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Clinical Course of Children with *Campylobacter* Gastroenteritis With and Without Co-Infection in Lima, Peru

Galo Amaro Munoz,[1]* Maribel Denise Riveros-Ramirez,[1,2] Elsa Chea-Woo,[1] and Theresa J. Ochoa[1,2,3]

[1]*School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru;* [2]*Medical Tropical Alexander von Humboldt Institute, Universidad Peruana Cayetano Heredia, Lima, Peru;* [3]*Department of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas*

Abstract. This study describes the clinical course of gastroenteritis caused by *Campylobacter* spp. as a single-infection versus coinfection and the corresponding changes that occur according to the treatment received, in children between 12 and 24 months of age. This descriptive study is based on the data of a pediatric cohort conducted between 2008 and 2011 of 555 children in Lima, Peru. Ninety-six diarrheal episodes with positive cultures for *Campylobacter* spp. were evaluated. In 52 episodes, empirical antibiotic treatment was started before pathogen isolation. Of these 96 episodes, 64.6% were coinfections with other pathogens. Coinfections were led by *Escherichia coli*, norovirus, and *Giardia*. Compared with single-infection episodes, coinfections had a mean symptom duration of 6.6 versus 5.7 days, a mean frequency of bowel movements per episode of 18.9 versus 14.8, and occurrence of vomiting and fever in 24.2% versus 14.7% of patients. Most of the patients with more severe clinical features at diagnosis were prescribed macrolides as empiric treatment. In the single-infection group, symptom duration was 7.2 ± 3.3 days in the macrolide-treated group and 7.9 ± 2.7 days in the nonmacrolide group. Diarrhea caused by coinfection appeared to be generally more severe than a single-pathogen. Patients with more severe clinical courses who received macrolides treatment might have had a faster recovery than patients who received nonmacrolides.

INTRODUCTION

Diarrhea is the second most common cause of death in children, with ~0.5 million deaths per year.[1] Approximately 9% of these are attributable to *Campylobacter*, making this genus the third leading bacterial cause of death in children.[2] *Campylobacter* infection is the third most common cause of moderate to severe diarrhea in children aged 24 to 59 months,[3] with 400 to 500 million cases each year in this age group.[4] *Campylobacter* gastroenteritis tends to be mild and self-limiting; however, severe symptoms such as dehydration, dysentery, and fever may lead to fatal outcomes. This presentation is particularly relevant for children under 5 years of age.[5–7] In Peru, *Campylobacter* spp. are the most frequent causes of acute bacterial diarrhea in all age groups, but with a higher incidence in children under 5 years of age.[6] Nevertheless, the prevalence of *Campylobacter* infections is unknown because of limitations in detecting causative pathogens in hospital laboratories.[6]

The use of antibiotics to treat *Campylobacter* infections remains controversial. Some studies suggest antibiotics may have limited efficacy against *Campylobacter* spp.,[8] whereas others insist on a small but significant benefit in terms of symptom control, particularly with fluoroquinolones.[9] On the basis of clinical assessment, patients often receive antibiotic treatment with macrolides and not fluoroquinolones, possibly because of concerns about resistant strains.[2,10–14] The stool samples of the patients included in this study were analyzed in a separate study, which showed significant antibiotic resistance for fluoroquinolones but minimal for macrolides.[11]

This study mainly sought to compare the clinical courses of single-infection and coinfection *Campylobacter* spp. gastroenteritis in children aged 12 to 24 months from a low-income population in Lima, Peru.

*Address correspondence to Galo Amaro Munoz, School of Medicine, Universidad Peruana Cayetano Heredia, Jr. Juan Fanning 109, Dpto 807-Barranco, Lima, Peru. E-mail: galo.munoz@upch.pe

