jae Shin³, Gun Dong Lee³, and Yeon-Joon Park³

¹Department of Pediatrics, ²The Vaccine Bio Research Institute, and ³Department of Laboratory Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

**Background:** Although Escherichia coli is a common cause of bacterial enteritis in Korea, reports on community-acquired E. coli enteritis in Korean children are scarce. This study aimed to determine the clinical characteristics and pathotype distribution of community-acquired E. coli enteritis diagnosed by a multiplex polymerase chain reaction (PCR) assay in Korean children.

**Materials and Methods:** The medical records of children aged 18 years or less who were diagnosed with acute gastroenteritis by the attending physician between 2013 and 2016 were retrospectively reviewed. The clinical characteristics of children diagnosed with E. coli enteritis were investigated and compared with those diagnosed with Salmonella enteritis. E. coli and Salmonella infections were diagnosed by a stool PCR assay.

**Results:** Among 279 children, in whom PCR assays for E. coli and Salmonella spp. were performed, Salmonella enteritis and E. coli enteritis were diagnosed in 43 (15.4%) and 39 (14.0%) children, respectively. Among the 39 children with E. coli enteritis, entero-pathogenic E. coli (n=21, 53.8%) and enteroaggregative E. coli (n=15, 38.4%) were the most common causative agents. Empirical antibiotics were administered to 33 (84.6%) children. A total of 31 (79.5%) children developed fever, and 25 (80.6%) of them had the fever for 3 days or less, which resolved a median of 1 day (range 0-3 days) after hospitalization. The most frequent gastrointestinal symptom was diarrhea (n=36, 92.3%). Significantly more children with E. coli enteritis were aged 2 years or less as compared with those with Salmonella enteritis (41.0% vs. 21.9%, $P=0.021$). Children with Salmonella enteritis more frequently complained of fever (97.7% vs. 79.5%, $P=0.012$), abdominal pain (90.7% vs. 64.1%, $P=0.004$), and hematochezia (46.5% vs. 10.3%, $P<0.001$) than those with E. coli enteritis. Erythrocyte sedimentation rate and C-reactive protein levels were significantly higher in children with Salmonella enteritis than those with E. coli enteritis ($P<0.001$).

**Conclusion:** Enteropathogenic E. coli was the most frequent pathotype in Korean children with E. coli enteritis that caused mild clinical symptoms. A stool PCR assay for E. coli may be useful for epidemiological purpose and for an early diagnosis of E. coli enteritis.

**Key Words:** Escherichia coli; Polymerase chain reaction; Child; Korea
Introduction

*Escherichia coli* is the major component of the normal intestinal flora; however, some pathogenic strains cause significant infectious diseases, such as gastroenteritis, urinary tract infection, and sepsis/meningitis [1]. Among the diarrheagenic *E. coli* (DEC) causing gastroenteritis, the enterotoxigenic *E. coli* (ETEC) is a common cause of traveler’s diarrhea in developed countries, while the enteropathogenic *E. coli* (EPEC) as well as ETEC are common causes of bacterial enteritis among younger children in developing countries [1]. In addition, Shiga toxin-producing *E. coli* (STEC) causes a severe complication, hemolytic uremic syndrome [1]. In Korea, outbreaks of food poisoning in schools due to enteropathogenic *E. coli* (EAEC) and ETEC have occurred [2, 3]. Nevertheless, most hospitals in Korea performed stool cultures for *Salmonella* spp. and *Shigella* spp. to evaluate patients with diarrhea because special media and biochemical methods are required for the identification of DEC in stool samples [4]. Accordingly, the molecular methods for identifying DEC in stool samples were developed [1], and several assays based on the polymerase chain reaction (PCR) test are now available. Moreover, multiplex PCR assays that can simultaneously evaluate several diarrheagenic pathogens including bacteria, viruses, and parasites were developed [5].

In Korea, stool PCR assays were performed in order to detect the presence of DEC [6-9], which has been the most frequent cause of bacterial enteritis since the 2000s [6, 7]. However, the clinical characteristics and the distribution of pathotypes of community-acquired *E. coli* enteritis have been rarely reported in Korean children [10, 11]. In addition, previous studies performed stool PCR assays using stool samples obtained from patients with diarrhea not only caused by acute gastroenteritis (AGE) but also caused by various clinical conditions [8-10]. Respiratory tract infections, urinary tract infections, allergic reactions, and some medications as well as AGE can cause acute diarrhea especially in children [12]; therefore, it is very difficult to differentiate between true diarrheagenic pathogens and intestinal colonizers in patients with diarrhea caused by various clinical conditions.

