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SHORT COMMUNICATION

Clinical significance of erythromycin-resistant *Campylobacter jejuni* in children☆

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Campylobacter has been recognized as the common cause of bacterial gastroenteritis in many countries. Increasing erythromycin resistance in *Campylobacter jejuni* infection is noted recently, but severe case was rarely reported. In this study, we aimed to clarify the clinical significance of the resistant strain of *C jejuni* in children. We reviewed the charts of children who were diagnosed with *C jejuni* enteritis in our hospital from January 2000 to December 2005, including 326 patients (117 males and 209 females). All the cases had positive stool culture. We divided them into two groups, the sensitive group (a total of 306 cases) and resistant group (a total of 20 cases), according to the drug sensitivity. We analyzed the clinical manifestations and laboratory data between the two groups. The mean age was 3.79 ± 3.24 years in the sensitive group and 3.03 ± 2.84 years in the resistant group. There was no significant difference between the two groups in clinical presentations and laboratory examinations. No mortality was found, and one case was initially presented with colonic perforation. This report demonstrates that infection by erythromycin-resistant strains of *C jejuni* has no clinical significance in children, despite the probably increased emergence of erythromycin resistance.

☆ The authors confirm that they have read the Journal's position on issues of ethical publication and affirm that this report is consistent with those guidelines. There is no financial support or any potential conflict of interest to be reported for this article.

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Introduction

Several countries, including Canada, Japan, and Finland, have reported *Campylobacter jejuni* isolates with low and stable rates of macrolide resistance. In contrast, the increasing level of macrolide resistance in *C jejuni* is becoming a major public health concern in other parts of the world, such as the United States, Europe, and Taiwan.[1,2] The available evidence suggests that those infected with resistant strains of *Campylobacter* experience illness that is prolonged and more severe than those with sensitive strains.[3] However, in comparison with several epidemiological studies examining the clinical impact of quinolone resistance in *Campylobacter* infections, there is limited information on the clinical consequence of erythromycin resistance in *Campylobacter* infection, especially in children.

In this study, focusing on *C jejuni* cultured from feces of pediatric patients, we assessed the antimicrobial susceptibility trends to erythromycin and its clinical significance more than a 6-year period (2000—2005).

Methods and results

We retrospectively reviewed the medical charts for *C jejuni* in pediatric patients from January 2000 to December 2005 at Chang Gung Memorial Hospital, Kaohsiung Medical Center, Taiwan. Patients were included in the study if they were younger than 17 years of age. All patients had stool cultures positive for *C jejuni*. The fecal samples were examined for *Campylobacter* species by direct inoculation of feces on to modified charcoal cefoperazone desoxycholate agar (CCDA; Oxoid, Basingstoke, United Kingdom). The CCDA was composed of *Campylobacter* growth supplement (Oxoid SR084). The plates were incubated for 48 hours at 42°C under microaerophilic conditions (5% O_2, 5% CO_2, 2% H_2, and 88% N_2 by volume) generated by oxoid microaerophilic gas pack. *Campylobacter jejuni* NCTC 11322 was incubated with each lot of plates as a positive control. Gray, flat, and spreading colonies, resembling those of *Campylobacter*, were selected for further identification. Oxidase- and catalase-positive colonies exhibiting a characteristic Gram stain appearance (gram-negative S-shaped rods) were reported as *Campylobacter* species. The ability to hydrolyze hippurate was evaluated by the British Standards Method (BS 5763 Part 17, 1996:9.5.5.5), and susceptibility to nalidixic acid was determined by disk diffusion with a 30-μg nalidixic acid disk applied to a blood agar plate inoculated with a suspension of the test isolate. Nalidixic acid—susceptible isolates capable of hippurate hydrolysis were reported as *C jejuni*, whereas nalidixic acid—susceptible, hippurate hydrolysis—negative isolates were reported as *Campylobacter coli*. Sensitivity testing for erythromycin was carried out using the disc diffusion method.

Clinical manifestations were recorded. Laboratory data, including white blood cell count, platelet count, C-reactive protein, sodium, potassium, blood urea nitrogen, sugar, carbon dioxide, treatment modalities, complications, and outcomes were collected.