MATERIALS AND METHODS

Study population. This descriptive study is based on the data of a pediatric cohort conducted between January 2008 and May 2011 in 555 children aged 12 to 24 months and living in a low-income community in periurban Lima.[15] Periurban communities in Lima are shantytowns. Each child was monitored with home visits for 6 months, five times a week, for data collection and lactoferrin administration. When the children presented diarrhea, samples were collected and tested for viruses, bacteria, and parasites. If severe diarrhea developed, community health workers and parents were instructed to bring the child to the emergency department or study clinic. If the culture was positive, patients received medical treatment at the health care center. In this cohort, there were no hospitalizations for diarrhea or dehydration. Of 1,235 diarrheal episodes, 96 (10.6%) were positive for *Campylobacter* spp. by stool culture and/or morphology.[15]

Definitions. A diarrheal episode was defined as $\geq$ 3 watery or semiwatery bowel movements per day or the presence of visible blood in loose stools. Each separate episode was preceded by at least 2 consecutive days with no occurrence of watery stools and followed by at least 3 consecutive days with no occurrence of watery stools.[15]

The dehydration status was categorized as absent, moderate, or severe based on a clinical assessment (skin turgor, mental status, and thirst) using the WHO 2006 dehydration guidelines.[15] In this cohort, there were no hospitalizations due to diarrhea or dehydration.

Procedures. The 96 diarrheal episodes were classified into three groups according to the treatment they received at the time of symptoms onset: 1) without antibiotics, if they received only hydration therapy; 2) no macrolides, defined as treatment with cotrimoxazole, ampicillin, amoxicillin, furazolidone, or nitrofurantoin; or 3) macrolides, defined as treatment with azithromycin or erythromycin. Once the causative pathogen was isolated from each sample, the treatments in seven cases were modified because symptoms persisted or

had worsened. However, these three treatment groups were established depending on the type of medication they received on the first day of treatment. In addition, cases were categorized according to whether the diarrhea was a single-pathogen infection or a coinfection by another pathogen was also detected. Pathogens were identified through polymerase chain reaction (diarrheagenic *Escherichia coli* and norovirus), immunochromatography (rotavirus and adenovirus), stool cultures (enteropathogenic *E. coli*, enteroaggregative *E. coli*, enterotoxigenic *E. coli*, *Shigella, Salmonella*, *Vibrio*, *Aeromonas*, and *Plesiomonas*), and parasitological studies (*Giardia*, *Blastocystis*, *Cryptosporidium*, *Cyclospora*, *Strongyloides*, *Chilomastix*, *Endolimax*, and *Entamoeba*) by standard microbiological procedures.[15]

This study was approved by the Ethics Committee of the Universidad Peruana Cayetano Heredia, Lima, Peru.

Statistical analysis. Descriptive and summary statistics were performed using Stata 14.0 (StataCorp LP, College Station, TX). Formal statistical comparisons between groups were not performed due to the small sample size.

RESULTS

Characteristics of diarrheal episodes and sociodemographic data. Ninety-six diarrheal episodes with positive stool culture and/or morphology for *Campylobacter* spp. were identified and included in this study. These episodes involved 83 children (37 girls and 46 boys), of which 11 (13.25%) had two or more episodes during the study, with similar characteristics.

At the time of the first diarrheal episode documented in the study, the mean age of the patients was 15.8 months with no evidence of acute malnutrition. However, six (7.2%) children were diagnosed with moderate chronic malnutrition (HFA < -2 Z score) (Table 1).

TABLE 1
Baseline demographic and socioeconomic characteristics and risk factors for diarrhea associated with *Campylobacter* spp.

No. of children	83
Age (months) at enrollment* Median (IQR)	16 (14–17)
Sex, Male, *n* (%)	46 (55.4)
Baseline anthropometry, Z score, mean ± SD	
HFA	−0.6 ± 0.9
WFH	0.2 ± 0.8
Duration of exclusive breastfeeding in months, mean ± SD	4.4 ± 3.04
Daycare attendance, *n* (%)	3 (3.7)
Water supply source, *n* (%)	
Pipe water inside the house	71 (86.6)
Pipe water outside the house	9 (11)
Water pit	2 (2.4)
Water storage, *n* (%)	
No storage	20 (24.1)
Water tank with tap	7 (8.4)
Water tank without tap	6 (7.2)
Water cylinder	31 (37.3)
Other†	19 (22.9)
Sewer system, *n* (%)	
Inside the house	71 (86.6)
Outside the house	2 (2.4)
Pit latrine	8 (9.7)
Irrigation ditch or canal	1 (1.2)
Poultry breeding inside the house	20 (24.4)

HFA = height-for-age; IQR = interquartile range; WFA = weight-for-height.
* Age range: 12–18 months.
† Pots, water pails.