In the present study, the clinical characteristics and pathotype distribution of community-acquired AGE due to DEC diagnosed by a multiplex PCR assay were investigated in Korean children, and only those diagnosed with AGE by the attending physician were included. The results of this study help predict the clinical usefulness of a stool PCR assay in children with community-acquired AGE.

Materials and Methods

1. Patients and study design

Among children aged 18 years or less, who were hospitalized in the Department of Pediatrics, Seoul St. Mary’s Hospital, College of Medicine, the Catholic University of Korea between January 2013 and December 2016, those in whom stool PCR assays for DEC and *Salmonella* spp. were performed were investigated. Among them, children who complained of gastrointestinal (GI) symptoms, such as vomiting, diarrhea, and abdominal pain, with or without fever, and who were diagnosed with AGE by the attending physician were included in the present study, and their medical records were retrospectively reviewed. Children with chronic underlying disorders and those prematurely born were excluded from this study. Those who complained of diarrhea longer than 2 weeks and in whom GI symptoms developed 48 hours after hospitalization were also excluded.

Demographic data including sex and age as well as clinical characteristics including accompanying GI symptoms, fever duration, and results of blood and stool tests were obtained from children diagnosed with *E. coli* enteritis using the multiplex PCR assay. The information was compared with that of the children diagnosed with *Salmonella* enteritis.

This study was approved by the Institutional Review Board of Seoul St. Mary’s Hospital with waiver for informed consent (Approval No.: KC17RESI0677).

2. Laboratory tests

Stool samples collected from the hospitalized children were immediately transferred to the laboratories, and were kept in 2-8°C. The DNA was extracted from the stool samples using the QIAamp DNA Stool Mini Kit (50) (QiaGen, Germantown, MD, USA). An in-house multiplex PCR assay targeting virulence genes, which were specific for each of the five pathotypes (EAEC, enteroinvasive *E. coli* [EIEC], EPEC, ETEC, STEC), was performed in accordance with the method introduced by Antikainen et al. [13]. In addition, an in-house PCR assay targeting the *invA* gene specific for *Salmonella* spp. was also performed in the same stool sample according to the method reported by Cunningham et al. [14]. Table 1 describes the target genes and sequences of primers for the PCR assay. The PCR assay was considered the goldstandard to diagnose *E. coli* and *Salmonella* infections in the present study.

3. Statistical analysis

The investigated factors were compared between children
with *E. coli* enteritis and those with *Salmonella* enteritis using the SPSS 21 program (IBM Corporation, Armonk, NY, USA). Categorical and continuous factors were compared using the chi-square and Mann-Whitney tests, respectively. The statistical significance was defined as a two-tailed *P*-value <0.05.

### Results

#### 1. Characteristics of children with *E. coli* enteritis

Within the study period, multiplex PCR assays for DEC were performed in 279 children who were diagnosed with AGE. Based on the PCR assay results, *Salmonella* enteritis and *E. coli* enteritis were diagnosed in 43 (15.4%) and 39 (14.0%) children, respectively (Table 2). Eight (2.9%) children were positive for *Salmonella* spp. and *E. coli*. These eight children were excluded from the comparison between children with *Salmonella* and *E. coli* enteritis because they represent the characteristics of both bacterial infections. There was a food-borne outbreak of salmonellosis in a middle school adjacent to our hospital in August 2014; however, any outbreaks of *E. coli* enteritis were not identified during the study period. Figure 1 shows the yearly and monthly distribution of patients diagnosed with *E. coli* and *Salmonella* enteritis.

**Table 1.** Target genes and primer sequences for diarrheagenic *Escherichia coli* according to pathotypes and *Salmonella* spp.

| Bacteria                        | Target genes | Primers (5’ to 3’) |
|---------------------------------|--------------|--------------------|
| Enteropathogenic *E. coli*      | *eaeA*       | F: TCAATGCAGTTCCGTTATCAGTT  
|                                 | *escV*       | R: GTCGCCCTTTTTCAAACCTCGAC |
| Shiga toxin-producing *E. coli* | *stx1*       | F: CGATGTACGGTTGTTACTGTGACAGC  
|                                 | *stx2*       | R: AATGCCACGCTTCACAAATTCG |
| Enteroinvasive *E. coli*        | *ipaH*       | F: GAAAAACCTTCTGCTCATCAGG  
|                                 |              | R: GCGGTCAGCCACCTCTGAGATAC |
| Enterotoxigenic *E. coli*       | *elt*        | F: GAACAGAGGTTCTGCGTTAGTG  
|                                 | *estb*       | R: CTTGATGGCTTTTTTTTTTTGGAGTC |
| Enteroaggregative *E. coli*     | *aggR*       | F: ACGCAGAGTTCGCCTGATAAAAG  
|                                 |              | R: AATACAGAATTCGTAGCAAGC |
| *Salmonella* spp.               | *invA*       | F: TGCATAATGCGACAGAAAGAG  
|                                 |              | R: ATCATTCTITGTTGTGCATTCCA |

F, forward; R, reverse.