We divided the patients into erythromycin-sensitive and erythromycin-resistant groups according to the drug sensitivity of stool culture. We analyzed differences in clinical manifestations and laboratory data, treatment modalities, complications, and outcomes between the two groups. The statistical analyses were performed using the Statistical Package for Social Science (SPSS, version 13, IBM Corporation, Somers, NY 10589, USA) software package. The *p* values less than 0.05 were considered statistically significant.

A total of 326 patients (117 males and 209 females) were enrolled in this study. The mean age at admission was 3.79 ± 3.24 years in the sensitive group and 3.03 ± 2.84 years in the resistant group.

There were a total of 306 cases in the sensitive group and 20 cases in the resistant group. The average rate of resistance was 6%. As shown in Figure 1, the antimicrobial resistance rates have increased in the past 3 years (2003—2005). There was no significant difference between the two groups in the laboratory profiles, including white blood cell count, platelet, C-reactive protein, glucose, sodium, potassium, carbon dioxide, and blood urea nitrogen levels (Table 1) or in clinical presentations and outcomes, including vomiting, abdominal pain, bloody diarrhea, duration of admission, duration of diarrhea and fever before and after admission, and symptoms of upper airway infection (Table 2). The cases who were prescribed erythromycin were recorded. Because this study was retrospective, the criteria of treatment were based on the physician's experience. There was no significant difference between the two groups. In our series, no mortality was noted in either group; however, one case in the sensitive group was initially presented as colonic perforation.

Discussion

Campylobacter species are among the most frequently identified bacterial causes of human gastroenteritis in the United States and other industrialized countries.[4] The most important *Campylobacter* species is *C jejuni*, accounting for more than 90% of infections.[5] The increasing level of macrolide resistance in *C jejuni* is becoming a major public health concern in some parts of the world, such as the United States, Europe, and Taiwan.[1,2] Furthermore, life-threatening systemic *Campylobacter* diseases are diagnosed more and more frequently.[6] Thus, it is imperative to investigate the clinical impact of macrolides resistance in *Campylobacter* infections.

Erythromycin is considered as the drug of choice for treating *Campylobacter* gastroenteritis, and ciprofloxacin and tetracycline are used as alternative drugs.[7,8] Quinolones and tetracycline are rarely used for treating pediatric

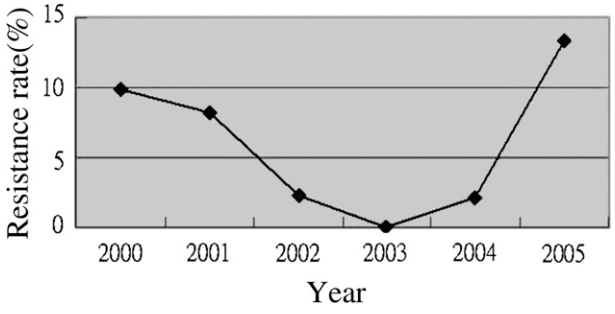

Figure 1. The erythromycin resistance rates for the years 2000—2005.

Table 1 Laboratory data of the patients in the erythromycin-susceptible and erythromycin-resistant groups

Laboratory data	Susceptible group	Resistant group	*p*
WBC/cmm	10,088 ± 4,304	10,456 ± 5,304	0.744
Platelet (1,000/cmm)	26.7 ± 8.33	25.5 ± 7.25	0.553
CRP (mg/L)	63.2 ± 55.6	48.1 ± 45.3	0.272
Na (mEq/L)	137.2 ± 3.36	137.4 ± 3.82	0.866
K (mEq/L)	4.28 ± 0.49	4.31 ± 0.70	0.871
CO_2 (mEq/L)	16.6 ± 2.72	17.2 ± 3.72	0.637
Glucose (mg/dL)	96.5 ± 21.9	89.67 ± 13.3	0.452
BUN (mg/dL)	9.5 ± 4.27	10 ± 4.24	0.873

BUN = blood urea nitrogen; CRP = C-reactive protein; WBC = white blood cell.

patients with *Campylobacter* enteritis in our cases. Thus, in this study, we have only considered the clinical impact of erythromycin resistance on *C jejuni* enteritis in children.