Single-pathogen infection by *Campylobacter* spp. and clinical characteristics. Thirty-four diarrheal episodes (35.4%) were caused solely by *Campylobacter* spp. Of these, 16 did not receive antibiotics, 10 received a nonmacrolide regimen, and eight received a macrolide regimen. Overall, the mean ± SD duration of symptoms was 5.7 ± 3.1 days, the mean frequency of bowel movements per episode was 14.8 ± 8.1, and 14.7% of patients presented both vomiting and fever. The patients with milder clinical symptoms received only symptomatic therapy. Among children with single-pathogen infections, the mean duration of diarrhea in the macrolide-treated group was 7.2 ± 3.3 versus 7.9 ± 2.7 in the nonmacrolide group.

Coinfections with additional pathogens and clinical characteristics. Coinfection with pathogens other than *Campylobacter* spp. was found in 62 episodes (64.6%). The most frequent coinfections were with diarrhea genic *E. coli* (35.1%), norovirus (32.9%), and *Giardia* (7.2%) (Table 2). The duration of coinfection diarrhea was 6.6 ± 4.7 days, the frequency of watery bowel movements per episode was 18.9 ± 13.8, and vomiting per episode was 3.2 ± 2.4 compared with single-pathogen infections (Table 3).

Clinical characteristics of *Campylobacter* spp. infections treated with macrolides, nonmacrolides, and symptomatic treatment. Coinfection episodes that received no antibiotic treatment might present the mildest characteristics. The group that received macrolides apparently presented greater severity, longer duration (9.0 ± 4.8 days, $P < 0.001$), and higher frequency of bowel movements per episode (25.2 ± 13.6, not statistically significant) compared with the other two treatment groups (Table 4). Analysis of the clinical characteristics after antibiotic treatment revealed a median diarrheal episode duration until resolution of 2.5 days (range 1–7) with macrolides versus 4.5 (range 3–7) without macrolides. The mean fever duration was 0.06 ± 0.2 days versus 0.3 ± 0.8 days, respectively. No statistical difference was found between

TABLE 2
Campylobacter spp. and coinfecting pathogens

Pathogens	*Campylobacter* spp. episodes *n*/*N* (%)
Enteric bacteria	
Shigella sp.*	5/96 (5.2)
Salmonella sp.*	1/96 (1)
Diarrheagenic *E. coli*†	33 (35.1)
EPEC	13/94 (13.8)
EAEC	10/94 (10.6)
DAEC	4/94 (4.3)
ETEC	4/94 (4.3)
AIEC	1/94 (1)
EPEC + ETEC	1/94 (1)
Enteric viruses	
Rotavirus‡	2/85 (2.3)
Adenovirus‡	1/85 (1.2)
Norovirus*	27/82 (32.9)
Enteric parasites	
Giardia§	4/96 (4.1)
Giardia + others‖	3/96 (3.1)
Entamoeba	2/96 (2.1)
Blastocystis	2/96 (2.1)

DAEC = diffusely adherent *E. coli*; EAEC = enteroaggregative *E. coli*; AIEC = adherent invasive *E. coli*; EPEC = enteropatogenic *E. coli*; ETEC = enterotoxigenic *E. coli*.
* According to stool culture.
† Polymerase chain reaction.
‡ Immunochromatography.
§ Parasitological study.
‖ *Chilomastix*, *Endolimax*, *Entamoeba*, *Enterobius*, *Diphylobothrium*, *Hymenolepis*, *Trichuris*, *Isospora*.

TABLE 3
Clinical characteristics of diarrheal episodes associated with *Campylobacter* spp.