**Table 2.** Distribution of bacterial pathogens

| Pathogen     | Age group | Total |
|--------------|-----------|-------|
|              | 0-2 years (n = 25) | 3-5 years (n = 29) | >5 years (n = 28) | Total (n = 82) |
| *Salmonella* spp. | 9 | 21 | 13 | 43 |
| *Escherichia coli* | | | | |
| EPEC         | 16 (68.8) | 8 | 15 | 39 |
| EAEC         | 4 (25.0)  | 1 (12.5) | 6 (40.0) | 11 (28.2) |
| ETEC         | 0         | 2 (25.0) | 0 | 2 (5.1) |
| STEC         | 0         | 0 | 1 (6.7) | 1 (2.6) |
| EIEC         | 0         | 0 | 0 | 0 |
| EPEC + STEC  | 1 (6.3)   | 0 | 1 (6.7) | 2 (5.1) |
| EAEC + ETEC  | 0         | 1 (12.5) | 1 (6.7) | 2 (5.1) |
| EAEC + EIEC  | 0         | 0 | 2 (13.3) | 2 (5.1) |

EPEC, enteropathogenic *E. coli*; EAEC, enteroaggregative *E. coli*; ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin-producing *E. coli*; EIEC, enteroinvasive *E. coli*. 
Kim Y, et al. • *E. coli* enteritis in children

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Figure 1. Yeraly and monthly distribution of patients with *Escherichia coli* (A) and *Salmonella* enteritis (B).

Table 3. Characteristics of children with *Salmonella* enteritis and *Escherichia coli* enteritis

| Factor                        | *Salmonella enteritis* (n = 43) | *Escherichia coli* enteritis (n = 39) | P-value |
|-------------------------------|---------------------------------|--------------------------------------|---------|
| Age group                     |                                 |                                      |         |
| 0-2 years                     | 9 (20.9)                        | 16 (41.0)                            | 0.021   |
| 3-5 years                     | 21 (48.8)                       | 8 (20.5)                             |         |
| > 5 years                     | 13 (30.2)                       | 15 (38.5)                            |         |
| Sex, male                     | 19 (44.2)                       | 28 (71.8)                            | 0.012   |
| Other concomitant diagnoses   | 5 (11.6)                        | 2 (5.1)                              | 0.436   |
| Accompanying symptoms         |                                 |                                      |         |
| Fever                         | 42 (97.7)                       | 31 (79.5)                            | 0.012   |
| Diarrhea                      | 43 (100.0)                      | 36 (92.3)                            | 0.103   |
| Abdominal pain                | 39 (90.7)                       | 25 (64.1)                            | 0.004   |
| Vomiting                      | 18 (41.9)                       | 24 (61.5)                            | 0.075   |
| Hematochezia                  | 20 (46.5)                       | 4 (10.3)                             | <0.001  |
| Fever duration                |                                 |                                      | <0.001  |
| No fever                      | 2 (4.7)                         | 8 (20.5)                             |         |
| 1-3 days                      | 17 (39.5)                       | 25 (64.1)                            |         |
| ≥4 days                       | 24 (55.8)                       | 6 (15.4)                             |         |
| Concurrent enteral viruses    |                                 |                                      |         |
| Rotavirus                     | 0 (0.0)                         | 7 (18.9)                             | 0.005   |
| Norovirus                     | 1 (2.6)                         | 3 (8.3)                              | 0.351   |
| Stool microscopic examination |                                 |                                      |         |
| White blood cells             | 18 (42.9)                       | 11 (29.7)                            | 0.227   |
| Occult blood                  | 21 (50.0)                       | 8 (21.6)                             | 0.009   |
| Blood tests                   |                                 |                                      |         |
| White blood cell count (/mm³) | 7,440 (4,700-16,940)            | 9,350 (1,950-24,520)                 | 0.061   |
| Absolute neutrophil count (/mm³) | 4,851 (1,968-12,367)            | 6,150 (332-22,313)                   | 0.134   |
| Erythrocyte sedimentation rate (mm/hr) | 28 (5-68) | 15 (2-48)             | <0.001  |
| C-reactive protein (mg/dL)    | 5.92 (0.27-26.42)               | 1.78 (0.02-10.25)                    | <0.001  |

*a* Rotavirus was tested in 39 children with *Salmonella* enteritis and 37 children with *E. coli* enteritis.