Since the 1990s, a significant increase in the prevalence of resistance to macrolides among *Campylobacter* species has been reported, and this is recognized as an emerging public health problem.[9] The incidence of erythromycin resistance among *C jejuni* is highly variable with respect to the country of isolation,[3] ranging from 0% to 7.3%. Furthermore, increased macrolide resistance among *C jejuni* and *C coli* has been reported in both developed and developing countries, but the situation seems to be deteriorating more rapidly in developing countries.[10] In Taiwan, a survey from 1994 to 1996 shows the rate of resistance to erythromycin to be 10%.[2] In our study, the rate of erythromycin resistance is 6%, but the resistance rate has been increasing in the past 3 years, as shown in Figure 1. It is unknown whether the trends displayed for the level of antimicrobial susceptibility reported here is the result of a biased result caused by the age of our study subjects. Another limitation of this study was the number of patients. In 2003, there were no erythromycin-resistant cases, which may have confounded the reported trend of erythromycin resistance.

In comparison with *Salmonella*, events of invasive illness and death (0.63%) were more rarely associated with *Campylobacter* infection.[11,12] However, in adults, a number of investigations from the United States, Thailand, and Denmark have shown that infections with macrolide-resistant *Campylobacter* isolates could be associated with an increased risk of adverse events, development of invasive illness, or death compared with infections with drug-susceptible isolates.[12–14] Antimicrobial resistance can have two effects on the outcome of infection: There can be an accompanying change in the virulence of the organism and there can be a poorer response to treatment because of the choice of an empiric antimicrobial to which the organism is resistant. In contrast to the above-mentioned reports, our study showed that differences in duration and severity of illness were not statistically significant between the erythromycin-susceptible and the erythromycin-resistant groups. Furthermore, the frequency of complications and long-term sequelae (e.g. Guillain-Barre syndrome or other severe reactive illness) did not increase in the resistant group. Unlike in other reports, the patients in our study were all younger than 17 years of age. There was only one case of *Campylobacter* bacteremia in a patient who was aged one and half months. He recovered with a treatment of ampicillin and gentamicin. During the same period of time, we found seven adult patients with *Campylobacter* bacteremia in our hospital, and one of them was infected by an erythromycin-resistant strain. Our data show that erythromycin-resistant strains may not be so "virulent" in pediatric groups. Underlying diseases may account for the different outcomes between adult and pediatric patients because a high percentage of adult patients had chronic illness, such as diabetes mellitus, cancer, and liver cirrhosis.

In summary, this report demonstrates that infection by erythromycin-resistant strains of *C jejuni* has no clinical significance in children, despite the probably increased emergence of erythromycin resistance.

Table 2 Clinical presentations of the patients in the erythromycin-susceptible and erythromycin-resistant groups

Clinical presentations	Susceptible group		Resistant group		*p*
Age at ad, yr	3.79 ± 3.24		3.03 ± 2.84		0.309
Duration of ad, d	3.73 ± 3.18		5.2 ± 5.00		0.057
Duration of diarrhea before ad, d	2.65 ± 3.96		2.52 ± 1.87		0.892
Duration of diarrhea after ad, d	2.25 ± 2.04		1.77 ± 1.56		0.335
Duration of fever before ad, d	2.22 ± 1.76		2.11 ± 1.78		0.796
Duration of fever after ad, d	1.64 ± 1.45		1.41 ± 1.18		0.514
Vomiting	101/223	45.29%	7/13	53.85%	0.579
URI	94/203	46.31%	5/11	45.45%	1.0
Abdominal pain	17/91	18.68%	2/8	25.00%	0.647
Bloody diarrhea	138/172	80.23%	10/10	100%	0.212
Use of erythromycin	237/306	77.45%	18/20	90.00%	0.266

ad = admission; d = days; URI = upper respiratory tract infection; yr = year.

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