Clinical characteristics	Only *Campylobacter* spp.	*Campylobacter* coinfection	Total *Campylobacter* infection
No. of diarrheal episodes	34	62	96
Duration in days			
Mean ± SD	5.7 ± 3.1	6.6 ± 4.7	6.4 ± 4.2
Median per episode (minimum–maximum)	6 (3–6)	5 (3–9)	5 (3–8)
Watery stools			
Total per episode, mean ± SD	14.8 ± 8.1	18.9 ± 13.8	17.6 ± 12.1
Maximum no. per day during episode, mean ± SD	4.6 ± 1.8	5.1 ± 2.3	4.9 ± 2.1
Vomiting			
Episodes with vomiting, n (%)	5 (14.7)	15 (24.2)	20 (20.8)
Total per episode, mean ± SD	2.2 ± 1.6	3.2 ± 2.4	2.9 ± 2.2
Median per episode (minimum–maximum)	2 (1–2)	2 (1–5)	2 (1–5)
Number of days per episode, mean ± SD	1.1 ± 0.4	1.4 ± 0.6	1.3 ± 0.6
Fever			
Episodes with fever, *n* (%)	5 (14.7)	15 (24.2)	20 (20.8)
No. of days with fever per episode, mean ± SD	2.0 ± 0.7	1.8 ± 1	1.8 ± 0.9
Median per episode (minimum–maximum)	2	1 (1–3)	2 (1–5)
Dehydration			
Moderate or severe (WHO), *n* (%)	0	1 (1.6)	1 (1)
Episodes with bloody stools, *n* (%)	1 (2.9)	5 (8)	6 (6.2)
Episodes with mucus stools, *n* (%)	11 (32.3)	20 (32.2)	31 (32.3)
Episodes with fecal leukocytes, n (%)*	11 (32.3)	19 (30.6)	30 (31.2)
< 10, n (%)	8 (23.4)	14 (15.1)	22 (22.8)
10–20 leukocytes, n (%)	1 (2.9)	3 (4.8)	4 (4.1)
20–50 leukocytes, n (%)	1 (2.9)	0	1 (1)
> 50 leukocytes, *n* (%)	1 (2.9)	2 (3.2)	3 (3.1)

* Leukocytes per high power field.

the groups regarding the mean frequency of bowel movements per episode and frequency of vomiting.

DISCUSSION

Most patients with a more severe clinical course by symptom onset (e.g., by frequency of watery bowel movements or duration of symptoms) were successfully treated with macrolides, which may have led to a faster clinical improvement. Although this could be an effect of the antibiotics, it is also a confounding factor because most episodes of *Campylobacter* gastroenteritis follow are self-limited over time.[16]

Campylobacter gastroenteritis symptoms can be easily confused with a viral infection, leading to a delay in treatment with macrolides.[16] Furthermore, a high prevalence of coinfection by *Campylobacter* spp. and other pathogens increases the severity and lengthens the course of illness.[16–19]

In Peruvian children, a high frequency of coinfections in gastroenteritis caused by *Campylobacter* spp. has been described, and synergism between different etiologies aggravates the symptoms,[4,5,17–19] as the present study also shows. Zambruni et al.[16] studied norovirus coinfections in the same cohort as this study and found that the most frequent coinfecting bacteria were *E. coli*, *Campylobacter* spp., and *Shigella* spp. In addition, the duration of diarrhea and the frequency of watery bowel movements per episode were consistently higher in mixed infections than either noroviral or bacterial (including *Campylobacter* spp.) single-pathogen infections.[16] However, whether *Campylobacter* spp. was the

TABLE 4
Clinical characteristics *Campylobacter* spp. episodes, according to type of treatment received