*b* Norovirus was tested in 38 children with *Salmonella* enteritis and 36 children with *E. coli* enteritis.

*c* Stool microscopic examination was performed in 42 children with *Salmonella* enteritis and 37 children with *E. coli* enteritis.

*d* Erythrocyte sedimentation rate was measured in 41 children with *Salmonella* enteritis and 34 children with *E. coli* enteritis.

*e* C-reactive protein levels were measured in 43 children with *Salmonella* enteritis and 38 children with *E. coli* enteritis.
Thirty-three (84.6%) of the 39 children with *E. coli* enteritis were infected by a single pathotype, whereas six (15.4%) children were infected by two or more pathotypes (Table 2). Including the co-infected cases, the EPEC (n = 21, 53.8%) was the most frequent *E. coli* pathotype, followed by the EAEC (n = 15, 38.4%). A total of 28 (71.8%) children were males, and the median age of the enrolled children was 4 years (range: 0-17 years) with 16 (41.0%) children aged 2 years or less (Table 3). Fever developed in 31 (79.5%) children: the median duration of fever was 3 days (range: 1-10 days), and 25 (80.6%) children had a fever for 3 days or less. Diarrhea (n = 36, 92.3%) was the most frequent GI symptom, followed by abdominal pain (n = 25, 64.1%) and vomiting (n = 24, 61.5%). Hematochezia occurred in four (10.3%) children.

Microscopic stool examinations were performed in 37 children: white blood cells (WBCs) were observed in 11 (29.7%) children, while occult blood (OB) was positive in eight (21.6%) children. The rotavirus was identified in seven (17.9%) of the 37 tested children, while norovirus was identified in three (8.3%) of the 36 tested children. Blood tests upon admission revealed the following results: a median WBC count of 9,350/mm³ (range: 1,950-24,520/mm³), a median erythrocyte sedimentation rate (ESR) of 15 mm/hr (range: 2-48 mm/hr) in the 34 children tested, and a median C-reactive protein (CRP) level of 1.78 mg/dL (range: 0.02-10.25 mg/dL) in the 38 children tested.

Empirical antibiotics were administered to 33 (84.6%) children. Aminopenicillin and β-lactamase inhibitor combination (n = 14, 35.9%) was most frequently administered, followed by a third-generation cephalosporin (n = 11, 28.2%). A total of 20 (51.3%) children received aminoglycoside concomitantly with a β-lactam agent. Fever resolved a median of 1 day (range: 0-3 days) after hospitalization.

### 2. Comparison between children with *E. coli* and *Salmonella* enteritis

In the comparison made between 39 children with *E. coli* enteritis and 43 children with *Salmonella* enteritis, results showed that those with *E. coli* enteritis were more likely males (71.8% vs. 44.2%, *P* = 0.012) and aged 2 years or less (41.0% vs. 21.9%, *P* = 0.021, Table 3). By contrast, children with *Salmonella* enteritis more frequently complained of fever (97.7% vs. 79.5%, *P* = 0.012), abdominal pain (90.7% vs. 64.1%, *P* = 0.004), and hematochezia (46.5% vs. 10.3%, *P* = 0.001) than those with *E. coli* enteritis. Fever lasted for 3 days or less in 84.6% of children with *E. coli* enteritis; however, it lasted for 4 days or more in 55.8% of children with *Salmonella* enteritis (*P* < 0.001). Stool OB was more likely positive in children with *Salmonella* enteritis than those with *E. coli* enteritis (50.0% vs. 21.6%, *P* = 0.009). The ESR and CRP levels were significantly higher in children with *Salmonella* enteritis than those with *E. coli* enteritis (*P* < 0.001).

### Discussion

In the present study, the clinical characteristics of children diagnosed with *E. coli* enteritis and the distribution of *E. coli* pathotypes in those patients were investigated. The EPEC was the most frequent pathotype in Korean children with community-acquired *E. coli* enteritis, and *E. coli* enteritis showed milder clinical symptoms than *Salmonella* enteritis.

The pathotype distribution of DEC in patients with AGE was reported in various geographic areas and showed different distributions according to the participants’ age, enrolled countries, and the degree of urbanization in the same country. For example, the ETEC was most common among diarrhea children in seven developing countries in Africa and Asia [15], whereas EPEC was most common in American children [16]. Another study conducted in the other areas of the United States reported EAEC as the most common pathotype in childhood diarrhea [17]. Although EAEC was the most common pathotype in adult and pediatric American patients with diarrhea [18], EPEC was most frequent in Europe [19]. In Nigeria, EPEC was most frequent in the urban areas, ETEC was most common in the rural areas [20], and EPEC was most common in both urban and rural areas in China [21]. In summary, EPEC and EAEC were common pathotypes in developed countries and urbanized areas replacing ETEC. In Korea, ETEC was the most frequent cause of *E. coli* enteritis in the 1980s [10]; however, EPEC was reported as the most frequent cause in the 2000s [11]. The nationwide surveillance results of the Korean Centers for Disease Control and Prevention showed that EPEC was the most frequent cause of bacterial diarrhea in the 2010s, followed by EAEC [7]. Therefore, a periodic nationwide surveillance for the pathotype distribution of DEC is necessary in each country to identify the changing trend.

The present study showed that children with *E. coli* enteritis experienced a milder clinical course than those with *Salmonella* enteritis: the frequencies of GI symptoms and fever were lower, and the fever duration was shorter in children with *E. coli* enteritis than those with *Salmonella* enteritis. If we consider that hematochezia occurred significantly more and the
ESR and CRP levels increased in children with Salmonella enteritis than in those with E. coli enteritis, E. coli infection should cause weaker GI inflammation than Salmonella infection. Because 25.6% of the children with E. coli enteritis were also positive for rotavirus or norovirus, some types of E. coli may be simple colonizers rather than true GI pathogens, and mild clinical manifestations of E. coli enteritis might represent those of the mixed viral AGE. Actually, the GI colonization of EPEC, the most frequent pathotype in this study, has been previously reported [22]. However, milder clinical manifestations of E. coli enteritis compared with Salmonella enteritis were also previously reported [11, 23], and rotavirus or norovirus rather than E. coli could be simple colonizers.

This study showed that the short fever duration in E. coli enteritis could represent its own mild natural clinical course of E. coli enteritis. However, most of the enrolled children received empirical antibiotics that are known to be effective for E. coli infection. Although antibiotic therapy for E. coli enteritis is not routinely recommended, it shortened the clinical course of EPEC, ETEC, and EIIEC infections [1, 24]. Therefore, the administered antibiotics might shorten the clinical course of E. coli enteritis in our patients. If so, a stool PCR assay for E. coli infection helps the early diagnosis and early improvement of clinical symptoms of E. coli enteritis through early antibiotic therapy. In addition, rapid detection of STEC infection by a PCR assay, in which antibiotic therapy may cause hemolytic uremic syndrome, can prevent the development of severe complications by excluding antibiotic therapy for those cases. In contrast, if we consider that only 14.0% of the children, in whom stool PCR assays were performed, were positive for E. coli, a multiplex PCR assay targeting more GI pathogens including E. coli will be more cost-effective than a PCR assay targeting only E. coli.

This study had some limitations. First, we could not determine a recent diarrhea history prior to the enrollment of participants in this study due to the retrospective study design. Therefore, it was difficult to determine whether the identified enteral viruses represented prolonged excretion caused by previous diarrhea illness. Second, this study included only hospitalized children; therefore, those with milder symptoms were excluded, and the proportion of Salmonella and E. coli infection in AGE children (32.3%) might be overestimated. In addition, Clostridium difficile and Campylobacter spp., which were reported as major GI pathogens [8, 16, 18, 25], were not routinely tested in the enrolled patients. Therefore, the exact epidemiology of bacterial enteritis was not determined in this study. Third, the possibility of EPEC colonization was not absolutely excluded. The pathogenic capacity of EPEC depends on the immune status and age of the infected host, the serotype and genotype of the infected EPEC, and the colony count of infected EPEC [22]. Although this study only included children primarily diagnosed with AGE in order to exclude the role of enteric colonizing E. coli, a quantitative PCR assay and concomitant culture study can be more useful for excluding colonization status.

In conclusion, E. coli caused relatively milder GI manifestations, and EPEC was the most frequent pathotype in Korean children with E. coli enteritis. A stool PCR assay for E. coli is useful in epidemiological studies and helpful in the early diagnosis and improvement of the clinical course of E. coli enteritis.

### Conflicts of Interest

No conflicts of interest.

### ORCID

Youle Kim https://orcid.org/0000-0002-6839-9244
Seung Beom Han https://orcid.org/0000-0002-1299-2137
Dae Chul Jeong https://orcid.org/0000-0003-9343-817X
Jin Han Kang https://orcid.org/0000-0003-1610-6742

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