Clinical characteristics	Without antibiotic	Nonmacrolides	Macrolides
No. of diarrheal episodes	44	22	30
Duration in days			
Mean ± SD	4.3 ± 3.1	7.1 ± 3.3	9.0 ± 4.8
Median per episode (minimum–maximum)	3.5 (3–5)	7 (4–9)	8 (5–11)
Watery stools			
Total per episode, mean ± SD	11.7 ± 9.5	18.5 ± 8.5	25.2 ± 13.6
Median per episode (minimum–maximum)	9 (7–13.5)	18 (12–26)	21 (14–34)
Maximum no. per day during episode, mean ± SD	4.5 ± 1.5	5.1 ± 2	5.5 ± 2.8
No. per day per episode, mean ± SD	2.8 ± 0.9	2.8 ± 0.9	3.2 ± 2.1
Median per episode (minimum–maximum)	2.2 (2.7–3)	2.3 (2.4–3.3)	2 (2.7–3.8)
Vomiting			
Episodes, *n* (%)	7 (15.9)	7 (31.8)	6 (20)
Total per episode, mean ± SD	0.3 ± 1.1	0.7 ± 1.4	0.9 ± 2.1
No. of days with vomiting per episode, mean ± SD	0.2 ± 0.5	0.3 ± 1.4	0.3 ± 0.7
Fever			
Episodes, *n* (%)	5 (11.3)	10 (45.4)	5 (16.6)
No. of days per episode, mean ± SD	0.2 ± 0.6	0.9 ± 1.2	0.2 ± 0.5
Dehydration, moderate or severe (WHO), *n* (%)	0	0	1 (3.3)
Episodes with bloody stools, *n* (%)	0	3 (13.6)	3 (10)

cause of the disease or a contributing factor could not be established.[16]

Among the *Campylobacter* single-pathogen infections, those with more severe clinical features received antibiotics, especially nonmacrolide, but showed no significant difference.

Campylobacter spp. has become resistant to first-line antibiotics such as cotrimoxazole and quinolones in recent decades.[20–22] Pollett et al.[23] reported a greater increase in resistance to quinolones than macrolides in treating *Campylobacter* infections among low-income Peruvian populations.

A parallel study conducted on the same strains included in the current study determined their antimicrobial susceptibilities: 94.1% (48/51) resistance to nalidixic acid, 90.2% (46/51) resistance to ciprofloxacin, and 93.5% (43/46) resistance to tetracycline.[11] For macrolides, *Campylobacter jejuni* presented 6.7% (2/30) resistance to erythromycin and/or azithromycin, whereas *Campylobacter coli* presented 28.6% (6/21) resistance to erythromycin and/or azithromycin.[11]

Salazar-Lindo et al.[24] showed that macrolides (erythromycin) exhibit greater efficacy when prescribed within the first 4 days. In addition, Vukelic et al.[25] reported that the administration of a single dose of azithromycin, ideally within the first 48 hours, eradicates the pathogen with significant clinical improvement, compared with a 5-day course of erythromycin. Finally, a meta-analysis by Ternhag et al.[26] on the effects of antibiotic treatment in *Campylobacter* infections showed that antibiotic treatment significantly decreased the duration of diarrhea by 1.32 days. However, due to antibiotic resistance, a restrictive attitude regarding the use of antibiotics is advisable.

This study has some limitations. First, it was observational, descriptive, and retrospective, and a small sample size was analyzed. Second, no strict criteria for starting treatment with antibiotics were outlined; the decisions were made empirically. Third, despite the similarity of symptoms in diarrhea with bacterial and viral etiologies, some cases only received symptomatic treatments. Fourth, whether the clinical course of gastroenteritis ended because of antibiotic treatment or natural self-limiting course of the disease could not be established. Finally, seven antibiotic switches were made throughout the study period; six were from nonmacrolide to macrolide antibiotics. Furthermore, given the small sample size, no analysis was performed in this group.

This study demonstrated that the clinical course of *Campylobacter* coinfections in pediatric patients are more severe compared with *Campylobacter* single-pathogen infections.

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Authors' addresses: Galo Amaro Munoz, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru, E-mail: galo.munoz@upch.pe. Maribel Denise Riveros-Ramirez, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru, and Medical Tropical Alexander von Humboldt Institute, Universidad Peruana Cayetano Heredia, Lima, Peru, E-mail: maribel.riveros@upch.pe. Elsa Chea-Woo, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru, E-mail: elsa.chea@upch.pe. Theresa J. Ochoa, Woodel School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru, Medical Tropical Alexander von Humboldt Institute, Universidad Peruana Cayetano Heredia, Lima, Peru, and Department of Epidemiology, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, E-mail: theresa.ochoa@upch.pe.

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